



PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION



Screening for Neoplastic Diseases



PERIODIC HEALTH EXAMINATION TASK FORCE 2021



DISCLAIMER

This guideline is intended to be used by specialists, general practitioners, allied health professionals who are primary care providers. Although adherence to this guideline is encouraged, it should not restrict the healthcare providers in using their sound clinical judgment in handling individual cases.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but this document should not be the sole basis for evaluating insurance claims. Recommendations from this guideline should not also be treated as strict rules on which to base legal action.

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ABBREVIATIONS AND ACRONYMS

ACTION	ASEAN Costs in Oncology
BIA	budget impact analysis
CBE	clinical breast examination
CIN	cervical intraepithelial neoplasia
COI	conflict of interest
CP	consensus panel
CPG	clinical practice guideline
CRC	colorectal cancer
CUA	cost-utility analysis
CXR	chest X-ray
DALY	disability-adjusted life year
DOH	Department of Health
DRE	digital rectal examination
EBRT	external beam radiation therapy
EBV	Epstein-Barr virus
ENT	ears-nose-throat
ERE	evidence review expert
ERSPC	European Randomized Study of Screening for Prostate Cancer
EtD	Evidence to Decision
FIT	fecal immunochemical test
FOBT	fecal occult blood test
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HADS-P	Hospital Anxiety and Depression Scale-Pilipino Version
HCC	hepatocellular carcinoma
HDS	herbal and dietary supplements
HNC	head and neck cancer
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
ICER	incremental cost effectiveness ratio
IMLP	indirect mirror examination and/or lymph node palpation
LDCT	low-dose CT
LEEP	loop electrosurgical excision procedure
LMIC	low- and middle-income countries
LYG	life-year gained
NCR	National Capital Region
NIH-ICE	National Institutes of Health – Institute of Clinical Epidemiology
NLR	negative likelihood ratio
NNS	number needed to screen
NOS	Newcastle-Ottawa Scale
NPCA	nasopharyngeal cancer
NPV	negative predictive value
NSCLC	non-small cell lung cancer
PCR	polymerase chain reaction
PESO	Philippine Costs in Oncology
PGH	Philippine General Hospital
PhilHealth	Philippine Health Insurance Corporation
PICO	population, intervention, comparator and outcome
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening
PLR	positive likelihood ratio
PSA	prostate-specific antigen
QALY	quality-adjusted life year

RCT	randomized control trial
RRT	red reflex test
SC	steering committee
SCLC	small-cell lung cancer
US	ultrasound
VIA	visual inspection with acetic acid
WHO	World Health Organization
YLD	year lost due to disability
YLL	year of life lost

ACKNOWLEDGMENT

This clinical practice guideline (CPG) on Philippine Periodic Health Examination (PHEX) 2021 was prepared by the National Institutes of Health - Institute of Clinical Epidemiology (NIH-ICE).

This project would not have been possible without the initiative and financial support from the Department of Health (DOH). The DOH neither imposed any condition nor exerted any influence on the operations and the final output formulation.

The NIH-ICE undertook extensive technical work in searching and synthesizing the evidence while ensuring objectivity in each stage of the process, in presenting the evidence in the panel discussion, and in documenting and writing the final report. They were also indispensable in carrying out the legwork, in coordinating among various individuals, groups, and committees, and in facilitating the *en banc* meeting. The CPG Central Steering Committee (SC) and the Task Force SC were responsible for overall organization and management and are accountable for the quality of the CPG.

Lastly, this guideline is invaluable because of the contribution and participation of panelists from different sectors of healthcare who committed their time and effort to share their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences in formulating the recommendations with consideration of patients and the current healthcare system in the country.

The content of this CPG is an intellectual property of the DOH. Kindly provide the proper citations when using any part of this document in lectures, research papers, and any other format presented to the public. The electronic version of this material can be accessed online on the DOH website.

Queries, suggestions, and other concerns regarding this CPG may be directed to the DOH National Practice Guidelines Program office by email (egmd@doh.gov.ph) or to DOH-HPDPB and UP-NIH.

