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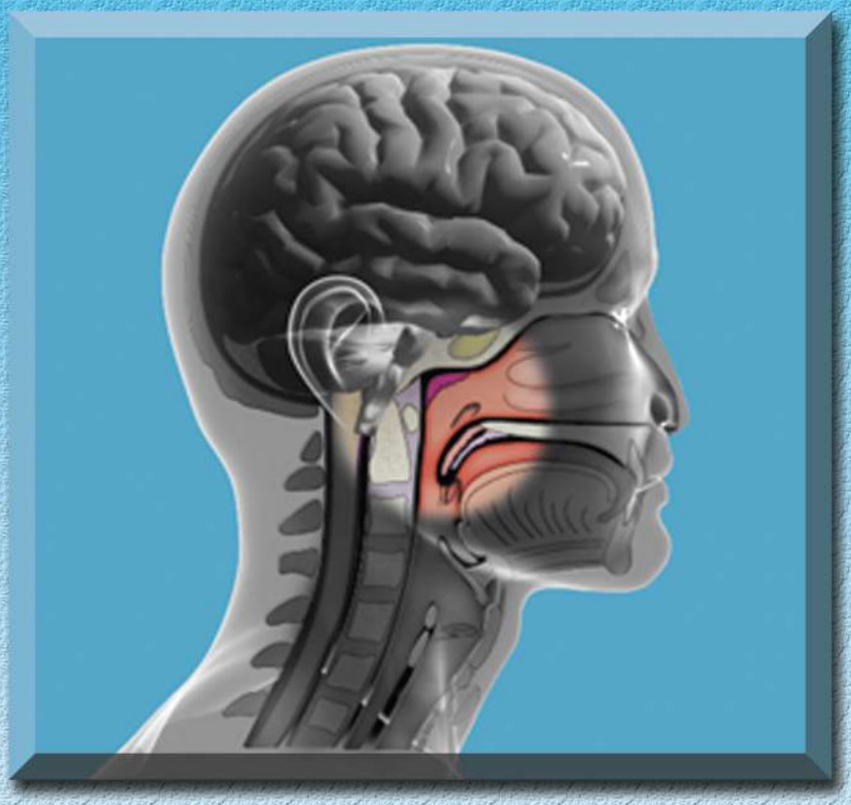
MINISTRY OF HEALTH MALAYSIA

NASOPHARYNGEAL CARCINOMA SCREENING



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MINISTRY OF HEALTH MALAYSIA

Health Technology Assessment Report

NASOPHARYNGEAL CARCINOMA SCREENING

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This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organisations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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EXECUTIVE SUMMARY

Background

Although cancer is a leading cause of death worldwide and projected to rise, more than 30% of the deaths are believed to be preventable. This can be done through early detection of the disease by having education and screening programme.

Nasopharyngeal Carcinoma (NPC) is more common in certain regions of Asia and Africa than elsewhere in the world in which certain factors are thought to predispose to its occurence. Despite improvements in radiotherapy techniques and better treatment outcomes with combination of chemotherapy and radiotherapy, only less than 10 % of NPC unscreened patients presented with early stage of the disease.

With the significant burden of disease of NPC in Malaysia and possible significant role of screening of the malignant condition, one of the strategies for screening and early detection in National Cancer Control Blueprint 2008-2010 is to provide NPC screening service.

Technical features

NPC is a cancer arising from the epithelial cells that cover the surface and line the nasopharynx. Screening methods for the disease includes Epstein-Barr virus EBV serology and nasopharyngoscopy. EBV is a member of the herpesvirus family. Lifelong dormant EBV infection in the immune system is associated with the occurrence of NPC. EBV antibodies include antibodies against Viral Capsid Antigen, Nuclear Antigen and Early D Antigen.

Objective

To assess the effectiveness and cost-effectiveness of NPC screening programme and to assess the diagnostic accuracy of the screening tests used in the NPC screening programme

Methods

Electronic scientific databases were searched for published literatures on NPC screening. They included Pubmed/Medline, Cochrane, Ovid, INAHTA, Proquest and Scopus websites. The reference lists of all retrieved literatures were searched to identify other relevant literatures. General search engine was also used to search for additional literatures. Experts in the field were also contacted to identify further literatures. There was no limitation applied in the search which ended on the 22 December 2009. All relevant studies were retrieved and appraised by one reviewer using Critical Appraisal Skills Programme (CASP) and graded according to level of evidence of US/Canadian Preventive Services Task Force.

Results and conclusion

There is no evidence on the effectiveness of NPC Screening in terms of reduction in mortality rate or increase in quality adjusted life years (QALY). Risks to have NPC are EBV infection and family history of NPC. However, the number of affected family members for risk of NPC is inconclusive. On the other hand, there is fair evidence to demonstrate acceptable diagnostic accuracy of the EBV serological test in a NPC screening programme.

Recommendation

Based on the above review, there was insufficient evidence to recommend a population-based NPC screening programme as a public health policy. EBV infection is a risk to NPC in individuals with a family history of the disease. In view of the acceptable diagnostic accuracy that it has, the EBV serology test is a promising tool for selective screening in those with a family history of NPC. However, standard guidelines should be developed in its application including follow up of those who are seropositive to EBV infection. Interpretation of such tests is complex and trained physician in EBV testing is necessary.

Evidence of high and good quality assessing the effect of such population-based screening, in terms of the reduction in mortality of NPC in the screened population, the risk-benefit ratio and cost-effectiveness is warranted to recommend a NPC Screening Programme.

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NASOPHARYNGEAL CANCER SCREENING

1 BACKGROUND

Cancer is a leading cause of death worldwide where it accounted for 7.4 million deaths or 13% of all deaths in 2004. More than 70% of all cancer deaths occurred in low- and middle-income countries. Deaths from cancer worldwide are projected to continue rising.[1]

According to the Malaysian Burden of Disease and Injury Study 2004, cancer ranks sixth in the overall burden of disease with almost 96% of the burden of cancer was contributed by the fatal component of it.[2] In fact, malignant neoplasm was the 10th principal cause of hospitalisation (3.1%) and the 3rd principal cause of death (10.6%) in the Ministry of Health (MOH) hospitals.[3]

More than 30% of cancer deaths can be prevented. Three categories of known carcinogens are viruses, physical agents and chemicals. Cancer can be reduced and controlled by implementing evidence-based strategies for cancer prevention, early detection of cancer and management of patients with cancer. About one-third of the cancer burden could be decreased if cases were detected and treated early. Two components of early detection are education and screening programmes.[1]

Nasopharyngeal Carcinoma (NPC) is more common in certain regions of Asia and Africa than elsewhere in the world. Viral, dietary and genetic factors are implicated in its causation.[4] It is usually recognised late in the course of the disease and often the first indication of a nasopharyngeal tumour is a fixed neck node. The inaccessible anatomic location of NPC and its rich lymphatic supply makes treatment clinically challenging.[5] Factors thought to predispose include Chinese (or Asian) ancestry, Epstein-Barr virus (EBV) exposure and unknown factors that result in very rare familial clusters.[6] In Malaysia, NPC was the third most common cancer among men. Based on the National Cancer Registry of 2006, the age-standardised incidence rate (ASR) of the disease was 8.5 and 2.6 per 100,000 population for males and females respectively. The disease was featured higher in Chinese compared to other races. For Peninsular Malaysia, the ASR for NPC among Chinese males was 14 per 100,000 population and Chinese females was 3.8 per 100,000 population compared to 4 and 1.3 per 100,000 for Malay males and females respectively. The Indian males and females reported low incidence rate that was 1.0 and 0.2 per 100,000 population respectively.[7]

Although there are improvements in radiotherapy techniques and better treatment outcomes with combination of chemotherapy and radiotherapy, the key to higher disease-free survival rates lies in early detection.[8] Good correlation has been shown between the stage of the disease and 5-year survival rates. For example, the overall survival decreases from 90% for stage I to below 60% for advanced stage IV disease. Unfortunately, only less than 10 % of NPC patients presented with stage I disease without screening. In areas of the world where it is much more common such as in some areas of China, screening may be offered to people at high risk of the disease.[9] Screening may include Epstein-Barr virus (EBV) serology or nasopharyngoscopy (examination of the nasopharynx using a tiny camera attached to the end of a flexible tube).

