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Screening for nasopharyngeal cancer (Review)

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[Intervention Review]

Screening for nasopharyngeal cancer

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ABSTRACT

Background

Nasopharyngeal cancer is endemic in a few well-defined populations. The prognosis for advanced nasopharyngeal cancer is poor, but early-stage disease is curable and a high survival rate can be achieved. Screening for early-stage disease could lead to improved outcomes. Epstein-Barr virus (EBV) serology and nasopharyngoscopy are most commonly used for screening. The efficacy and true benefit of screening remain uncertain due to potential selection, lead-time and length-time biases.

Objectives

To determine the effectiveness of screening of asymptomatic individuals by EBV serology and/or nasopharyngoscopy in reducing the mortality of nasopharyngeal cancer compared to no screening. To assess the impact of screening for nasopharyngeal cancer on incidence, survival, adverse effects, cost-effectiveness and quality of life.

Search methods

The Cochrane Ear, Nose and Throat Disorders Group (CENTDG) Trials Search Co-ordinator searched the CENTDG Trials Register; Central Register of Controlled Trials (CENTRAL 2015, Issue 6); PubMed; EMBASE; CINAHL; Web of Science; Clinicaltrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 6 July 2015.

Selection criteria

Randomised controlled trials (RCT) and controlled clinical trials (CCT) evaluating screening for nasopharyngeal cancer versus no screening. Randomisation either by clusters or individuals was acceptable.

Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration. Our primary outcome measure was nasopharyngeal cancer-specific mortality. Secondary outcomes were incidence of nasopharyngeal cancer by stage and histopathological classification at diagnosis, survival (two-year, three-year, five-year and 10-year), harms of screening (physical and psychosocial), quality of life (via validated tools such as the SF-36 and patient satisfaction), cost-effectiveness and all-cause mortality.

Main results

We identified no trials that met the review inclusion criteria. We retrieved 31 full-text studies for further investigation following the search. However, none met the eligibility criteria for a RCT or CCT investigation on the efficacy of screening for nasopharyngeal cancer.

Authors' conclusions

No data from RCTs or CCTs are available to allow us to determine the efficacy of screening for nasopharyngeal cancer, or the cost-effectiveness and cost-benefit of a screening strategy. High-quality studies with long-term follow-up of mortality and cost-effectiveness are needed.

PLAIN LANGUAGE SUMMARY

Screening for nasopharyngeal cancer

Review question

Does screening individuals without symptoms using an Epstein-Barr virus blood test or nasopharyngoscopy (or both) reduce the mortality associated with nasopharyngeal cancer?

Background

Nasopharyngeal cancer is a rare cancer worldwide, but it is common in the Cantonese population of southern China. Due to its deep location in the nose and non-specific initial symptoms nasopharyngeal cancer is often detected late. While the prognosis for advanced nasopharyngeal cancer is very poor, early-stage nasopharyngeal cancer is potentially curable. Therefore early identification by screening might lead to improved outcomes. There are two common screening tests: the Epstein-Barr virus (EBV) blood test and nasopharyngoscopy (a procedure that allows the internal surfaces of the nose and throat to be examined with a fibre-optic instrument). Studying the benefits of screening for nasopharyngeal cancer started in the 1970s, but the value of this approach remains uncertain.

Study characteristics

This review intended to investigate the efficacy of a programme of screening and treatment using the EBV test and nasopharyngoscopy as a screening test for nasopharyngeal cancer. However, we did not identify any randomised or controlled clinical trials evaluating such a strategy.

Key results

There is a need for high-quality studies to determine the effectiveness of a screening programme for nasopharyngeal cancer, especially studies that assess long-term outcomes, such as mortality, and cost-effectiveness.

Quality of the evidence

This review is up to date to July 2015.

BACKGROUND

Description of the condition

Nasopharyngeal cancer is relatively rare on a world scale, but it is endemic in a few well-defined populations (Parkin 2002). In 2002, there were 80,000 new cases worldwide, accounting for 0.7% of all cancers and making it the 23rd most common new cancer in the world (Parkin 2005). In contrast, it was the fourth most common new malignancy in Hong Kong (Parkin 2002). Based on geographic distribution, the age-standardised incidence rate of nasopharyngeal cancer for both males and females is less than 1 per 100,000 person-years in most regions. However, dramatically elevated rates are observed in the Cantonese population of southern China (including Hong Kong), and intermediate rates are observed in several indigenous populations in South East Asia and in natives of the Arctic region, North Africa and the Middle East (Parkin 2002). In terms of sex distribution, nasopharyngeal cancer is diagnosed more frequently in males than in females, with an approximate ratio of 2 to 3:1 (Parkin 2002). Further, nasopharyngeal cancer has a bimodal age distribution: the peak incidence is at around 50 to 60 years of age and declines thereafter, and a small peak is observed among adolescents and young adults (Andejani 2004; Balakrishnan 1975; Ellouz 1978; Kamal 1999; Levin 1980; Nwaorgu 2004).

Nasopharyngeal cancer was classified into three subtypes by the World Health Organization (WHO) in 1979 on the basis of the findings of light microscopy (Rothwell 1979): keratinising squamous cell carcinoma (WHO type I), non-keratinising carcinoma (WHO type II) and undifferentiated carcinoma (WHO type III). The most recent WHO classification defines the histological types as squamous cell, non-keratinising (differentiated and undifferentiated carcinomas) and basaloid squamous cell carcinoma (Leon 2005). Squamous cell carcinoma is typically found in the older adult population and in non-endemic areas, and has the worse prognosis. Non-keratinising carcinoma is the most common type in endemic and non-endemic areas, and is associated with Epstein-Barr virus (EBV) infection (Leon 2005).

There is clearly a strong genetic component to risk, as shown by the elevated risk in migrant populations of Chinese or North African origin, and also in their children born in a new host country. Infection with EBV is most strongly associated with non-keratinising nasopharyngeal carcinoma, as shown by the raised levels of antibodies against EBV in most patients with nasopharyngeal cancer, presence of EBV DNA or RNA in all tumour cells, and the presence of EBV in a clonal episomal form in the precursor lesions of nasopharyngeal cancer (IARC 1997). In addition, various environmental factors have also been found to play a role. The most important are dietary, and in particular the consumption of certain salted fish, other salt-preserved foods and fermented dietary items (Armstrong 1998; Gallicchio 2006; Yuan 2000).