EXECUTIVE SUMMARY

This clinical practice guideline for the Periodic Health Examination (Neoplastic Diseases) is an output from the joint undertaking of the Department of Health and National Institutes of Health - Institute of Clinical Epidemiology.

This clinical practice guideline is a systematic synthesis of evidence to address screening for the following neoplastic diseases: retinoblastoma among children; nasopharyngeal carcinoma among asymptomatic, at-risk adults; liver cancer among asymptomatic, apparently healthy individuals; cervical cancer among asymptomatic, apparently healthy women; oral cancer among asymptomatic apparently healthy adults; colorectal cancer among apparently healthy, average-risk adults; breast cancer among asymptomatic, apparently healthy women; prostate cancer among asymptomatic, 40–80-year old men; lung cancer among asymptomatic, apparently healthy adults; and gastric cancer among asymptomatic apparently healthy adults.

The guideline development process followed the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation or the GRADE approach including GRADE Adolopment¹, a systematic process of adapting evidence summaries and the GRADE Evidence to Decision or EtD² framework. It included 1) identification of critical questions and critical outcomes, 2) retrieval of current evidence, 3) assessment and synthesis of the evidence base for these critical questions, 4) formulation of draft recommendations, 5) convening of a multi-sectoral stakeholder panel to discuss values and preferences and assess the strength of the recommendations, and 6) planning for dissemination, implementation, impact evaluation and updating.

The guideline provides twenty (20) recommendations on prioritized questions in the screening for certain disease conditions. These recommendations are based on the appraisal of the best available evidence on each of the ten (10) identified clinical questions. The guideline is intended to be used by general practitioners and specialists in the primary care setting, policy makers, employers and administrators, allied health practitioners and even patients.

The recommendations in this CPG shall hold and will be updated after 3 years or when new evidence arise.

¹ Schunemann H, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa R, Manja V. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLPMENT. *J Clin Epidemiol*. 2017;81:101-10.

² Schunemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol*. 2016;76:89-98.

SUMMARY OF RECOMMENDATIONS

Recommendation	Certainty of Evidence	Strength of Panel Recommendation
Question 1: Among children, should we do annual ophthalmologic examination compared to no screening?		
1.1. Among all children less than 5 years, we suggest screening for retinoblastoma from the newborn period through serial ophthalmologic examinations using the red reflex test.	Very low	Weak
Question 2: Among asymptomatic populations at risk for nasopharyngeal cancer, should we use EBV blood test and/or nasopharyngoscopy compared with no screening?		
2.1. Among asymptomatic apparently healthy adults, we suggest against screening for nasopharyngeal cancer using an EBV DNA test and/or nasopharyngoscopy.	Low	Weak
2.2. Among asymptomatic apparently healthy adults with a first-degree relative with a known nasopharyngeal cancer, we suggest screening for nasopharyngeal cancer using EBV DNA test and/or nasopharyngoscopy.	Very low	Weak

Question 3: Among otherwise healthy adults, should we do semi-annual or annual performance of the following tests alone or in combination (liver ultrasound and/or AFP)?

- | | | |
|--|----------|--------|
| 3.1. Among asymptomatic, apparently healthy adults, we suggest against the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma. | Low | Weak |
| 3.2. Among patients at risk to develop hepatocellular carcinoma who have or have not progressed to cirrhosis, we recommend the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma. | Moderate | Strong |
-

Question 4: Among women, should we use HPV testing alone, cytology alone, or co-testing (i.e., cytology with HPV testing)?

- | | | |
|---|----------|--------|
| 4.1. Among women aged 21 to 29 years, we recommend against screening for cervical cancer or any alternative screening tests. | Low | Strong |
| 4.2. Among women aged 30 to 65 years, we recommend screening for cervical cancer every 3 years with cervical cytology alone or every 5 years with high-risk HPV testing alone. | Low | Strong |
| 4.3. Among women aged 30 to 65 years, we recommend against screening for cervical cancer every 5 years with high-risk HPV testing in combination with cytology (co-testing). | Very low | Strong |
| 4.4. Among asymptomatic women aged 30 to 65 years old, we recommend screening for cervical cancer every 3 years using visual inspection with acetic acid, as an alternative to Pap smear. | Moderate | Strong |
-

Question 5: Among otherwise healthy adults, should we do annual ENT screening exam and dental check-up compared to no screening?