With the significant burden of disease of NPC in Malaysia and possible significant role of screening of the malignant condition, one of the strategies for screening and early detection in National Cancer Control Blueprint 2008-2010 is to provide NPC screening service. Therefore, a Health Technology Assessment (HTA) is requested to study the possibility of introducing a screening programme for early detection of NPC by Disease Control Division, Ministry of Health Malaysia.

2 TECHNICAL FEATURES

2.1 Nasopharyngeal Carcinoma

NPC is a cancer arising from the epithelial cells that cover the surface and line the nasopharynx. Three subtypes of NPC are recognised in the World Health Organization (WHO) classification and the cancer can extend within or out of the nasopharynx to the other lateral wall and/or posterosuperiorly to the base of the skull or the palate, nasal cavity or oropharynx. It then typically metastases to cervical lymph nodes.[10]

NPC has a reputation for delayed diagnosis and poor prognosis even though it is both radiosensitive and chemosensitive.[11] It may occur at any age, but the peak incidence is between 50 and 69 years old. The disease is more common in men and the most frequent symptom is a neck mass. Three major aetiologic factors with NPC include the following: [10, 12 - 15]

i. Genetic predisposition, hence the geographic variation in incidence. Although the pathogenetic mechanism of NPC is still unclear, its familial aggregation has been well documented by many epidemiological studies

ii. Dietary factors in particular the consumption of salt-cured fish and meat. It is belief that cooking these foodstuffs aerosolises carcinogenic nitrosamines that are inhaled.

iii. Infection with Epstein-Barr virus (EBV) which occurs in virtually all cases where individuals will have some antibodies to EBV. It appears that the viral DNA is incorporated into the tumour cells. The 10-year risk of developing NPC has been estimated to be up to 200 times higher in the antibody positive group. A negative evaluation does not eliminate the possibility of later development of the disease.

The geographical pattern of NPC incidence suggests a unique interaction of environmental and genetic factors. It is presumed that early changes of dysplasia are due to environmental changes such consumption of salted fish. Latent Epstein-Barr virus (EBV) infection plays a part in causing severe dysplasia after that. Once the diagnosis is suspected on clinical grounds, histological confirmation is mandatory which is facilitated by using fiberoptic nasopharyngoscope. The primary tumour extent should be evaluated by computed tomography (CT) or magnetic resonance imaging (MRI). NPC is one of the very few cancers in which cure can be anticipated even in advance stage. Although the initial remission rate is substantial with radiotherapy alone, the subsequent both local and distant failure rates are high. As NPC is highly chemosensitive, chemotherapy is incorporated into the primary treatment of the disease.[15]

2.2 Screening

2.2.1 Screening Programme

Two major components of early detection of cancer are education to promote early diagnosis and screening.[16] Screening by definition is the presumptive identification of unrecognised disease or defects by means of tests, examinations, or other procedures that can be applied rapidly. Screening programme should be undertaken only when: [17]

- effectiveness of the programme has been demonstrated
- resources (such as personnel and equipment) are sufficient to cover nearly all of the target group
- facilities exist for confirming diagnoses, treatment and follow up of those with abnormal results
- prevalence of the disease is high enough to justify the effort and costs of screening

Non-compliance to a screening programme will not improve disease outcome and also reduce the waste of resources. Such programme that concentrates solely on a high risk group is rarely justified as identified risk groups usually represent only a small proportion of the cancer burden in a country.[17] However, in high-risk areas of NPC like in China, efforts should be focused in developing screening programmes or annual physical examinations including EBV serology tests.[13] The success of a screening programme depends heavily on the existence of a well defined population at risk. For NPC, family history is perhaps one of the simplest and logical to be used in initiating a screening programme in an endemic region.[10] The tests usually used as screening tests are EBV serology and nasopharyngoscopy.[12,13, 18]

Based on criteria for appraising the viability, effectiveness and appropriateness of a screening programme 2003 (refer to Appendix 4), one of the criteria mentioned is evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. In fact, there should also be evidence that the complete screening programme (test, diagnostic procedures and treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.

2.2.2 Screening tests

2.2.2.1 Epstein-Barr virus (EBV) Serology

Epstein-Barr virus or EBV is a member of the herpesvirus family and causes one of the commonest human virus infections worldwide. Lifelong dormant EBV infection in some cells of the body's immune system is associated with the occurrence of some cancers such as Burkitt's lymphoma and NPC though it is probably not the sole cause of the diseases. EBV infection is transmitted through intimate contact with the saliva of an infected person.[19]

Epstein-Barr virus antibodies include:[20]

- Epstein-Barr Virus Antibody (Ab) to Viral Capsid Antigen (VCA), immunoglobulin M (IgM)
- Epstein-Barr Virus Antibody to VCA, immunoglobulin G (IgG)
- Epstein-Barr Virus Antibody to Nuclear Antigen, IgG
- Epstein-Barr Virus Antibody to Early D Antigen, IgG
- Heterophile Antibodies

There are a number of EBV-specific laboratory tests that can be used to test EBV infection. Effective laboratory diagnosis can be made by testing for antibodies to several EBV-associated antigens simultaneously such as VCA, the early antigen, and the EBV nuclear antigen (EBNA). IgM to the viral capsid antigen appears early in infection and disappears within four to six weeks while the IgG to the same antigen persists for life. On the other hand, IgG to the early antigen generally falls to undetectable levels after three to six months. Antibody to EBNA, detected by immunofluorescent test, appears two to four months after onset and persists for life after that. However, EBNA enzyme immunoassays, may detect antibody within a few weeks of onset. Interpretation of laboratory results is somewhat complex and should be left to physicians who are familiar with EBV testing and who have access to the entire clinical picture of a person.[20]

A raised immunoglobulin A (IgA) VCA Ab titre and a computed tomography (CT) scan findings suggestive of a lesion in the fossa of Rosenmuller should be presumed to be due to NPC. Thus, it is essential to confirm the diagnosis by biopsy and repeated if necessary.[11] MF Ji *et al*., in a prospective study conducted in a high-incidence area in southern China, identified a serologic window preceding diagnosis when antibody levels are raised and sustained. This window can persist for as long as 10 years, with a mean duration estimated to as 37±28 months. A total of 91% of NPC cases exhibited such a window. NPC risk levels among seropositive subjects were also highest within two years of screening.[21] These statements indicate that interpretation of serological tests should be done by trained personal so that necessary actions can be taken appropriately.