The prognosis for advanced nasopharyngeal cancer is poor because more than 80% of cases are diagnosed late due to the deep location of the suspected tumour and the non-specificity of the initial symptoms. The late diagnosis leads to decreased survival (Sham 1990). For patients with UICC-AJC stage III or IV nasopharyngeal cancer, the two-year survival rate is only 20% to 30% despite aggressive concurrent chemoradiation therapy (Cheng 1997; Cheng 2000), and the lesions often develop distant metastases despite local control. However, early-stage

nasopharyngeal cancer is basically curable; in patients with UICC-AJCC Stage I or II disease the 10-year survival rate could reach 90% or even higher (Chua 2003). Unfortunately, most diagnosed nasopharyngeal cancer patients have stage III or IV disease. Screening strategies for early-stage nasopharyngeal cancer diagnosis and administration of treatment are therefore needed to reduce disease-specific morbidity and mortality.

Description of the intervention

There are a number of diagnosis methods for nasopharyngeal cancer, but EBV serology and nasopharyngoscopy are the most commonly used for screening.

The commonly used EBV serology examinations test IgA antibodies against viral capsid antigen (VCA), early antigen (EA) and nuclear antigen (EBNA-1), DNase and IgG antibodies against EBV transactivator protein (ZEBRA), detected by immunofluorescence test or enzyme-linked immunosorbent assay (ELISA). In IgA anti-VCA, the IgA level rises as the stage of nasopharyngeal cancer increases, as demonstrated by seroepidemiological studies (Henle 1976). It presents long before the occurrence of nasopharyngeal cancer and is often used for early detection in mainland China and Taiwan (Chien 2001; Zeng 1982; Zeng 1983). IgA anti-EA was first demonstrated by Henle (Henle 1976). This antibody increases with stage of disease and tumour burden at presentation, decreases with successful therapy and reappears or increases with tumour relapse or development of distant metastasis (de-Vathaire 1988; Henle 1977; Naegel 1982). EBNA-1 is the only viral protein required for the replication of EBV in latently infected cells and is found in all EBV-associated nasopharyngeal cancer tissues. It is regarded as critical for initiating and developing tumours (Leight 2000), and is widely used for nasopharyngeal cancer diagnosis and prognosis (de The 2005). In DNase assay, the level of antibody-neutralising EBV DNase activity is found to increase in the sera of nasopharyngeal cancer patients (Cheng 1980). The presence of this antibody is demonstrated in nasopharyngeal cancer patients before the appearance of clinical symptoms (Chen 1987; Chen 1989; Chien 2001). ZEBRA switches EBV from a latent to a productive cycle, and IgG anti-ZEBRA presents higher titers in young nasopharyngeal cancer patients compared with VCA and EA markers (Dardari 2000). A large-scale screening in China showed that IgG anti-ZEBRA had high sensitivity in detecting early nasopharyngeal cancer (Zhang 2006).

Nasopharyngoscopy is also a useful tool for examining the nasopharyngeal space and is a convenient, cheap and simple operation (Burkey 1994), but the sensitivity is low. The reason for this might be that the macroscopic appearance of the mucosa does not necessarily associate well with the occurrence of early nasopharyngeal cancer (Wei 1991).

Other diagnostic methods for nasopharyngeal cancer include physical examination, EBV DNA or RNA by quantitative polymerase chain reaction (PCR) detection, liquid-based cytology, radiology, computed tomography (CT), magnetic resonance imaging (MRI) and evaluation of cranial nerve function and hearing. However, these methods are either too expensive or inconvenient to be used as screening tests, or have poor sensitivity or specificity for detecting precursor lesions and early nasopharyngeal cancer. Moreover, physical examination may only be reliable when the cancer is relatively advanced. We did not, therefore, include these diagnostic methods in the review.

A successful screening test should be simple, quick and accurate, with an effective second follow-up test and treatment. For nasopharyngeal cancer, the confirmation diagnosis among patients in whom nasopharyngeal cancer is suspected is made by biopsy. Treatment for early-stage disease, including radiotherapy and chemotherapy, is effective. Radiotherapy is the standard treatment; chemotherapy acts as a radiosensitiser for radiotherapy and helps decrease the rate of distant metastasis. Concomitant chemoradiotherapy is the standard treatment for locally advanced and/or node-positive patients (Guigay 2006).

How the intervention might work

Several large mass serological screenings have demonstrated that nasopharyngeal cancer patients have elevated levels of antibodies to EBV antigens and that EBV-related antigens have a high detection rate in predicting the early occurrence of this tumour and thus are valuable detection markers. These have included studies involving 32,465 persons in Taiwan and 7000 to 338,868 persons in mainland China (Chen 1989; Deng 1995; Ji 2007; Zeng 1982; Zeng 1983; Zhang 2006). A mass screening study of 9699 Taiwanese people, with 16 years of follow-up, revealed that seropositivity for IgA anti-VCA and antibodies against EBV DNase in patients led to a higher cumulative incidence of nasopharyngeal cancer than in the seronegative patients (Chien 2001). Another screening study involving 1199 asymptomatic people demonstrated that EBV serological screening could achieve a higher overall five-year survival rate than general nasopharyngeal cancer patients (Ng 2010). Moreover, a cluster-randomised controlled trial (RCT) of IgA anti-VCA and EBNA-1 screening tests versus no screening is being conducted in Zhongshan, China (NCT00941538).

A mass screening study of nasopharyngoscopy in southern China, with 13 years follow-up, showed a combination of nasopharyngoscopy and EBV-related antigens to be helpful in detecting early-stage asymptomatic patients and significantly increased the five-year survival rate to 87.18% (Ji 2003).

Why it is important to do this review

Extensive research has been conducted into EBV serology examination for nasopharyngeal cancer screening in high-risk areas, but there are many inconsistent, sometimes even contrary reports of the same serological marker in terms of sensitivity and specificity (Dardari 2000; Lin 2001; Sheen 1998; Sigel 1994), and there is no consensus on which is a better detection test for the early diagnosis of nasopharyngeal cancer. Reasons may include the different sources of EBV antigens, different antibody assays and the selection of cases from different geographic origins. Moreover, although previous studies on early screening strategies and treatment have shown a high survival rate, this has been demonstrated to be inadequate to assess the effectiveness of screening or treatment due to lead-time and length-time biases (Welch 2000). These inconsistencies therefore need to be clarified and the true effectiveness of these screening tests evaluated through systematic review.

Furthermore, other problems related to screening tests need to be systematically assessed, such as bleeding as a result of nasopharyngoscopy examination, potential false negatives, false positives contributing to psychological trauma and other complications. Equally, the cost-effectiveness of screening, potential follow-up tests and treatment needs to be assessed.