- | | | | |
|------|--|----------|--------------|
| 5.1. | Among asymptomatic apparently healthy adults aged 35 years and older, we suggest screening for oral cancer once every 3 years by trained health workers. | Low | No consensus |
| 5.2. | Among adults aged 35 years and older who are smokers and/or alcohol drinkers, we recommend screening for oral cancer using visual and tactile inspection once every 3 years by trained health workers. | Moderate | Strong |
-

Question 6: Among otherwise healthy adults, should fecal immunochemical test be used instead of fecal occult blood test or no screening?

Among averaged risk and apparently healthy adults, there is insufficient evidence to suggest screening for colorectal cancer using fecal immunochemical test over fecal occult blood test.

Question 7: Among apparently healthy asymptomatic adults, should we do mammogram, breast ultrasound or clinical breast examination?

- | | | | |
|------|--|----------|--------|
| 7.1. | Among apparently healthy asymptomatic women aged 50 to 69 years, we recommend screening for breast cancer every one to two years using mammography. | Low | Strong |
| 7.2. | Among apparently healthy asymptomatic women aged 50 years and older, we recommend performing biennial clinical breast examination to screen for breast cancer. | Moderate | Strong |
-

Question 8: Among asymptomatic men aged 40 to 80 years old, should we do annual PSA determination with or without digital rectal exam or digital rectal exam alone compared to no screening?

Among asymptomatic males with age from 50 to 64 years old, we suggest shared decision making before biennial screening with PSA and digital rectal exam for prostate cancer.

Low

Weak

Question 9: Among asymptomatic apparently healthy adults, should low-dose CT compared to chest X-ray be used?

- | | | | |
|------|---|----------|------|
| 9.1. | Among asymptomatic apparently healthy adults with low risk for lung cancer, we suggest against annual low-dose CT scan to screen for lung cancer. | Very low | Weak |
| 9.2. | Among asymptomatic apparently healthy adults with high risk for lung cancer, we suggest annual low-dose CT scan to screen for lung cancer. | Very low | Weak |

Question 10: Among asymptomatic populations at risk for gastric cancer, should we do screening (i.e., upper gastrointestinal series, upper endoscopy) compared with no screening?

- | | | |
|--|----------|------|
| 10.1. Among apparently healthy adults aged 40 to 70 years without risk factors, we suggest against routine screening for gastric cancer using either upper endoscopy or upper gastrointestinal series. | Very low | Weak |
| 10.2. Among apparently healthy adults with risk factors, we suggest shared decision making before doing active screening for gastric cancer using upper gastrointestinal series or upper endoscopy. | Very low | Weak |

1. INTRODUCTION

The Philippine Guidelines on Periodic Health Examination (PHEX) was first published in 2004.(1) It was a comprehensive appraisal and synthesis of evidence on screening interventions committed to providing early prevention services among apparently healthy Filipinos. It was a long-awaited publication and the first to offer evidence-based recommendations for screening tests, which were made possible through the concerted effort of various medical and paramedical organizations composed of more than a hundred experts, researchers, and stakeholders.(1) It was inspired by the Canadian and the US Preventive Services Task Forces, but it was tailored to the Philippine setting.

Due to the evolving technology, scientific evidence, and health policies, there is a pressing need to update this guideline. This 2021 Philippine Guidelines will support the objectives stated in the Universal Health Care Act that all Filipinos are given access to quality and affordable medical services, including primary care benefits.(2)

In the guideline development, evidence-based recommendations for the prioritized health screening were formulated using the GRADE Evidence-to-Decision (EtD) framework.(3,4) The EtD framework aims to facilitate the adaptation of recommendations and decisions of experts and stakeholders based on specific contexts, essential health outcomes, benefits, and harms while looking through the equity, applicability, and feasibility lenses.