2.2.2.2 Fiberoptic Nasopharyngoscopy

Nasopharyngoscopy enables the doctor to examine and have direct view of the internal surfaces of the nasopharynx. Fiberoptic nasopharyngoscope used in the procedure is flexible with a 2-way articulation providing inline view with photo and video capabilities. It can have a distal diameter as small as 2 mm. The device also provides clearer visualisation and better access to nasopharyngeal anatomy compared to alternative techniques such as indirect laryngoscopy and laryngoscopy by angled telescope. A biopsy (tissue sample) may be done together in this procedure.[11, 22]

Fiberoptic nasopharyngoscopy is indicated when visualisation of the nasopharyngeal anatomy is needed for diagnosis or treatment. For example, in the nasopharynx, the nasopharyngoscope can help identify suspected tumours or adenoidal hypertrophy. A biopsy of the tissue may be done in the procedure as well. Nasopharyngoscopy is considered a benign procedure with few contraindications and complications in experienced hands. Contraindications include epiglotitis and coagulopathies. In the former, inexperienced personnel may cause laryngospasm which may lead to airway obstruction.[23] Laceration, bleeding, respiratory collapse and vomiting are the very rare complications related to it.[11]

3 POLICY QUESTIONS

3.1 Should nasopharyngeal carcinoma screening programme be introduced as part of the National Cancer Control Programme?

3.2 What is the best screening test for nasopharyngeal carcinoma screening programme?

4 OBJECTIVES

4.1 To assess the effectiveness and cost-effectiveness of nasopharyngeal carcinoma screening programme

4.2 To assess the diagnostic accuracy of the screening tests used in nasopharyngeal carcinoma screening programme

5 METHODOLOGY

5.1 Literature search strategy

Electronic scientific databases were searched for published literatures pertaining to NPC screening. The search was applied to Medline/Pubmed (August 2009 and January 2010), EBM Reviews - Cochrane Database of Systematic Reviews (2005 to August 2010) EBM Reviews - Cochrane Central Register of Controlled Trials 3rd Quarter 2010, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2010, EBM Reviews - Health Technology Assessment 3rd Quarter 2010, EBM Reviews - NHS Economic Evaluation Database 3rd Quarter 2010 (all EBM Reviews were searched via OVID), INAHTA database, Proquest database and Scopus database. The last search was run in May 2010. No limits were applied to the search. The reference lists of all retrieved literatures were searched to identify other relevant literatures. General search engine was also used to get additional web-based information. Experts in the field were contacted to identify further literatures.

The following MeSH terms or free text were used either singly or in combination: “Nasopharyngeal Neoplasms”[Mesh], “Nasopharyngeal Cancer”, “Nasopharyngeal Tumour”, nasopharyngeal carcinoma, “Mass Screening”[Mesh], “Early Detection of Cancer”[Mesh]), Screen*, effect*, “detection rate”, “survival rate”, “quality-adjusted life years”, QALY, “adverse events”, cost-effect*, “Epstein-Barr virus serology”, nasopharyngoscopy**,** **“**diagnostic imaging”.

5.2 Study Selection

Studies included in this health technology report met the following criteria:

5.2.1 Inclusion criteria:-

a. Studies with full text

b.	Study design :	Systematic Review, Randomised Controlled Trial, observational studies and economic studies for effectiveness and cost-effectiveness
c.	Population :	Adults and children
d.	Intervention 1 :	NPC screening
	Intervention 2 :	Nasopharyngoscopy, EBV serology, diagnostic imaging or other screening tests
e.	Comparators:	No screening/usual care
f.	Outcome 1:	Detection rate, survival rate, quality adjusted life years (QALY), adverse events, cost and cost-effectiveness
	Outcome 2:	Sensitivity, specificity, positive predictive value, negative predictive value and number needed to screen (NNS)

5.2.2 Exclusion criteria:-

Study conducted in animals

Based on the above eligibility criteria, search for studies was carried independently by a reviewer. The titles and abstracts of all studies were selected using the above criteria.

5.3 Quality assessment strategy

The methodological quality of all retrieved studies was assessed using Critical Appraisal Skills Programme (CASP) tool based on the study design. The assessment was conducted by one reviewer. All of the articles were graded according to the level of evidence of the US/Canadian Preventive Services Task Force (Appendix 2).

5.4 Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (Evidence Table as shown in Appendix 5). Details on: (1) methodology including study design, (2) characteristics of study population, (3) type of intervention such as EBV serology and comparator; and (4) outcome measures such as detection rate, survival rate, quality adjusted life years (QALY), adverse events, cost and cost-effectiveness were extracted. The extracted data were presented and discussed with the Expert Committee.

6 RESULTS

Search strategy yielded 543 published studies related to screening for NPC. The search yielded 543 studies. After vetting the titles, 77 abstracts were reviewed. Out of these, 23 full text articles were retrieved. There were four cohort studies, five case-control studies, 13 cross-sectional studies and one systematic review. Out of these, 19 articles were excluded due to poor methodology, hospital-based study population and tools used were not for screening purpose. They are listed in Appendix 6. Therefore, only four population-based studies were included. They were conducted in the Chinese population only who are known to be at risk of developing NPC.