In this review we therefore aimed to assess the evidence regarding the impact of these screening methods on mortality, their ability to detect nasopharyngeal cancer, the possible harms associated, quality of life and cost-effectiveness.

OBJECTIVES

Primary objective

To determine the effectiveness of screening of asymptomatic individuals by EBV serology and/or nasopharyngoscopy in reducing the mortality of nasopharyngeal cancer compared to no screening.

Secondary objectives

To assess the impact of screening for nasopharyngeal cancer on incidence, survival, adverse effects, cost-effectiveness and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) and controlled clinical trials (CCTs). Randomisation by clusters or individuals was acceptable.

Types of participants

All participants enrolled in studies evaluating screening for nasopharyngeal cancer were eligible for this review, with no restriction on ethnicity or age. Participants from both high-risk and general areas were eligible for inclusion (high-risk areas are defined as areas where the age-standardised incidence rate is higher than 1 per 100,000).

Types of interventions

All types of nasopharyngeal cancer screening, including mass screening, targeted screening and opportunistic screening using EBV serology (including IgA anti-VCA, EA and EBNA-1, DNase assay and IgG anti-ZEBRA) and nasopharyngoscopy as screening tests, individually or in combination, were eligible for the review. The comparison between groups we sought was screening versus no screening.

Types of outcome measures

We planned to analyse these outcomes in the review, but they were not to be used as a basis for including or excluding studies.

Primary outcomes

- Nasopharyngeal cancer-specific mortality

Secondary outcomes

- Incidence of nasopharyngeal cancer by stage and histopathological classification at diagnosis
- Survival (two-year, three-year, five-year and 10-year)
- Harms of screening (physical and psychosocial)
- Quality of life (via validated tools such as the SF-36 and patient satisfaction)
- Cost-effectiveness
- All-cause mortality

Search methods for identification of studies

The Cochrane Ear, Nose and Throat Disorders Group (CENTDG) Trials Search Co-ordinator (TSC) conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 6 July 2015.

We contacted original authors for clarification and further data if trial reports were unclear and we arranged translations of papers where necessary.

Electronic searches

The TSC searched:

- the CENTDG Trials Register (searched 6 July 2015);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 6);
- PubMed (1946 to 6 July 2015);
- Ovid EMBASE (1974 to 2015 week 26);
- EBSCO CINAHL (1982 to 6 July 2015);
- Ovid CAB Abstracts (1910 to 2015 week 26);
- LILACS, lilacs.bvsalud.org (searched 6 July 2015);
- KoreaMed, <http://www.koreamed.org> (searched 6 July 2015);
- IndMed, www.indmed.nic.in (searched 6 July 2015);
- PakMediNet, www.pakmedinet.com (searched 6 July 2015);
- Web of Knowledge, Web of Science (1945 to 6 July 2015);
- CNKI, www.cnki.com.cn (searched via Google Scholar 6 July 2015);
- ClinicalTrials.gov (searched via the Cochrane Register of Studies 6 July 2015);
- ICTRP, www.who.int/ictip (searched 6 July 2015);
- ISRCTN www.isrctn.com (searched 6 July 2015);
- Google Scholar, scholar.google.co.uk (searched 6 July 2015);
- Google, www.google.com (searched 6 July 2015)

In searches prior to November 2013, we also searched BIOSIS Previews 1926 to 2012.

The TSC modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))). Search strategies for major databases including CENTRAL are provided in [Appendix 1](#).

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the TSC searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two independent authors (Wen YY and Zhao YQ) reviewed the titles, abstracts and keywords of all records retrieved to determine whether the studies were relevant to this review. Where the title and abstract did not provide adequate information, we assessed the full study and contacted the authors of the study if additional information was required for further clarification. We resolved disagreement by discussion.

Data extraction and management

Two authors (Yang SJ and Zhang YY) independently extracted the data using a piloted data extraction form. Data collected included the following.

1. General information: published/unpublished, language, authors, article title, journal title and year, issue, page and funding source.
2. Design of the trial: sample size, type of control, randomisation, allocation concealment, blinding and statistical methods.
3. Participants: total number and numbers in comparison groups, baseline characteristics, age, gender, inclusion criteria, exclusion criteria and study setting.
4. Intervention: type of screening test, screening frequency, controls, withdrawals, drop-outs and loss to follow-up.
5. Outcomes: primary and secondary outcomes, and the number and type of adverse events.

We planned to use the Review Manager software (RevMan 5.3) to double-enter all the data ([RevMan 2014](#)). When information regarding any of the above was unclear, we attempted to contact the authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two independent authors (Yang SJ and Chen XY) were to grade the risk of bias of the included studies independently. Any disagreement would be resolved by discussion between the review authors. We were to contact authors of the original reports, if necessary, for clarification.

We planned to assess the risk of bias for RCTs based on the following two criteria outlined in the *Cochrane Handbook of Systematic Reviews of Interventions* version 5.1.0 ([Handbook 2011](#)).

1. Adequate sequence generation: Yes (computer-generated random numbers, table of random numbers, coin tossing or similar); Unclear (the trial was described as randomised, but the generation of the allocation sequence was not described); No (other methods).
2. Allocation concealment: Yes (central randomisation, sealed envelopes or similar); Unclear (the allocation concealment was not described); No (open table of random numbers or similar).

All RCTs and CCTs were to be assessed on the following three criteria:

1. Incomplete outcome data addressed: Yes (no missing outcome data; number and reasons for missing outcome data are unlikely to be related to true outcome; numbers or reasons for

missing outcome data are balanced in numbers across groups; missing data have been imputed with appropriate methods); Unclear (numbers or reasons for missing outcome data were not described); No (reasons for missing outcome data are likely to be related to true outcome; numbers or reasons for missing outcome data did not balance across groups; potentially inappropriate use of simple imputation for missing outcome data).

2. Free of selective outcome reporting: Yes (the study protocol is available; all the pre-specified outcomes of the study have been reported; study protocol not available, but the expected outcomes including pre-specified outcomes are clear in the published reports); Unclear (the protocol and pre-specified outcomes were not described); No (not all the pre-specified primary outcomes have been reported; one or more primary outcomes comprises measurements, analysis methods or subsets of the data that were not pre-specified; one or more outcomes of interest in the review are reported incompletely).
3. Free of other bias: Yes (study is free of other sources of bias); Unclear (no other risk of bias was described); No (study had a potential source of bias related to the specific study design used, stopped early due to some data-dependent process, had extreme baseline imbalance, or had been claimed to have been fraudulent).