The evidence collated to answer the research questions on screening tests are used in formulating the recommendations. They can be classified into two: screening for a risk factor, and screening for early disease. Screening for the former is directed towards determining the effective management of the condition as a risk factor, and screening for the latter is focused on the performance of the tests that will be used to detect and subsequently treat that early disease and prevent it from progressing.

Health screening also carries potential harm, for example, mislabeling the person as being ill. It can pose a threat to the psychological, social, or physical well-being and even to the individual's financial stability. Because of these probable adverse effects of screening, criteria are set to determine if screening for a particular condition can be beneficial and pragmatic. The voting panel members used these criteria (4) aligned with the EtD framework: (a) burden of illness must be high, (b) screening tests must be accurate enough, (c) early treatment must be more effective than late treatment, (d) confirmatory tests and early management must be safe and available, and (e) costs of screening must be proportional with the potential benefit.

Aside from the regulatory agencies and policymakers in the national government, the target users of this guideline on screening strategies include primary care providers, general physicians, specialists, training institutions, payors, patients, the general public, and industry partners.

Cancers are among the leading causes of death in the Philippines, with an age-standardized morality rate of 100 deaths per 100,000 persons.(5) Incidence of cancers in the Philippines is estimated to be 162 cases per 100,000 persons, where the most frequently detected cancers in both sexes are breast cancer, lung cancer, colorectal cancer, liver cancer, and prostate cancer.(5) However, despite the high incidence and mortality in the country, the Philippines has yet to implement a national early detection or screening program for cancers.(6)

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2. SCOPE & PURPOSE

Cancers are among the leading causes of death in the Philippines, with an age-standardized mortality rate of 100 deaths per 100,000 persons.(5) Incidence of cancers in the Philippines is estimated to be 162 cases per 100,000 persons, where the most frequently detected cancers in both sexes are breast cancer, lung cancer, colorectal cancer, liver cancer, and prostate cancer.(5) However, despite the high incidence and mortality in the country, the Philippines has yet to implement a national early detection or screening program for cancers.(6)

For this CPG, the clinical questions involved the following cancers: retinoblastoma, nasopharyngeal cancer, liver cancer, cervical cancer, oral cancer, colorectal cancer, breast cancer, prostate cancer, lung cancer, and gastric cancer. All clinical questions will involve asymptomatic or apparently healthy adults, except for retinoblastoma which will involve early detection among children. The population of interest for breast and cervical cancer are women, while men are of interest for prostate cancer. The following general outcomes were considered: all-cause mortality, cancer-related mortality, adverse effects due to screening or to treatment, diagnostic accuracy of screening, and cost-effectiveness of the screening tool.

3. GUIDELINE DEVELOPMENT METHODOLOGY

3.1 Organization of the Process

Following the international standards, the DOH (1) outlined the guideline development process into four phases, as stated in the Manual for CPG Development: (a) preparation and prioritization, (b) CPG generation, (c) CPG appraisal, and (d) implementation.

In the preparation and prioritization phase, the SC set the CPG objectives, scope, target audience, and clinical questions. They consulted different stakeholders in prioritizing and developing the guideline questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included.

The Evidence Review Experts (ERE) or the technical working group were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the Consensus Panel (CP) members to finalize the recommendations.

The CP comprised of multisectoral representatives tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, they prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations and voted on each recommendation and its strength.

3.2 Creation of the Evidence Summaries

The clinical questions were developed using the PICO (population, intervention, comparator and outcome) format. The ERE searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the Canadian Task Force on Preventive Health Care, US Preventive Services Task Force, National Institute for Health and Care Excellence. If the CPGs were of good quality and done within 5 years (2016-2021), the evidence summaries of the CPG were adopted.