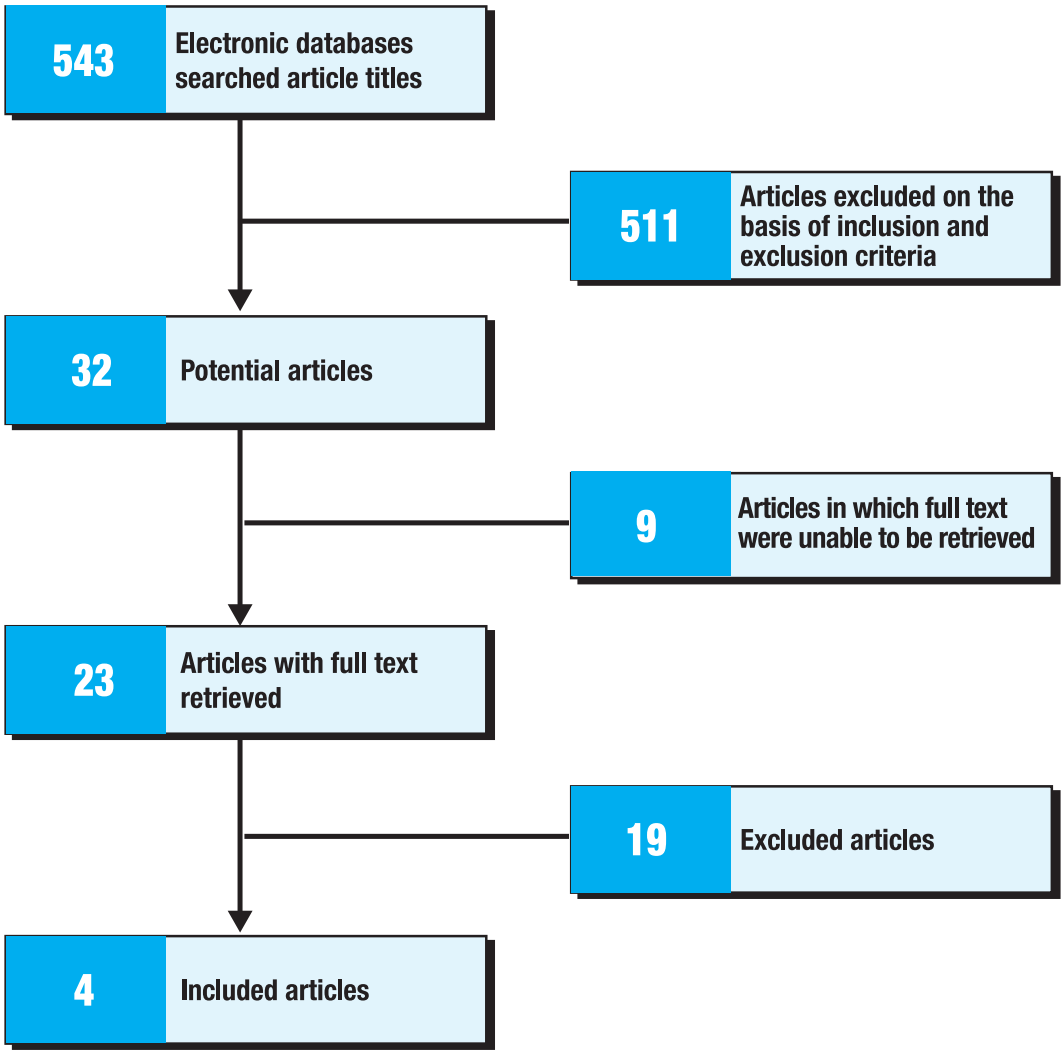

Figure 1: Flow diagram for identified studies

6.1 EFFECTIVENESS OF NPC SCREENING PROGRAMME

There was no retrievable study addressing mortality rate, quality adjusted life years (QALY), adverse events, cost and cost-effectiveness in relation to screening of NPC. All four population-based studies used in this report were conducted in countries where NPC is prevalent such as China, Hong Kong and Taiwan. They were all cohort studies and used EBV serological markers to screen the study population. There was no mention on length of follow up that should be done on those with positive serology but negative biopsy or those with negative serology. However, Chien YC *et al.* found that the longer the duration of follow up, the greater the difference in the cumulative incidence of NPC between seropositive and seronegative subjects.[24, level II-2]

A cohort study among 9,699 Taiwanese men in six townships was performed by Chien YC *et al*. between 1984 and 1986. These townships recorded the highest age-standardised NPC mortality rate in the country. The study aimed to determine whether antibodies against EBV were present before NPC occurrence (risk of EBV infection exposure prior to NPC occurrence). Each participant received serologic testing for IgA against EBV VCA, anti-EBV DNA antibodies (anti-EBNA) and otorhinolaryngologic examinations. The total follow up duration was 131,981 person-years. There were nine cases out of 1,220 seropositive subjects and 13 cases out of 8,413 seronegative subjects. This gave rise to a NPC incidence of 16.7 per 100,000 person-years. The incidences of IgA against EBV VCA, anti-EBV DNA antibodies and both types of antibodies were highest among subjects older than 50 years of age ($p<0.001$). After adjustment for age and family history of NPC, the relative risk (RR) of NPC was 32.8 for subjects with both IgA against EBV VCA and anti-EBV DNA antibodies (95% CI 7.3 to 147.2) and 4.0 for subjects with one marker (95% CI 1.6 to 10.2) as compared to subjects with neither marker. The study concluded that IgA antibodies against EBV VCA and EBV DNA are predictive of NPC.[24, level II-2]

In another study conducted between December 1986 and April 1988, Zong YS *et al*. studied IgA against VCA of Epstein-Barr virus in the detection of asymptomatic NPC (detection rate of NPC using serological marker). This large population-based cohort study involved apparently 52,450 healthy subjects residing in Zhongshan City and Shantou in the southern Guangdong province of China. However, analysis was focused only on 42,048 individuals from Zhongshan City which had high incidence of NPC. From 2,823 study subjects found to be seropositive in the city, 41 of them developed histologically confirmed asymptomatic NPC through yearly nasopharynx examinations in the first two years after screening (a detection rate of 1.5%). Most of these cases were localised NPC or earlier stages of NPC i.e. 80.5% were at earlier stages and none in Stage IV. Those symptomatic cases of NPC seen in the same region without screening were at worse stages of NPC i.e. 89.9% in Stage III & IV ($p=0.001$). This study also showed that the risk of NPC occurrence increased with age ($p=0.0090$) and males gender ($p=0.0227$) in seropositive individuals.[25, level III]

Ng WT *et al*. screened a cohort of 929 family members (first degree relatives) of patients with NPC between March 1994 and March 2001. Study subjects were offered annual examination including serological test against EBV, physical examination and endoscopic examination of nasopharyngeal region. Two different techniques for serology tests were used; indirect immuno-fluorescent (IF) test for IgA against VCA; and starting in 1997 enzyme-linked immunosorbent assay (ELIZA) against nuclear antigen and VCA.

This necessitates cautious interpretation of the results. In a 2,560 person-years of follow up, 68% participants complied with annual screening programme at time of analysis. An additional telephone contact of defaulters (32%) was attempted and 52% of them replied with no evidence of NPC. There was no mention on verification of such information. A total of 12 cases of NPC were diagnosed, giving an incidence rate of 469/100,000 person-years. Out of these, 41% cases had Stage I disease. They were six EBV-positive cases detected at the first visit, three cases detected on 204 person-years follow up on 78 screenees with positive serology at first visit (after an interval of 6 to 32 months) and another three cases detected out of 845 initially EBV-negative screenees in 2,337 person-years follow up (after an interval of 12 to 45 months). Risk of having the disease was much higher for those seropositive with a RR of 30.2 (95% CI 8.3 to 109.3) compared to those with negative EBV test. There was no significant finding in risk of having disease according to number of diseased family members. Risk of NPC in more than 1 diseased family members was 3.3 (95% CI 0.9 to 12.0) compared to only 1 family member. This study also showed that family members of known patients do show a substantially higher risk of developing NPC and regular screening improved the chance of early detection of the disease.[26, level II-2]

The most recent study, published in 2009, was conducted by Ng WT *et al*. to look at outcomes of NPC screening in high risk family members in Hong Kong. A cohort of 1,199 asymptomatic study subjects who were first degree relatives of NPC cases participated in a screening programme using EBV serology and nasopharyngoscopy. Compared to his earlier study above, only 52.4% participants complied with the annual screening programme but there was no attempt to trace defaulters this time. In a total follow up of 6,771 person-years, 18 cases of NPC were detected out of 1,199 study subjects regardless of serological results (detection rate of 1.5%). This gave rise to an incidence rate of 266 per 100,000 person-years. From these 18 cases, 15 were seropositive at screening either at first or subsequent visits. The staging distribution and survival outcomes of these cases were compared with 1,185 consecutive symptomatic patients diagnosed in the same period through general referral. The comparison showed that active screening programme resulted in early detection of asymptomatic cancer with 59% presented at early stage (stage I and II) compared to 24% of symptomatic cancers ($p<0.001$) and also improvement in disease-free survival ($p = 0.04$). The hazard ratio for cancer recurrence or death among screened patients was 0.32 (95% CI 0.10 to 0.99) compared to unscreened patients. This study also supported author's earlier study findings whereby those with seropositive EBV among the screened population had a RR of 30.7 (95% CI 9.0 to 104.9) in developing NPC. Contrary to the earlier study too, the number of diseased family members at the time of diagnosis was associated with a significant higher risk namely RR for ≥2 diseased members was 3.25 (95% CI 1.09, to.67) compared to those with 1 diseased family member.