Based on these criteria, each study would be grouped into the following three categories:

1. low risk of bias for all key quality criteria: low risk of bias;
2. unclear risk of bias for one or more key quality criteria: unclear risk of bias;
3. high risk of bias for one or more key quality criteria: high risk of bias.

Measures of treatment effect

For dichotomous outcomes, we planned to express the measure of effect as an odds ratio (OR) or risk ratio (RR), with 95% confidence intervals (CI). We planned to analyse pooled results using either a fixed-effect or random-effects model, depending on the level of heterogeneity.

We planned to express measures of effect for continuous outcome scores as mean differences (MD) with 95% CI. For continuous outcomes, if studies reported the outcome using the same scale, we intended to analyse measures using mean difference (MD) and the 95% CI in the analysis. If the studies used different scales to measure outcome, we were to present the standardised mean difference (SMD) with 95% CI. The use of either a fixed-effect or random-effects model depended on the level of heterogeneity. We planned to pool homogenous data using a fixed-effect model. If unexplained heterogeneity was demonstrated, we would have analysed data using a random-effects model. If there was substantial clinical or statistical heterogeneity, we would combine study results in meta-analysis.

We planned to use the method of survival analysis to summarise time-to-event data and express the intervention effect as a hazard ratio (HR) for each study when possible, and combine into an overall summary estimate using the methods of Whitehead et al (Whitehead 1991).

Unit of analysis issues

Studies may employ 'cluster-randomisation' (such as randomisation by clinician or practice) where analysis and pooling of clustered data would lead to a 'unit of analysis' error (whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated). We planned to combine data from cluster-randomised trials using the generic inverse variance method. If the study had been analysed as if the randomisation was based on individuals rather than on the clusters, we would correct the analyses by extracting the number of clusters or the average size of each cluster, the outcome data ignoring the clustering design for the total number of individuals and an estimate of the intra-cluster correlation coefficient (ICC). We would reduce the size of each trial to its 'effective sample size' (Rao 1992). The effective sample size of a single intervention group in a cluster-randomised trial is its original sample size divided by a quantity called the 'design effect'. The design effect is $1 + (M-1) ICC$ (Donner 2002), where M is the average cluster size and ICC is the intra-cluster correlation coefficient. If the ICC was not reported we would assume it to be 0.1 (Unnebrink 2001).

Dealing with missing data

We planned to acquire any missing or unpublished data by contacting the authors of identified studies by email. When the data were not missing at random, we would have used the principles cited in the *Cochrane Handbook for Systematic Reviews of Interventions* for dealing with missing data (Handbook 2011), performing intention-to-treat (ITT) analysis, or imputing the missing data using the last reported observation carried forward (LOCF). This means that the most recently observed outcome measure is assumed to hold for all subsequent outcome assessment times (Lachin 2000; Unnebrink 2001). We would also have contacted the original investigators to request missing data. If the data could not be accessed or were missing at random, we would analyse only the available data and address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We planned to identify heterogeneity by graphical interpretation and the results of the I^2 statistic and χ^2 test. Heterogeneity is judged substantial if the I^2 is $> 50\%$ (Higgins 2003) and the P value of the χ^2 test is < 0.1 . This could be interpreted as the percentage of variation observed between the studies that is attributable to between-study differences rather than sampling error (chance).

Assessment of reporting biases

We planned to use funnel plots to examine the possibility of reporting biases if sufficient studies (15) were found.

Data synthesis

We intended to summarise data statistically using RevMan 5.3 (RevMan 2014), if they were available, sufficiently similar and of sufficient quality. We planned to perform statistical analysis according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Handbook 2011).

Subgroup analysis and investigation of heterogeneity

As it was impossible to combine different screening interventions as a group for meta-analysis, we planned to conduct subgroup analysis for different screening interventions. We would then have performed the following subgroup analyses if sufficient data were available:

1. Different stage and histopathological classification of nasopharyngeal cancer (UICC-AJCC Stage and WHO classification).
2. Sex, age and ethnicity.
3. Frequency of screening.
4. Different treatment for nasopharyngeal cancer patients after screening (radiotherapy alone and neoadjuvant chemotherapy, concurrent chemoradiotherapy and adjuvant chemotherapy).
5. Duration of follow-up after screening.
6. Family history (whether the participants have first-degree relatives with nasopharyngeal cancer or not).

Sensitivity analysis

We would have performed sensitivity analysis to examine the effects of the following:

1. Repeating the analysis excluding unpublished studies (if there are any).
2. Repeating the analysis taking account study risk of bias, as specified above;
3. Repeating the analysis excluding studies using the following filters: language of publication, industry funded and country.

RESULTS

Description of studies

Results of the search

The searches in July 2015 retrieved 5358 results ([Figure 1](#)). After an initial sift for duplicates and obviously irrelevant studies we were left with 910 references. Two authors independently reviewed the references and finally retrieved 31 studies (full-text) from the search for further investigation. However, none met the eligibility criteria for a RCT or CCT investigation on the efficacy of screening for nasopharyngeal cancer. Therefore, it was not possible to include any data for further analysis.

Figure 1. Process for sifting search results and selecting studies for inclusion

Included studies

No studies met the inclusion criteria for the review.

Excluded studies

See [Characteristics of excluded studies](#).

Among the 31 excluded studies, 10 case-control diagnostic studies described the sensitivity, specificity and other diagnostic values of screening methods for nasopharyngeal cancer ([Abdulmir 2010](#); [Breda 2010](#); [Cai 1983](#); [Chen 2001](#); [Cheng 2002](#); [Jan 2009](#); [Leung 2004](#); [O 2007](#); [Ren 2006](#); [Zhang 2006](#)).

Twelve case-control diagnostic studies described the positive rate of EBV antibody titers, VCA-IgA, VCA-IgG, EA-IgA and EA-IgG in nasopharyngeal cancer cases and controls ([Breda 2010](#); [Gurtsevitch 1986](#); [Jen 1987](#); [Kantakamalakul 2000](#); [Karray 2005](#); [Li 2000](#); [Low 2000](#); [Ng 2014](#); [Pickard 2004](#); [Shao 2004](#); [Shimakage 2000](#); [Zeng 1983](#)).

One hospital-based cohort study evaluated four screening tests including EBV antibody titers, VCA-IgA, VCA-IgG, EA-IgA and EA-IgG, and described the sensitivity, specificity and other diagnostic values for nasopharyngeal cancer ([Chang 2008](#)).

One uncontrolled mass screening study and one uncontrolled screening study described the incidence of nasopharyngeal cancer after screening ([Chien 2001](#); [Deng 1995](#)).