The results of the appraisal of existing CPGs and their evidence summaries determined the need for a systematic search in electronic databases (MEDLINE via PubMed, CENTRAL, Google Scholar) to do de-novo systematic reviews and meta-analyses for each question. All searches were done from May to Nov. of 2021. Details on the time periods were discussed under the specific questions. Please see evidence summaries in Appendices. Relevant local databases and websites of medical societies were also utilized in the search. Keywords were based on the PICO (MeSH and free text) set for each question. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. The search strategy and inclusion criteria were based on the PICO question and are included in their respective evidence summaries. The ERE appraised the directness, methodological validity, results, and applicability of each relevant article included. RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE generated evidence summaries for each of the ten (10) questions. Each evidence summary included evidence on the burden of the problem, diagnostic performance, benefits, harm, and social and economic impact of the screening test/intervention. Evidence/information that will facilitate in the decision (i.e., cost of screening test, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The quality of evidence was assessed using the GRADE approach.(2) See Table 1.

Table 1. Basis for Assessing the Quality of the Evidence using GRADE Approach

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Factors that lower quality of the evidence are:	
• Risk of bias	

- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

3.3 Composition of the CPG Panel

The SC convened the CP, considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual.(1) Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different settings (e.g., public primary care settings, private practice, occupational health settings). In the choice of CP, the task force made sure that all stakeholders were part of the target population for the CPGs (See PERIODIC HEALTH EXAMINATION TASK FORCE ON NEOPLASTIC DISEASES 2021)

3.4 Formulation of the Recommendations

Draft recommendations were formulated based on the quality of evidence and trade-offs between benefit and harm. Prior to the series of online CP meetings, the CP received the draft recommendations together with evidence summaries based on the EtD framework shown in Table 2. These recommendations, together with the evidence summaries, were presented during their respective *en banc* meetings.

Table 2. Detailed considerations based on the EtD framework (3)

1. Is the problem a priority?
2. How accurate is the test?
3. How substantial are the desirable anticipated effects?
4. How substantial are the undesirable anticipated effects?
5. What is the certainty of the evidence of test accuracy?
6. Is there important uncertainty about or variability in how much people value the main outcomes, including adverse effects and burden of the test and downstream outcomes of clinical management guided by the test results?
7. Does the balance between desirable and undesirable effects favor the test or the comparison?
8. How large are the resource requirements (costs)?
9. What is the certainty of the evidence of resource requirements (costs)?
10. Does the cost-effectiveness of the test favor the test or the comparison?
11. What would be the impact on health equity?
12. Is the test acceptable to key stakeholders?
13. Is the test feasible to implement?

The strength of each recommendation (i.e., strong or weak) was determined by the panel considering all the factors mentioned above. A strong recommendation means that the panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects”, while weak recommendation means that the “desirable effects

of adherence to a recommendation probably outweigh the undesirable effect but is not confident."(4)

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed.(2) If consensus was not reached in the first voting, questions, and discussions were encouraged. Two further rounds of voting on an issue were conducted. The evidence-based draft recommendations were also revised based on input arrived at by consensus in the *en banc* discussions with considerations of the quality of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps. The CPG will be submitted to the Central SC for third party review prior to submitting to DOH.

[3.5 Managing Conflicts of Interest](#)

The Central Executive Committee convened an Oversight Committee (OC) whose task was to thoroughly review the declaration of conflict of interest (DCOI) of each of the Task Force members particularly the Consensus Panelists (CP) and make recommendations on how to manage the COI. For TF members with potential significant COIs, the member of OC conducted additional investigations with due diligence to ensure the integrity of the CPG process and the final recommendations.

All task force members submitted a DCOI and their curriculum vitae (CV) prior to the initiation of guideline development process. The disclosure included a 4-year period of personal potential intellectual and/or financial conflicts of interest (COI).

Management of the COI of the Consensus Panel, Technical Coordinators, and Task Force Steering Committees were deliberated and decided by the OC, using the pre-agreed criteria. A full description of the methods can be found in the [Final Technical report](#).

Those with significant potential COI were either not allowed to join or vote depending on the COI. See [Conflict of Interest Declaration](#) at the end of the document.