The author concluded that screening asymptomatic family members of NPC patients annually leads to earlier detection of NPC and clinically valuable survival advantage among these family members. However, this study failed to mention the number and family history of the unscreened population.[27, level II-2]

A systematic review entitled Screening for nasopharyngeal carcinoma is being conducted by the Cochrane Group based on the posted protocol in its website on 7 May 2010.

6.2 ACCURACY OF NPC SCREENING TEST

Only two studies assessed the diagnostic accuracy of using EBV infection as serological marker in a screening. However, the studies used different cut off point to differentiate positive and negative results of serology. An antibody titre of ≥10 was considered as positive serology in the 2005 study by Ng WT *et al*.[26, level II-2] while a titre of ≥20 was considered as positive serology in his later study in 2009.[27, level II-2] All study subjects with positive results in these studies underwent biopsy of the nasopharyngeal area.[26, level II-2; 27, level II-2] In the first study conducted in 2005, EBV serology (combined ELIZA and immunoflourescent techniques) was found to have a sensitivity and specificity of 75% and 92% respectively.[26, level II-2] However in 2009, Ng WT *et al.* showed that the sensitivity and specificity of EBV serology were 83% and 87% respectively.[27, level II-2] ELIZA was found to have a better sensitivity and specificity (100% and 92%) compared to immunoflourescent technique (57% and 92%).[26, level II-2] The calculated positive Likelihood Ratio (LR) was 6.43 and Negative LR was 0.19 which means moderate impact on the likelihood to detect NPC.

There were no studies retrieved on accuracy of NPC screening using fiberoptic nasopharyngoscopy.

6.3 COST-EFFECTIVENESS OF NPC SCREENING PROGRAMME

There were no studies addressing cost-effectiveness of NPC screening. However, Hospital Kuala Lumpur and Pusat Perubatan Universiti Kebangsaan Malaysia charge between RM5 to RM20 for an EBV serological test (personal communication with officers at Finance Department of Hospital Kuala Lumpur and Pusat Perubatan Universiti Kebangsaan Malaysia)

7 CONCLUSION

7.1 EFFECTIVENESS OF NPC SCREENING PROGRAMME

There is no evidence on the effectiveness of NPC screening in terms of reduction in mortality rate or increase in QALY. More information will be obtained if the systematic review to be conducted by the Cochrane Group is completed. Risks to have NPC are EBV infection (seropositive) and family history of NPC. However, the number of affected family members on risk of NPC is inconclusive.

7.2 ACCURACY OF EBV SEROLOGY IN NPC SCREENING

There is fair evidence to demonstrate acceptable diagnostic accuracy of the EBV serological test in a NPC screening programme.

7.3 COST-EFFECTIVENESS OF NPC SCREENING PROGRAMME

There is no evidence on cost-effectiveness of using the serological tests in a NPC screening.

8 RECOMMENDATION

i. Based on the above review, there was insufficient evidence to recommend a population-based NPC screening programme as a public health policy. EBV infection is a risk to NPC in individuals with a family history of the disease. In view of the acceptable diagnostic accuracy that it has, the EBV serology test is a promising tool for selective screening in those with a family history of NPC. However, standard guidelines should be developed in its application including follow up of those who are seropositive to EBV infection. Interpretation of such tests is complex and trained physician in EBV testing is necessary.

ii. Evidence of high and good quality assessing the effect of such population-based screening, in terms of the reduction in mortality of NPC in the screened population, the risk-benefit ratio and cost-effectiveness is warranted to recommend a NPC Screening Programme.

9 REFERENCES

1. Cancer. Retrieved from http://www.who.int/mediacentre/factsheets/fs297/en/index.html on 2 January 2010
2. Institute for Public Health, Malaysia. Malaysian Burden of Disease and Injury Study, Health Prioritization: Burden of Disease Approach. Kuala Lumpur: The Institute; 2004
3. Statistik – Fakta Kesihatan 2006. Retrieved from http://www.moh.gov.my/static/health_facts_2006.pdf on 2 January 2010
4. Nasopharyngeal carcinoma. Retrieved from http://en.wikipedia.org/wiki/Nasopharyngeal_carcinoma on 2 January 2010
5. Sasaki CT, Jassin B. Cancer of the pharynx and larynx. Am J Med. 2001 Dec 3;111 Suppl 8A:118S-123
6. Nasopharyngeal Cancer Treatment. Retrieved from http://www.cancer.gov/cancertopics/pdq/treatment/nasopharyngeal/HealthProfessional/page2 on 2 January 2010
7. Ministry of Health Malaysia. National Cancer Statistics Data and Figure Peninsular Malaysia 2006. Kuala Lumpur: the Ministry; 2009
8. Guidelines on Cancer Prevention, Early Detection & Screening Nasopharyngeal carcinoma (NPC). Retrieved from http://www.hkacs.org.hk/uploadimages/download/00147/Guideline%20on%20NPC%20prevention,%20detection%20&%20screening%20(full%20recommendation).pdf on 2 January 2010
9. Nasopharyngeal carcinoma. Retrieved from http://www.mayoclinic.com/health/nasopharyngeal-carcinoma/DS00756/DSECTION=tests-and-diagnosis on 2 January 2010
10. Brennan B. Nasopharyngeal carcinoma. Orphanet J Rare Dis. 2006 Jun 26;1:23
11. Prasad U. Nasopharyngeal carcinoma. Medical Progress. 2006 July;11-16
12. Titcomb CP Jr. High Incidence of Nasopharyngeal Carcinoma in Asia. J Insur Med. 2001;33(3):235-8
13. Jia WH, Huang QH, Liao J, *et al.* Trends in incidence and mortality of nasopharyngeal carcinoma over a 20-25 year period (1978/1983-2002) in Sihui and Cangwu counties in southern China. BMC Cancer. 2006 Jul 6;6:178
14. Ng WT, Choi CW, Lee MC, *et al*. Familial nasopharyngeal carcinoma in Hong Kong: epidemiology and implication in screening. Fam Cancer. 2009;8(2):103-8
15. Chan AT, Teo PM, Johnson PJ. Nasopharyngeal carcinoma. Ann Oncol. 2002 Jul;13(7):1007-15
16. Screening and early detection of cancer. Retrieved from http://www.who.int/cancer/detection/en/index.html on 3 February 2010
17. Screening for various cancers. Retrieved from http://www.who.int/cancer/detection/variouscancer/en/index.html on 3 February 2010

18. Wei WI, Sham JST. Nasopharyngeal carcinoma. The Lancet. 2005; Vol. 365, Issue 9476: 2041 – 2054

19. Epstein-Barr Virus and Infectious Mononucleosis. Retrieved from http://www.cdc.gov/ncidod/diseases/ebv.htm on 3 February 2010

20. Epstein-Barr Virus Antibodies. Retrieved from http://www.labtestsonline.org/understanding/analytes/ebv/test.html on 3 February 2010

21. Ji MF, Wang DK, Yu YL, *et al.* Sustained elevation of Epstein-Barr virus antibody levels preceding clinical onset of nasopharyngeal carcinoma. Br J Cancer. 2007 Feb 26;96(4):623-30