An uncontrolled screening study described the diagnostic values of a liquid-based cytology test for nasopharyngeal cancer and survival rate of nasopharyngeal cancer patients ([Ng 2010](#)).

Three mass screening studies using cancer registration data or general patients as the control group and reported the incidence of nasopharyngeal cancer ([Huang 1993](#); [Zeng 1982](#); [Zeng 1985](#)).

One study reported the incidence of nasopharyngeal cancer in two incomparable groups by using the EBV DNase screening test ([Chen 1989](#)).

One cohort study using VCA-IgA testing for a large sample size group of participants, and divided participation into two groups according to positive and negative VCA-IgA levels. This study reported a higher incidence of nasopharyngeal cancer in the positive VCA-IgA level group when compared with the negative group ([Chen 2012](#)).

Finally, one RCT conducted screening testing of 29,129 participants and gave no intervention to 146,000 controls. However, in this study the authors only reported the overall nasopharyngeal cancer detection rate and the early diagnosis rate in the screening group, but did not report the morbidity and incidence of nasopharyngeal cancer in the control group. We therefore could not extract data for a comparison between the screening and no screening groups ([Liu 2013](#)).

Risk of bias in included studies

There were no included studies, so risk of bias could not be evaluated.

Effects of interventions

There were no included studies, so effects of interventions could not be evaluated.

DISCUSSION

Summary of main results

We expected to find evidence to allow us to explore the efficacy of screening for nasopharyngeal cancer. In this review we found only one randomised controlled trial (RCT) examining the efficacy of screening by Epstein-Barr virus (EBV) serology and nasopharyngoscopy, however because there was no comparison between the screening and no screening group we could not extract any data ([Liu 2013](#)). We can therefore make no judgement as to effectiveness of screening in reducing the mortality of nasopharyngeal cancer due to the lack of methodological rigour in the available studies. Further research on this question would be worthwhile.

Do screening tests improve the outcomes of nasopharyngeal cancer?

A successful screening programme should be based on knowledge of whether the screening test improves outcomes (most importantly mortality), however we could not include any randomised controlled trials or controlled clinical trials (CCTs) in order to answer this question definitively. Three mass screening studies ([Liu 2013](#); [Ng 2010](#); [Zeng 1982](#); [Zeng 1985](#)) and one uncontrolled screening study ([Huang 1993](#)) have described the incidence of nasopharyngeal cancer. They reported the cancer incidence in the EDAb, VCA/IgA and EA/IgA positive group to be 8.3-fold and more than 30 times as high as that in the EDAb negative or same age group from cancer registration, respectively. We can conclude from these studies that the incidence of nasopharyngeal cancer is high in EBV serology-positive cases, but we cannot conclude that the EBV serology screening method is effective. Firstly, the high incidence may be induced by selection bias due to the lack of a comparable control. Secondly, whether the screening test could lead to a better prognosis (mortality) than in the normal control group is unclear. One hospital-based cohort study reported that complementary EBV IgA to early antigen and nuclear antigen-1 (EA + EBNA-1) had a very high sensitivity, specificity and area under the curve ([Chang 2008](#)). Eight case-control diagnostic studies reported that the EBV serology test had high sensitivity and specificity in detecting nasopharyngeal cancer ([Abdulmir 2010](#); [Cai 1983](#); [Chen 2001](#); [Cheng 2002](#); [Jan 2009](#); [Leung 2004](#); [O 2007](#); [Ren 2006](#); [Zhang 2006](#)). Twelve case-control diagnostic studies reported that the EBV serology test showed a high positive detection rate for nasopharyngeal cancer ([Breda 2010](#); [Deng 1995](#); [Gurtsevitch 1986](#); [Jen 1987](#); [Kantakamalakul 2000](#); [Karray 2005](#); [Li 2000](#); [Low 2000](#); [Ng 2014](#); [Pickard 2004](#); [Shao 2004](#); [Shimakage 2000](#); [Zeng 1983](#)). However, the high sensitivity, specificity and positive detection rate only demonstrate that the screening test can detect more nasopharyngeal cancer patients. It can therefore only show high incidence; the real effect of screening is unknown.

The [Hong Kong Anti-Cancer Society 2008](#) and [Ng 2010](#) reported that the regular EBV serology test and nasopharyngoscopy could detect more than 40% of cases presenting with stage I disease. The five-year survival rate was also much higher, exceeding 90% for those cancers detected in the screening programme. If the survival data are not derived from RCTs, this could be induced by lead-time bias (increasing the proportion of life with knowledge of cancer, without actually extending the duration of life) and it could also be induced by length-time bias (screening is more likely to detect slow-growing disease, rather than altering the duration of life).

A Markov chain model study evaluated IgA/VCA screening for nasopharyngeal cancer and estimated a 33% reduction in mortality from nasopharyngeal cancer, attributed to intensive indirect mirror examination of annual screening versus no screening (Chen 1999). Another recent study using a Markov model evaluated four screening strategies over a period of 12 years; it indicated that triennial screening for participants tested EBV-negative and annual screening once could increase the five-year overall survival rate by 10% to 12% over a no screening strategy (Choi 2011). However, this model is easily affected by baseline assumptions; that is, the result is sensitive to the prevalence of nasopharyngeal cancer and changes in the diagnostic accuracy of the screening strategy, thus the result is easily changed from an effective strategy to an ineffective one.

Methodological bias in the available studies meant that we were unable to judge the effectiveness of the EBV serology test and nasopharyngoscopy. Further RCTs are needed to evaluate the effect of screening on mortality.

Are screening tests cost-effective?

This issue is both practical and important for a screening programme. Whether screening is cost-effective could guide public health policy, but we found no RCTs or CCTs to answer this question and no studies have evaluated the cost-effectiveness and cost-benefit of screening strategies. RCTs are needed to determine this.

Are screening tests acceptable?

We found no RCTs on this question. Patients undergoing nasopharyngoscopy may have a potential risk of bleeding, but one study has reported that nasopharyngoscopy had no adverse influence on the local tumour (Teo 1991). For the EBV serology test, no adverse effects, such as psychological trauma, over-diagnosis and over-treatment because of false positive results, were found. The impact of adverse effects on the outcome and cost-effectiveness of screening tests needs to be determined by further research.

We do not plan to update this review until new trials are published.

AUTHORS' CONCLUSIONS

Implications for practice

The effectiveness of screening for reducing the mortality of nasopharyngeal cancer cannot currently be determined. Only one randomised controlled trial (RCT) was found by this systematic review, but could not be included because no data could be extracted for a comparison between the screening and no screening groups. Mass screening studies have shown that the incidence of nasopharyngeal cancer is high in Epstein-Barr virus (EBV) serology-positive cases, but we cannot conclude that the EBV serology screening method is effective.