[3.6 External Review Process](#)

The CPGs were reviewed by independent stakeholders, who were not members of the Task Force. They were also presented in conferences and to relevant societies for their comments and suggestions.

[3.7 Planning for Dissemination and Implementation](#)

The SC discussed with relevant stakeholders, such as DOH and PhilHealth, to prepare a dissemination plan that will actively promote the adoption of this guideline with strategies for copyrights. Suggestions ranged from making the guidelines available on websites, press conferences, social media sites, professional society conventions, and journal publications.

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4.RECOMMENDATIONS AND PANEL DISCUSSION

4.1 Red Reflex Test in Screening for Retinoblastoma

RECOMMENDATIONS

1. Among all children less than 5 years, we suggest screening for retinoblastoma from the newborn period through serial ophthalmologic examinations, using the red reflex test.
(weak recommendation, very low certainty evidence)
2. Among infants and children with a high risk of developing retinoblastoma (i.e., positive family history), there is insufficient evidence to suggest for or against screening for retinoblastoma using the red reflex test.
(no recommendation, insufficient evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Retinoblastoma is deemed a priority health problem.
- There is currently no screening test that could detect retinoblastoma at the preclinical stage. Early detection, rather than screening, is performed.
- Evidence is lacking on the use of the RRT as a screening tool for retinoblastoma among high-risk children.
- Children with suspicious findings using the RRT or who have risk factors (e.g., family history) are referred directly to an ophthalmologist.
- Early detection was favorable with small harm, although the panelists deemed that there was uncertain diagnostic accuracy and that the certainty of evidence for the balance of effects is very low.
- There were no studies to make judgments upon for the certainty of evidence on cost and for the cost-effectiveness of RRT
- Screening with RRT was perceived as equitable, acceptable, and feasible.

4.1.1 Burden of disease

Disease Frequency

Retinoblastoma is the most common pediatric ocular malignancy worldwide. A significant proportion (43%) of cases came from six countries in the Asia-Pacific region: India, China, Indonesia, Pakistan, Bangladesh, and the Philippines.(1) It is also the most common ocular malignancy in children, but it is still rare overall, making up 2% of cases of all childhood cancers.(5) The most common presenting sign is leukocoria (white pupil) followed by strabismus (crossed eyes).

In a 10-year review published by the Philippine Eye Research Institute, retinoblastoma was the most common tumor of the eye and ocular adnexa, accounting for 90.9% of all intraocular cancers and 43.2% of all malignant tumors in this series.(2) Unfortunately, this study found that diagnosis and treatment were often delayed. Most of these patients, of whom 23% had bilateral disease, were enucleated at an advanced stage.(2) Another local study at the Philippine General Hospital (PGH) saw that 69% of unilateral and 56% of bilateral retinoblastoma cases experienced delay from symptom onset to diagnosis.(3) Advanced intraocular stage was seen in 63–71.6% among those with unilateral tumors and in 56–60% of those with bilateral tumors. Financial cost (71.4%) was the most common reason for this delay, followed by misdiagnosis (24.5%) and inaccessibility of medical facilities (2.0%).(3)

It is crucial to address diagnostic and treatment delay because metastasis generally developed within 1 year after diagnosis, and the mortality rate could reach 99% if left untreated. Thus, the primary goal in the management of retinoblastoma is patient survival, with preservation of the globe and visual acuity being important secondary goals.(3) While retinoblastoma in low-income countries is associated with low patient survival (~30%), prognosis is excellent (>95%) among high-income countries where diagnosis and treatment are done early.(4)

Retinoblastoma is typically diagnosed between the ages of 4 months and 4 years, and rarely occurs in children >6 years, but the best outcomes are achieved when the diagnosis is made by 2 years of age.(4) Only 10–15% of patients are children with a positive family history of retinoblastoma, making most cases sporadic and more difficult to detect early.(6)