22. Nasopharyngoscopy. Retrieved from http://www.noseandsinus.net/PDF%20Documents/Nasopharyngoscopy_PT-INFO.pdf on 3 February 2010

23. Fiberoptic Nasopharyngoscopy. Retrieved from http://emedicine.medscape.com/article/149703-overview on 3 February 2010

24. Chien YC, Chen JY, Liu MY, *et al.* Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. N Engl J Med. 2001 Dec 27;345(26):1877-82

25. Zong YS, Sham JS, Ng MH, *et al.* Immunoglobulin A against viral capsid antigen of Epstein-Barr virus and indirect mirror examination of the nasopharynx in the detection of asymptomatic nasopharyngeal carcinoma. Cancer. 1992 Jan 1;69(1):3-7

26. Ng WT, Yau TK, Yung RW, *et al.* Screening for family members of patients with nasopharyngeal carcinoma. Int J Cancer. 2005 Mar 1;113(6):998-1001

27. Ng WT, Choi CW, Lee MC, *et al.* Outcomes of nasopharyngeal carcinoma screening for high risk family members in Hong Kong. Fam Cancer. 2009 Sep 25

APPENDIXES

APPENDIX 1

ABBREVIATIONS

ASR	Age-standardised incidence rate
CI	Confidence Interval
CT	Computed Tomography
EBV	Epstein-Barr virus
EBNA	EBV nuclear antigen
ELISA	Enzyme-linked immunosorbent assay
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MOH	Ministry of Health
NPC	Nasopharyngeal carcinoma
RR	Relative Risk
VCA	Viral capsid antigen

APPENDIX 2

LEVEL OF EVIDENCE

LEVELS OF EVIDENCE	
LEVEL	**STUDY DESIGN**
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE

APPENDIX 3

HEALTH TECHNOLOGY ASSESSEEMENT (HTA) PROTOCOL NASOPHARYNGEAL CARCINOMA SCREENING

1. BACKGROUND INFORMATION

Cancer is a leading cause of death worldwide accounting for 13% of all deaths in 2004. More than 30% of cancer deaths can be prevented. According to the Malaysian Burden of Disease and Injury Study 2004, cancer ranks sixth in the overall burden of disease and almost 96% of the burden of cancer was contributed by the fatal component of it. In fact, malignant neoplasm was the 10th principal causes of Ministry of Health (MOH) hospitalisation (3.1%) and the 3rd principal cause of deaths (10.6%) in MOH hospitals.

Cancer can be reduced and controlled by cancer prevention, early detection of cancer and management of patients with cancer. Two components of early detection are education and screening programmes. Nasopharyngeal cancer (NPC) is more common in certain regions of East Asia and Africa than elsewhere. Factors thought to predispose to it include Chinese (or Asian) ancestry and Epstein-Barr virus (EBV) exposure. In Malaysia, NPC featured higher in Chinese compared to other races.

The key to higher disease-free survival rates lies in early diagnosis. Unfortunately, only less than 10% of NPC patients presented with stage I disease without screening. In areas of the world where it is much more common such as in some areas of China, screening may be offered to people at high risk of the disease. Screenings may include Epstein-Barr virus serology or nasopharyngoscopy.

With the significant burden of disease of NPC in Malaysia and possible significant role of screening of the malignant condition, one of the strategies for screening and early detection in National Cancer Control Blueprint 2008-1010 is to provide NPC screening service. Therefore, a Health Technology Assessment (HTA) is required to look into the issue of this screening either as a population-based or at least high-risk population programme. This HTA is requested by Dr. Nor Saleha Ibrahim Tamin, Principal Assistant Director of Cancer Unit, Disease Control Division, MOH Malaysia.

2. POLICY QUESTION

2.1 Should nasopharyngeal carcinoma screening programme be conducted on high risk population as part of the National Cancer Control Programme?

2.2 What is the best modality for nasopharyngeal carcinoma screening?

3. OBJECTIVE

3.1 To assess the effectiveness and cost-effectiveness of nasopharyngeal carcinoma screening programme

3.2 To assess the diagnostic accuracy of the screening modalities (tests) used in nasopharyngeal carcinoma screening programme

4. METHODOLOGY

4.1 Search Strategy

4.1.1 Published literatures on nasopharyngeal carcinoma screening will be searched through scientific electronic databases: MEDLINE/Pubmed, Cochrane Database, INAHTA Database and EBM Reviews Database.

4.1.2 Additional literatures will be identifies from the bibliographies of the related articles. General search engine will be used to get additional web-based information.

4.1.3 There will be no limitation applied in the search.

4.1.4 The search strategy used the terms, which are either used singly or in various combinations: “Nasopharyngeal Neoplasms”[Mesh], “Nasopharyngeal Cancer”, “Nasopharyngeal Tumour”, “Mass Screening”[Mesh], screen*, “Early Detection of Cancer”, effect*, cost-effect*

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

a. Study design : Cross sectional, cohort, RCT, Systematic Review

b. Population : All

c. Intervention 1 : Nasopharyngeal carcinoma screening
Intervention 2 : Endoscopy, EBV serology, diagnostic imaging or other screening modality

d. Comparison : No screening

e. Outcome 1 : Detection rate, survival rate, quality adjusted life years (QALY), adverse events, cost and cost-effectiveness

Outcome 2 : Sensitivity, specificity, positive predictive value, negative predictive value *NNS

4.2.2 Exclusion criteria

Animal study

Based on the above inclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion. A third person will be consulted when the disagreement persist after discussion.

4.3 Data extraction strategy

The following data will be extracted:

1. Details of methodology
2. Details of characteristics of study population
3. Details of intervention and comparator
4. Details of individual outcomes in relation to effectiveness, safety and cost-effectiveness
5. Details on diagnostic accuracy of screening modalities (tests)

Data will be extracted from selected studies by two reviewers using a pre-designed data extraction form. Disagreements will be resolved by discussion. A third person will be consulted when the disagreement persist after discussion.

4.4 Quality assessment strategy

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) by two reviewers.

4.5 Methods of analysis/synthesis

Data on effectiveness, safety and cost-effectiveness of each screening modality will be presented in tabulated format with narrative summary. No meta-analysis will be conducted from this Health Technology Assessment.

5. Report writing

APPENDIX 4

CRITERIA FOR APPRAISING THE VIABILITY, EFFECTIVENESS AND APPROPRIATENESS OF A SCREENING PROGRAMME

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested for, should be clearly set out.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an ‘informed choice’ (for example, Down’s syndrome and cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially. and ethically acceptable to health professionals and the public.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
18. Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the screening programme.
19. All other options for managing the condition should have been considered (for example, improving treatment and providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
20. Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
22. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members

Source: Screening Criteria. Retrieved from

http://www.gp-training.net/training/tutorials/management/audit/screen.htm on 3 September 2010

APPENDIX 5

Evidence Table : Effectiveness of NPC Screening
Questions : Should NPC Screening Programme be conducted on high risk population?

What is the best modality for nasopharyngeal carcinoma screening?