Implications for research

No data from RCTs or controlled clinical trials (CCTs) are available to allow us to determine the efficacy of screening for nasopharyngeal cancer, or the cost-effectiveness and cost-benefit of a screening strategy. High-quality studies with long-term follow-up of mortality and cost-effectiveness are therefore needed.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdulmir 2010	ALLOCATION:

Screening for nasopharyngeal cancer (Review)

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Study	Reason for exclusion
	<p>Case-control diagnostic study The results concern sensitivity and specificity</p> <p><i>Characteristics:</i></p> <p>Participants: 122 HNCA patients; 3 groups of 100 control participants</p> <p>Intervention: EBV IgG antibody</p> <p>Results: sensitivity, specificity and cut-off threshold of this diagnostic method</p>
Breda 2010	<p>ALLOCATION: Hospital-based cohort study, not a RCT</p> <p><i>Characteristics:</i></p> <p>Participants: 49 nasopharyngeal cancer patients, 45 hospital controls</p> <p>Results: positive EBV detection rate</p>
Cai 1983	<p>ALLOCATION: Case-control diagnostic study, not an intervention study The results concern diagnostic values including sensitivity and specificity</p> <p><i>Characteristics:</i></p> <p>Participants: 4 groups of participants, each consisting of 50 persons: 200 participants selected</p> <p>Intervention: 4 EBV antibody titers, VCA-IgA, VCA-IgG, EA-IgA and EA-IgG</p> <p>Results: sensitivity, specificity and other diagnostic values for detecting nasopharyngeal cancer</p>
Chang 2008	<p>ALLOCATION: Hospital-based cohort study, not a RCT or CCT</p> <p><i>Characteristics:</i></p> <p>Participants: 4 groups of participants, each consisting of 50 persons: 200 participants selected</p> <p>Intervention: 4 EBV antibody titers, VCA-IgA, VCA-IgG, EA-IgA and EA-IgG</p> <p>Results: sensitivity, specificity and other diagnostic values for detecting nasopharyngeal cancer</p>
Chen 1989	<p>ALLOCATION: Case-control diagnostic study Same intervention used for 2 groups and the 2 groups are incomparable</p> <p><i>Characteristics:</i></p> <p>Participants: 2 groups of people respectively from routine health examination and individuals residing in nasopharyngeal cancer high-risk areas</p> <p>Intervention: EBV DNase</p> <p>Results: incidence of nasopharyngeal cancer</p>
Chen 2001	<p>ALLOCATION: Case-control diagnostic study The results concern diagnostic values</p> <p><i>Characteristics:</i></p>

Study	Reason for exclusion
	<p>Participants: 314 nasopharyngeal cancer patients, 244 hospital controls and 263 in community control group</p> <p>Intervention: IgA anti-VCA and DNase-neutralisation test</p> <p>Results: sensitivity and specificity for detecting nasopharyngeal cancer</p>
Chen 2012	<p>ALLOCATION: Cohort study, not a RCT The results concern incidence, onset time and clinical characteristics of nasopharyngeal cancer</p> <p><i>Characteristics:</i></p> <p>Participants: 586 participants with stable, fluctuating or ascending VCA-IgA level and 9889 control participants who were negative in the first test of VCA-IgA</p> <p>Intervention: VCA/IgA tests</p> <p>Results: hazard ratio (HR) for the incidence of nasopharyngeal cancer</p>
Cheng 2002	<p>ALLOCATION: Case-control diagnostic study The results concern diagnostic values</p> <p><i>Characteristics:</i></p> <p>Participants: 121 nasopharyngeal cancer patients and 332 healthy participants</p> <p>Intervention: EBNA 1/IgA, EBNA 1/IgG and zta/IgG by ELISA and VCA/IgA tests</p> <p>Results: sensitivity and specificity for detecting nasopharyngeal cancer</p>
Chien 2001	<p>ALLOCATION: No control, mass screening study</p> <p><i>Characteristics:</i></p> <p>Participants: 9699 men were enrolled between 1984 and 1986</p> <p>Intervention: IgA antibodies against EBV capsid antigen and neutralising antibodies against EBV-specific DNase</p> <p>Duration: 131,981 person-years of follow-up</p> <p>Results: cumulative incidence</p>
Deng 1995	<p>ALLOCATION: No control, mass screening study</p> <p><i>Characteristics:</i></p> <p>Participants: 338,868 persons were enrolled between 1991 and 1993</p> <p>Intervention: IgA antibodies against EBV capsid antigen</p> <p>Results: positive rate of diagnostic methods and incidence of nasopharyngeal cancer among the positive rate cases</p>
Gurtsevitch 1986	<p>ALLOCATION: Case-control diagnostic study The results concern the positive rate of diagnostic methods</p> <p><i>Characteristics:</i></p>

Study	Reason for exclusion
	<p>Participants: 132 nasopharyngeal cancer patients and 227 controls with other tumours except for nasopharyngeal cancer</p> <p>Intervention: VCA/IgA and IgG, EA and EBNA tests</p> <p>Results: positive rate of diagnostic methods</p>
Huang 1993	<p>ALLOCATION: Case-control diagnostic study; no control group The results concern the incidence of nasopharyngeal cancer</p> <p><i>Characteristics:</i></p> <p>Participants: 5030 normal individuals were given DNase screening; 98 normal individuals were given DNase test, and divided into EDAB positive and negative groups</p> <p>Intervention: DNase test</p> <p>Duration: 52 months follow-up and 3 months follow-up</p> <p>Results: incidence of nasopharyngeal cancer</p>
Jan 2009	<p>ALLOCATION: Cohort study; no control group The results concern diagnostic values</p> <p><i>Characteristics:</i></p> <p>Participants: 84 consecutive patients were enrolled in the study</p> <p>Intervention: liquid-based cytology test</p> <p>Results: sensitivity, specificity and other diagnostic values for detecting nasopharyngeal cancer</p>
Jen 1987	<p>ALLOCATION: Case-control diagnostic study; the results concern diagnostic positive rate</p> <p><i>Characteristics:</i></p> <p>Participants: 154 patients with nasopharyngeal cancer (nasopharyngeal cancer), 374 with other cancers, 1000 normal controls from Government Employees' Clinic Center (GECC) and 3642 individuals of various ethnic-dialect groups living in high-risk areas for nasopharyngeal cancer</p> <p>Intervention: EBV-specific DNase test</p> <p>Results: positive rate of EBV-specific DNase test for different groups</p>
Kantakamalakul 2000	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 58 nasopharyngeal cancer patients and 24 non-nasopharyngeal cancer patients</p> <p>Intervention: EBV DNA and serum-specific VCA antibodies tests</p> <p>Results: positive rates of the 2 detection tests</p>
Karray 2005	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p>