Management of the Disease

Retinoblastoma is a cancer for which early diagnosis, rather than screening, is applicable, according to the World Health Organization (WHO).(7) In an early diagnosis program, the target population will be all patients of a specific age group and/or sex who are prone to developing a specific cancer, and who are presenting with early signs and symptoms suggesting the presence of that cancer. In the case of retinoblastoma, the recommended target population would be all children presenting with leukocoria and strabismus.(7) At this time, there has been no evidence showing the efficacy of a retinoblastoma screening program, and there is no screening test capable of detecting disease in the preclinical phase.(8)

In a prior United States Preventive Services Task Force Vision Screening Recommendation Statement, it was stated that there was insufficient evidence to evaluate the balance of benefits and harms of vision screening for children <3 years of age.(9) A reply in the form of a commentary from the American Academy of Pediatrics highlighted the United States Preventive Services Task Force's omission of the red reflex test (RRT), which was the backbone of infant and toddler vision screening.(10) The American Academy of Pediatrics recommended that the assessment of the fundus red reflex with a direct ophthalmoscope should be performed in the newborn and at regular intervals during infancy to rule out retinoblastoma, cataract, and other media opacities to

help prevent unnecessary loss of vision or life.(10) Subsequently, all infants or children with an abnormal or absent red reflex, as well as those whose parents or other observers report possible leukocoria, should be referred immediately to an ophthalmologist who is skilled in examining pediatric patients.(11) High-risk patients, including children with a positive family history of retinoblastoma or other vision-threatening ocular disorders that can present in infancy, should be evaluated with a complete eye examination by an ophthalmologist who is experienced in examining children, regardless of the findings of the initial RRT.(11)

Simple enucleation is often curative when retinoblastoma is diagnosed early, such as when it is still confined inside the eye. To avoid enucleation, several globe salvage modalities are available that also result in good survival outcomes. These include systemic chemotherapy, intra-arterial chemotherapy, intravitreal chemotherapy, brachytherapy, external beam radiation therapy (EBRT), and recently, tumor endoresection via pars plana vitrectomy.(12)

There are no randomized control trials (RCTs) investigating the treatment outcomes associated with these therapeutic modalities since it is unethical to subject children with active cancer to non-intervention.(10,12) But based on observational studies done in low- and middle-income countries (LMIC), noncompliance and treatment abandonment are major causes of death from retinoblastoma.(12)

4.1.2 Benefits and Harms of Screening Tests

To prove association and to control for potential bias, an RCT with one arm following the screening (or treatment) protocol and one arm without screening (or treatment) would be necessary. However, this methodology cannot be applied in infants and young children for ethical reasons. Furthermore, the overall rarity of familial retinoblastoma and the absence of universally agreed upon screening protocols and treatment recommendations also complicate the initiation of RCTs. Thus, we can only rely mostly on retrospective studies.(13) The search strategies used are indicated in Appendix A.

Retinoblastoma-Related Mortality

Two retrospective studies (n=487; very low certainty of evidence) evaluated the impact of early diagnosis versus late diagnosis (using a designated cutoff of 6 months) on the 5-year overall survival rate among children with retinoblastoma (Table 3). In both studies, a statistically significant improvement in 5-year overall survival rate was observed with early diagnosis.(14, 15) In the study by Mattosinho et al. (14), early diagnosis was associated with a survival rate of 87.7% versus 71.5% with delayed diagnosis ($p=0.017$). Similarly, the study by Rodrigues et al. (15) demonstrated a survival rate of 91% versus 78% in favor of early diagnosis ($p<0.001$).(15) However, both studies were deemed to have a high risk of bias based on the Newcastle-Ottawa Scale (NOS) (see Appendix A).