Bibliographic citation	Chien YC, Chen JY, Liu MY et al. Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. N Engl J Med. 2001 Dec 27;345(26):1877-82
Study type	• Cohort study • Aim: To determine whether antibodies against EBV present before NPC • Standardised personal interview • Blood at enrolment • Positive cases referred to NPC clinic for fiberoptic endoscopy • Newly diagnosed cases of NPC identified by linkage with computerised profiles in National Cancer Registry with National Death Certification & medical chart.
LE	II-2
Number of patients	9,699
Patient characteristics	• Study subjects from 6 townships in Taiwan with highest age-standardised rates of death due to NPC between 1984 & 1986 • Male, ≥30 years of age • Each participant received serologic testing for IgA against EBV capsid antigen, anti-EBV DNase antibodies, & otorhinolaryngo-logic examinations & medical consultations • None of residents knew serologic status before recruitment
Intervention	Not applicable
Comparison	No screening
Length of follow up	16 years 131,981 person-years
Outcome measures/ Effect size	Results: • Prevalence of IgA against EBV capsid antigen, anti-EBV DNase Abs, & both types of Abs highest among subjects older >50 years of age ($p<0.001$) • 22 pathologically confirmed new cases of NPC diagnosed >1 year after recruitment • Cumulative risk of NPC per 100,000 person-years was 11.2 for subjects tested positive for neither serologic marker, 45.0 for those with one marker, & 371.0 for those with both markers • After adjustment for age & presence/absence of a family history of NPC, RR of NPC was 32.8 for subjects with both markers (95% CI 7.3 to 147.2) & 4.0 for subjects with one marker (95% CI 1.6 to 10.2), as compared with subjects with neither marker • Longer the duration of follow up, the greater the difference in cumulative incidence of NPC between seropositive & seronegative subjects Conclusion: • IgA antibodies against EBV capsid antigen & neutralising antibodies against EBV DNase are predictive of nasopharyngeal carcinoma Measurement of IgA antibodies against EBV capsid antigen & anti-EBV DNase antibodies may be useful for early detection of NPC in high-risk populations
General comments	• Clear clinical question • Quality checks on diagnosis • Statistical analysis explained, but no mention of sampling method although confounding factors addressed • Long follow up Limitation discussed

Evidence Table : **Effectiveness of NPC Screening**
Questions : **Should NPC Screening Programme be conducted on high risk population?**

What is the best modality for nasopharyngeal carcinoma screening?

Bibliographic citation	Zong YS, Sham JS, Ng MH, et al. Immunoglobulin A against viral capsid antigen of Epstein-Barr virus and indirect mirror examination of the nasopharynx in the detection of asymptomatic nasopharyngeal carcinoma. Cancer. 1992 Jan 1;69(1):3-7
Study type	• Cohort study • Aim: To evaluate efficacy of population screening for early stage NPC in southern China • Between Dec 1986 & Apr 1988
LE	II-2
Number of patients	• 42,048 & 10,402 apparently healthy subjects residing in a high incidence (Zhongshan City) & a low incidence area (Shantou) respectively • However, analysis was focused only on 42,048 individuals from Zhongshan City
Patient characteristics	• Ages of 30 & 59 years • Age & sex distribution of study subjects were representative for the populations as a whole • Each participant had serum for IgA against viral capsid antigen (IgA/VCA) of EBV. Titre of antibody ≥1:10 considered positive. Seropositive individuals were subjected to indirect mirror examination for lesions suggestive of NPC within 6/12 after serology. Punch biopsy for histologic confirmation 140 cases of symptomatic NPC, seen in the Zhongshan City Cancer Institute during 12 months immediately preceding the current study
Intervention	Not applicable
Comparison	No screening
Length of follow up	2 years
Outcome measures/ Effect size	Results (analysis on subjects in high incidence area: • From high incidence area, 2,823 were found to be seropositive. In follow up with yearly nasopharynx examinations ± biopsy; 41 found to have histologically confirmed asymptomatic NPC in first 2 years of follow up. Mostly, tumours were localised & at earlier stages than tumours of symptomatic cases of NPC seen in same region before screening (p=0.001). • Screening for early NPC on first occasion didn't appear to have depleted the cohort of disease; no. of cases detected in following year similar to no. of cases which expected to occur in cohort • Yearly indirect mirror examination of nasopharynx effectively identified most tumours at stage of asymptomatic disease. Risk of harbouring NPC different among different sex & age subgroups of seropositive individuals. Occurrence of NPC increase with age (p=0.0090), males than females (p=0.0227) • Sensitivity & specificity of the programme for first 2 years was 93.2% & 30.2% respectively Conclusion: By limiting such screening to those who are at exceedingly high risk, cost of screening can be kept within spending of public health authority, & effectiveness of screening also is improved
General comments	• Clinical question not that clear • Sampling & sample size estimation not mention • Statistical analysis not mentioned • Assessment of results not elaborated (risk of bias) • Sensitivity and specificity calculation of screening not clear Results can be applied locally

Evidence Table : Effectiveness of NPC Screening
Questions : Should NPC Screening Programme be conducted on high risk population?

What is the best modality for nasopharyngeal carcinoma screening?

Bibliographic citation	Ng WT, Yau TK, Yung RW, et al. Screening for family members of patients with nasopharyngeal carcinoma. Int J Cancer. 2005 Mar 1;113(6):998-1001
Study type	• Cohort study • March 1994 –March 2001 • Screenees who defaulted follow up assessments were traced by letter/telephone, those who refused to return for further assessments contacted by phone to inquire whether they had NPC diagnosed by other centres during interim 2 different methods used for serology test: indirect immuno-fluorescent (IF) test for IgA against viral capsid antigen; & starting 1997 enzyme-linked immunosorbent assay (ELIZA) against nuclear antigen & viral capsid antigen. A titre ≤1:10 was considered as negative.
LE	II-2
Number of patients	929
Patient characteristics	• First degree relatives of patients with NPC & ≥18 years old • Annual examination including serological test against EBV & endoscopic examination of nasopharyngeal region.
Intervention	Not applicable
Comparison	No screening
Length of follow up	2,559.9 persons years of follow up
Outcome measures/ Effect size	Results • Median duration of observation from first to latest assessment for whole group was 29/12 • 68% participants complied with annual screening program at time of analysis • Additional telephone contacts of defaulters attempted & 17% replied with no evidence of disease • 12 cases of NPC diagnosed, giving a detection rate of 5/1,155 (433/100,000) person-year for male & 7/1,404 (499/100,000) person-year for female participants observed • 41% of these detected cases had Stage I disease, only 2% referred to department for 1o treatment • 6 cases detected at first visit, & all were EBV-positive. Another 78 screenees with positive serology at first visit were follow up for 204 person years, & NPC detected in 3 after an interval of 6 – 32 months • Of 845 initially EBV-negative screenees follow up for 2,337 person-years, NPC was detected in 3 after an interval of 12 – 45 months. One showed seroconversion at time of diagnosis • Based on initial serology results, EBV serology (IF and ELIZA combined) achieved a sensitivity of 75% & a specificity of 92%. Corresponding initial sensitivity & specificity are 57% & 92% for IF, 100% & 92% for ELIZA, respectively. • RR of having disease is much higher if serology test is positive. RR based on EBV serological status is 30.2 (95% CI 8.3 to109.3) • NS increase in risk of having disease according to number of diseased family members involved. RR for ≥2 vs. 1 family member involved is 3.3 (95%CI 0.91 to, 11.99) Conclusion: Family members of known patients do show a substantially higher risk of developing NPC, & regular screening by current method improves the chance of early detection
General comments	• Clinical question not clearly stated (aim not clearly stated) • Methodology explained only briefly, no sample size estimation stated • Universal sampling • 2 different laboratory tests used, also sensitivity & specificity given are combined of both • Very wide RR for positive EBV Results can be applied locally

Evidence Table : Effectiveness of NPC Screening
Questions : Should NPC Screening Programme be conducted on high risk population?
What is the best modality for nasopharyngeal carcinoma screening?