Study	Reason for exclusion
	<p>Participants: 117 primary diagnosis nasopharyngeal cancer patients and 21 post-treatment monitoring nasopharyngeal cancer patients</p> <p>Intervention: EBNA1, EA and VCA antigens</p> <p>Results: positive rates and agreement of the 3 diagnostic tests</p>
Leung 2004	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 139 new cases of nasopharyngeal cancer and 178 healthy individuals</p> <p>Intervention: EBV DNA and IgA-VCA</p> <p>Results: sensitivity, specificity and other diagnostic values for detecting nasopharyngeal cancer</p>
Li 2000	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 76 nasopharyngeal cancer participants and 70 non-nasopharyngeal cancer participants as controls</p> <p>Intervention: EBV-DNA (PCR), EBV-VCA-IgA and EBV-EA-IgA</p> <p>Results: positive rates of the 3 tests</p>
Liu 2013	<p>ALLOCATION: Randomised controlled trial</p> <p>PARTICIPANTS: 29,129 participants received screening test and about 146,000 participants acted as controls without any intervention</p> <p>INTERVENTION: Anti-EBV antibody testing and nasopharynx and/or lymphatic palpation</p> <p>OUTCOMES: The authors only reported the overall nasopharyngeal cancer detection rate and an early diagnosis rate in the screening group, but did not report the morbidity and incidence of nasopharyngeal cancer in the controls. Therefore, we could not extract data regarding the comparison between the screening group and no screening group</p>
Low 2000	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 111 consecutive patients with nasopharyngeal cancer and an equal number of control participants</p> <p>Intervention: EA and VCA</p> <p>Results: positive rates of the 2 tests</p>
Ng 2010	<p>ALLOCATION: Mass screening study; control was general nasopharyngeal cancer patients - incomparable controls</p>

Study	Reason for exclusion
	<p><i>Characteristics:</i></p> <p>Participants: 1199 asymptomatic family members of nasopharyngeal cancer patients</p> <p>Intervention: EBV serology and nasopharyngoscopy</p> <p>Duration: 1994 to 2005</p> <p>Results: sensitivity and specificity of screening test, and incidence of nasopharyngeal cancer as well as 5-year survival rate</p>
Ng 2014	<p>ALLOCATION: Diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 600 nasopharyngeal cancer patients</p> <p>Intervention: EBV DNA detection and pathologic diagnosis</p> <p>Results: specificity and sensitivity of the EBV DNA detection</p>
O 2007	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 155 new nasopharyngeal cancer patients and 155 controls</p> <p>Intervention: an otolaryngologic examination and serial blood testing for serologic markers</p> <p>Results: sensitivity, specificity and other diagnostic values for detecting nasopharyngeal cancer</p>
Pickard 2004	<p>ALLOCATION: Case-control diagnostic study The results concern diagnostic positive rate</p> <p><i>Characteristics:</i></p> <p>Participants: 1229 healthy members of families in which 2 or more individuals were affected with nasopharyngeal cancer and 320 controls from the community at large</p> <p>Intervention: EBV VCA, EBNA-1 and EBV DNase</p> <p>Results: positive rates of the 3 tests</p>
Ren 2006	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 59 patients with nasopharyngeal cancer and 59 healthy volunteers</p> <p>Intervention: C-terminal two-thirds of BRLF1</p> <p>Results: sensitivity, specificity and other diagnostic values for detecting nasopharyngeal cancer</p>
Shao 2004	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: primary (n = 120 patients), locally recurrent (n = 8 patients) and distant metastatic nasopharyngeal cancer (n = 21 patients) among 76 patients with nasopharyngeal cancer after the</p>

Study	Reason for exclusion
	<p>completion of radiotherapy, in 60 patients with nasopharyngeal cancer in clinical remission, in 38 patients with non-nasopharyngeal tumours and in 47 control individuals</p> <p>Intervention: EBV DNA and VCA/IgA</p> <p>Results: positive rate of the detection tests</p>
Shimakage 2000	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 16 cases of nasopharyngeal cancer and 12 normal controls</p> <p>Intervention: IgA/VCA and EBNA2</p> <p>Results: positive rate of the detection test</p>
Zeng 1982	<p>ALLOCATION: Mass screening study; the control is the retrospective data from cancer registration in the same city and the control group also include the intervention group - incomparable control</p> <p><i>Characteristics:</i></p> <p>Participants: 12,932 persons between the ages of 40 and 59</p> <p>Intervention: VCA/IgA and EA/IgA</p> <p>Results: incidence of nasopharyngeal cancer</p>
Zeng 1983	<p>ALLOCATION: Case-control diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 96 nasopharyngeal cancer patients</p> <p>Intervention: IgA/VCA and IgA/EA</p> <p>Results: positive rate of the detection test</p>
Zeng 1985	<p>ALLOCATION: Case-control diagnostic study; the control is the retrospective data from cancer registration in the same city and the control group also include the intervention group - incomparable control</p> <p><i>Characteristics:</i></p> <p>Participants: 1136 IgA/VCA-positive persons</p> <p>Intervention: VCA/IgA</p> <p>Results: incidence of nasopharyngeal cancer</p>
Zhang 2006	<p>ALLOCATION: Diagnostic study</p> <p><i>Characteristics:</i></p> <p>Participants: 288 nasopharyngeal cancer patients</p> <p>Intervention: IgA/VCA, IgA/EA and IgG/EA</p> <p>Results: specificity and sensitivity of the 3 methods</p>

CCT: controlled clinical trial
EA: early antigen
EBNA: Epstein-Barr nuclear antigen
EBV: Epstein-Barr virus
HNCA: head and neck cancer
IgA/IgG: immunoglobulin A/G
PCR: polymerase chain reaction
RCT: randomised controlled trial
VCA: viral capsid antigen

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
#1 MeSH descriptor Nasopharyngeal Neoplasms explode all trees	((("Nasopharyngeal Neoplasms"[Mesh] OR NPC[tw])	1 exp nasopharynx tumor/
#2 NPC	OR ("Nasopharyngeal Diseases"[MeSH] OR "Nasopharynx"[Mesh] OR nasophar*	2 NPC.tw
#3 MeSH descriptor Nasopharyngeal Diseases explode all trees	OR rhinophar*[tw] OR naso-phar*[tw] OR chonae[tw])	3 exp pharynx disease/
#4 MeSH descriptor Nasopharynx explode all trees	AND ("Neoplasms"[Mesh] OR carcinom*[tw] OR cancer*[tw] OR precancer*[tw]	4 exp nasopharynx/
#5 nasophar* OR rhinophar* OR naso-phar* OR chonae	OR pre-cancer*[tw] OR neoplas*[tw] OR tumor*[tw] OR tumour*[tw] OR malignan*[tw] OR premalignan*[tw] OR pre-malignan*[tw])) AND ("Early Diagnosis"[Mesh] OR "Mass Screening"[Mesh] OR "Diagnosis"[Mesh] OR "Serologic Tests"[Mesh] OR "Serology"[Mesh] OR "Virology"[Mesh] OR "Epstein-Barr Virus Infections"[Mesh] OR "Endoscopy"[Mesh] OR screen*[ti] OR detect*[ti] OR diagnos*[ti] OR serolog*[ti] OR virolog*[ti] OR nasopharyngoscop*[ti] OR nps[ti] OR naso-pharyngoscop*[ti] OR endoscop*[ti] OR rhinoscop*[ti] OR test*[ti])) OR ("Nasopharyngeal Neoplasms/diagnosis"[Mesh] OR "Nasopharyngeal Neoplasms/virology"[Mesh])	5 (nasophar* or rhinophar* or naso-phar* or chonae).tw.
#6 (#3 OR #4 OR #5)		6 3 or 4 or 5
#7 MeSH descriptor Neoplasms explode all trees		7 exp neoplasm/
#8 carcinom* OR cancer* OR precancer* OR precancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR premalignan* OR pre-malignan*		8 (carcinom* or cancer* or precancer* or pre-cancer* or neoplas* or tumor* or tumour* or malignan* or premalignan* or pre-malignan*).tw.
#9 (#7 OR #8)		9 7 or 8
#10 (#6 AND #9)		10 6 and 9
#11 (#1 OR #2 OR #10)		11 1 or 2 or 10
#12 MeSH descriptor Early Diagnosis explode all trees		12 exp early diagnosis/
#13 MeSH descriptor Mass Screening explode all trees		13 exp mass screening/
#14 MeSH descriptor Diagnosis explode all trees		14 exp diagnosis/
#15 MeSH descriptor Serologic Tests explode all trees		15 exp serology/
#16 MeSH descriptor Serology explode all trees		16 exp virology/
#17 MeSH descriptor Virology explode all trees		17 exp endoscopy/
#18 MeSH descriptor Epstein-Barr Virus Infections explode all trees		18 (screen* or detect* or diagnos* or serolog* or serodiag* or virolog* or nasopharyngoscop* or nps or naso-pharyngoscop* or endoscop* or rhinoscop* or test*).ti
#19 MeSH descriptor Endoscopy explode all trees		19 12 or 13 or 14 or 15 or 16 or 17 or 18
#20 screen* OR detect*:ti OR diagnos*:ti OR serolog*:ti OR serodiag*:ti OR virolog*:ti OR nasopharyngoscop*:ti OR nps:ti OR naso-pharyngoscop*:ti OR endoscop*:ti OR rhinoscop*:ti OR test*:ti		20 11 and 19
#21 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)		21 exp nasopharynx tumor/di [Diagnosis]
#22 (#11 AND #21)		22 20 or 21
#23 MeSH descriptor Nasopharyngeal Neoplasms explode all trees with qualifiers: DI,VI		
#24 (#22 OR #23)		

(Continued)

CINAHL (EBSCO)	Web of Science (Web of Knowledge)	Trial Registries
S1 (MH "Nasopharyngeal Neoplasms") S2 TX npc S3 (MH "Pharyngeal Diseases+") S4 (MH "Nasopharynx") S5 TX (nasophar* or rhinophar* or naso-phar* or chonae) S6 (MH "Neoplasms+") S7 TI ((carcinom* or cancer* or precancer* or pre-cancer* or neoplas* or tumor* or tumour* or malignan* or premalignan* or pre-malignan*)) or AB ((carcinom* or cancer* or precancer* or pre-cancer* or neoplas* or tumor* or tumour* or malignan* or premalignan* or pre-malignan*)) S8 S3 OR S4 OR S5 S9 S6 OR S7 S10 S8 AND S9 S11 S1 OR S2 OR S10 S12 (MH "Early Diagnosis+") S13 (MH "Cancer Screening") S14 (MH "Diagnosis+") S15 (MH "Serology") S16 (MH "Virology") S17 (MH "Endoscopy+") S18 TI (screen* or detect* or diagnos* or serolog* or serodiag* or virolog* or nasopharyngoscop* or nps or naso-pharyngoscop* or endoscop* or rhinoscop* or test*) S19 S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 S11 AND S19 S21 (MH "Nasopharyngeal Neoplasms/DI") S22 S20 OR S21	# 1 TS=(nasophar* OR rhinophar* OR naso-phar* OR chonae OR NPC) # 2 TS= (carcinom* OR cancer* OR precancer* OR pre-cancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR premalignan* OR pre-malignan*) # 3 TI=(screen* OR detect* OR diagnos* OR serolog* OR serodiag* OR virolog* OR nasopharyngoscop* OR nps OR naso-pharyngoscop* OR endoscop* OR rhinoscop* OR test*) # 4 #3 AND #2 AND #	ICTRP nasophar* AND screen* OR nasophar* AND diagnos* OR nasophar* AND detect* Clinicaltrials.gov (via the Cochrane Register of Studies) NPC OR ((nasopharynx OR nasopharyngeal) AND (cancer OR neoplasm OR carcinoma)) AND (screening OR diagnosis OR detect)

CONTRIBUTIONS OF AUTHORS

This full review was written by Yang SJ and Wen YY. The database searches were mainly done by Gemma Sandberg and Samantha Faulkner. Study selection was done by Yang SJ, Wen YY and Zhao YQ. Assessment of risk of bias was done by Yang SJ and Chen XY. Data extraction was done by Yang SJ, Zhang YY, Zhou J, Wu SY and Wang J.

DECLARATIONS OF INTEREST

Shujuan Yang: declares no conflicts of interest in this review.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Asymptomatic Diseases; Carcinoma; Early Detection of Cancer; Endoscopy [*methods]; Epstein-Barr Virus Infections [*diagnosis]; Herpesvirus 4, Human [*isolation & purification]; Mass Screening; Nasopharyngeal Carcinoma; Nasopharyngeal Neoplasms [*diagnosis] [virology]

MeSH check words

Humans