Bibliographic citation	Ng WT, Choi CW, Lee MC, et. al. Outcomes of nasopharyngeal carcinoma screening for high risk family members in Hong Kong. Fam Cancer. 2009 Sep 25
Study type	• Cohort study Aim: To investigate performance of EBV serology & potential benefits of screening of family members of NPC patients. Stage distribution & treatment outcomes of NPC diagnosed within screening population were compared with those presented symptomatically through general referral during same study period.
LE	II-2
Number of patients	1,199
Patient characteristics	• During 1994 –2005, first-degree relatives of NPC patients aged 18, & above without NPC history & asymptomatic were invited to participate voluntarily in screening programme with EBV serology (2 different methods) & nasopharyngoscopy
Intervention	Not applicable
Comparison	No screening
Length of follow up	Median duration of observation from initial to latest assessment was 61.9 months (range: 0 – 153)
Outcome measures/ Effect size	Results: • Median age was 38 years • Only 52.4% participants compiled with annual screening programme • Total person-year of follow up was 6771 • 18 participants of screening programme developed NPC; 17 treated in institute, of whom 16 detected in screening • Performance of screening programme: Sensitivity & specificity of EBV serology were 83.3 & 87.0%, respectively, & for the programme they were 88.9 & 87.0%, respectively • Treatment outcome of screening programme: Stage distributions & survival outcomes of 17 cases were compared with that of 1,185 consecutive symptomatic patients diagnosed in same period through general referral screening programme resulted in early detection of cancer, with 59% presenting at early stage (stage I: 41%, stage II: 18%) compared to 24% (stage I: < 1%, stage II: 23%) of symptomatic cancers ($p < 0.001$), & improvement in disease-free survival ($p = 0.04$) • Treatment outcome; Cancer specific survival & overall survival rate at 5-year are also higher (92 vs. 77% & 92 vs. 70%, respectively), although nonsignificance • Risk of disease: RR based on EBV serological status (seropositive vs. negative) is 30.7 (95%CI 8.98 to 104.86). Number of diseased family members at time of diagnosis is also associated with a higher risk: RR for ≥2 vs. 1 diseased family member was 3.25 (95%CI 1.09 to 9.67) Conclusion: • Screening asymptomatic family members of NPC patients annually leads to earlier detection of NPC & clinically valuable survival advantage among these family members A larger sample size is needed to confirm its full potential in survival benefit
General comments	

APPENDIX 6

LIST OF EXCLUDED STUDIES

1. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet. 2005 Jun 11-17;365(9476):2041-54
2. Low WK, Leong JL, Goh YH *et al.* Diagnostic value of Epstein-Barr viral serology in nasopharyngeal carcinoma. Otolaryngol Head Neck Surg. 2000 Oct;123(4):505-7
3. Chang KP, Hsu CL, Chang YL *et al.* Complementary serum test of antibodies to Epstein-Barr virus nuclear antigen-1 and early antigen: a possible alternative for primary screening of nasopharyngeal carcinoma. Oral Oncol. 2008 Aug;44(8):784-92
4. O TM, Yu G, Hu K *et al.* Plasma Epstein-Barr virus immunoglobulin A and DNA for nasopharyngeal carcinoma screening in the United States. Otolaryngol Head Neck Surg. 2007 Jun;136(6):992-7
5. Ayadi W, Karray-Hakim H, Feki L *et al.* IgA antibodies against the Epstein-Barr nuclear antigen1 as a valuable biomarker for the diagnosis of nasopharyngeal carcinoma in Tunisian patients. J Med Virol. 2009 Aug;81(8):1412-21
6. Abdulamir AS, Hafidh RR, Abdulmuhaimen N *et al.* The distinctive profile of risk factors of nasopharyngeal carcinoma in comparison with other head and neck cancer types. BMC Public Health. 2008 Dec 5;8:400
7. Krishna SM, James S, Kattoor J *et al.* Serum EBV DNA as a biomarker in primary nasopharyngeal carcinoma of Indian origin. Jpn J Clin Oncol. 2004 Jun;34(6):307-11
8. Hao SP, Tsang NM, Chang KP. Screening Nasopharyngeal Carcinoma by Detection of the Latent Membrane Protein 1 (LMP-1) Gene with Nasopharyngeal Swabs. Cancer. 2003 Apr 15;97(8):1909-13
9. Hao SP, Tsang NM, Chang KP *et al.* Molecular diagnosis of nasopharyngeal carcinoma: detecting LMP-1 and EBNA by nasopharyngeal swab. Otolaryngol Head Neck Surg. 2004 Nov;131(5):651-4
10. Fachiroh J, Prasetyanti PR, Paramita DK *et al.* Dried-blood sampling for epstein-barr virus immunoglobulin G (IgG) and IgA serology in nasopharyngeal carcinoma screening. J Clin Microbiol. 2008 Apr;46(4):1374-80
11. Wong MM, Lye MS, Cheng HM *et al.* Epstein-Barr virus serology in the diagnosis of nasopharyngeal carcinoma. Asian Pac J Allergy Immunol. 2005 Mar;23(1):65-7
12. Leung SF, Tam JS, Chan AT *et al.* Improved accuracy of detection of nasopharyngeal carcinoma by combined application of circulating Epstein-Barr virus DNA and anti-Epstein-Barr viral capsid antigen IgA antibody. Clin Chem. 2004 Feb;50(2):339-45
13. Wei WI, Sham JS, Zong YS *et al.* The efficacy of fiberoptic endoscopic examination and biopsy in the detection of early nasopharyngeal carcinoma. Cancer. 1991 Jun 15;67(12):3127-30
14. King AD, Vlantis AC, Tsang RK *et al.* Magnetic resonance imaging for the detection of nasopharyngeal carcinoma. AJNR Am J Neuroradiol. 2006 Jun-Jul;27(6):1288-91
15. Cheng WM, Chan KH, Chen HL *et al.* Assessing the risk of nasopharyngeal carcinoma on the basis of EBV antibody spectrum. Int J Cancer. 2002 Feb 1;97(4):489-92
16. Loh KS, Goh BC, Lu J *et al.* Familial nasopharyngeal carcinoma in a cohort of 200 patients. Arch Otolaryngol Head Neck Surg. 2006 Jan;132(1):82-5
17. Chang AR, Liang XM, Chan AT *et al.* The use of brush cytology and directed biopsies for the detection of nasopharyngeal carcinoma and precursor lesions. Head Neck. 2001 Aug;23(8):637-45
18. Dennis Lo Y.M, LisaY.S, Kwok-Wai Lo *et al.* Quantitative analysis of cell-free Epstein-Barr Virus DNA in plasma of patients with nasopharyngeal carcinoma. Cancer Research. 1999; 59: 1188-1191
19. Kuan C.C, Jeng Ma, Lung S.L *et al.* Serum responses to the combination of Epstein-Barr Virus antigens from both latent and acute phases in nasopharyngeal carcinoma: Complimentary test of EBNA-1 with EA-D. Cancer Epidemiology, Biomarkers & Prevention. 1997; 6: 363