Table 3. Retrospective studies evaluating early diagnosis versus late diagnosis on 5-year OS

Study ^a	Country	N	5-year OS (%)				p-value
			Early diagnosis ^b	95% CI	Late diagnosis ^b	95% CI	

Mattosinho (14)	Brazil	160	87.7	76.7, 93.7	71.5	59.9, 80.3	0.017
Rodrigues (15)	Brazil	327	91	–	78	–	<0.001

CI confidence interval; OS overall survival

^a studies have a high risk of bias according to the Newcastle-Ottawa Scale; ^b cutoff was 6 months

Loss of Vision

Two retrospective studies (n=105; very low certainty of evidence) demonstrated that screening resulted in significantly improved ocular outcomes versus no screening among retinoblastoma patients with a positive family history (Table 4).(13,16) In the study by Rothschild et al. (13), the enucleation rate was only 5% in the screening group versus 65% in the non-screened subjects ($p<0.0001$). Yousef et al. (16) showed that out of 77 affected eyes (of 46 patients), the eye salvage rate was 100% among screened eyes versus only 52% in the non-screened eyes ($p=0.0023$). Both studies were deemed to be of poor quality based on the NOS (see Appendix A).

Table 4. Retrospective studies evaluating screening of retinoblastoma on loss of vision

Study *	Country	N	Screened		Non-screened		RR (95% CI)	p-value	NNT
			Enucleation rate (%)	Eye salvage rate (%)	Enucleation rate (%)	Eye salvage rate (%)			
Rothschild (13)	France	59	5	95	65	35	0.08 (0.03, 0.24)	<0.0001	1.686
Yousef (16)	Jordan	46 (77 eyes)	0	100	48	52	0.01 (0.00, 0.21)	0.0023	2.108

CI confidence interval; NNT number needed to treat; RR risk ratio

* studies have a high risk of bias according to the Newcastle-Ottawa Scale

Adverse Events

The RRT is generally considered safe. Occasionally, there may be a need to dilate the eyes of the subject in order to facilitate the examination. Pupillary dilation has been performed routinely for many years even in pediatric patients with a very low incidence of toxicity.(11) Dilating the eyes seems to be safe when performed in an office setting on infants older than 2 weeks.

As with any other medical procedure, physicians should routinely discuss the nature and purpose of the examination with the parents. Any potential risks associated with the procedure or accompanying medications including (but not limited to) pain, discomfort, bradycardia, respiratory depression, and hypertension, particularly when dealing with preterm infants should also be discussed.(11) Furthermore, false-positive findings may lead to parental anxiety and may result in over-referral of healthy infants for ophthalmological evaluation.(17)

4.1.3 Diagnostic Performance of Screening Tests

The role of a screening test is to detect a specific abnormality with high sensitivity and specificity. However, for a test to screen for a potentially life-threatening condition such as retinoblastoma, a lower sensitivity (i.e., more false-positives) and higher specificity

(i.e., fewer false-negatives) would be tolerated more than the reverse. Unfortunately, the ability of the RRT to detect retinoblastoma is difficult to evaluate because of the low overall incidence of this disease.(18) At this time, the available literature only evaluates the RRT as a diagnostic tool for ocular abnormalities in general.

Ocular Abnormalities

A recent meta-analysis (11 observational studies, n=56,556; very low certainty of evidence) demonstrated that the pooled sensitivity and specificity of the RRT for diagnosing ocular abnormalities were 0.23 (95% CI 0.21 to 0.24) and 0.98 (95% CI 0.98 to 0.98), respectively.(19) The poor sensitivity was mostly attributed to the low sensitivity of the RRT in the detection of posterior segment abnormalities compared to anterior segment problems. The positive likelihood ratio (PLR) was 32.52 (95% CI 7.89 to 134.15), which further supports the strong evidence for RRT-positive newborns with disease. The negative likelihood ratio (NLR) was 0.69 (95% CI 0.55 to 0.88), indicating a low false-negative value of the RRT. The calculated diagnostic odds ratio was 138.48 (95% CI 23.85 to 803.97), denoting that the RRT has high discriminatory power for the detection of an abnormal ophthalmological condition.

Based on the QUADAS-2 tool applied by the reviewers, the risk of bias was low for six studies, unclear for three, and high for two studies. Owing to the observational nature of the included studies, statistically significant heterogeneity was observed for the sensitivity ($\chi^2=849.01$, $p=0.000$) and specificity ($\chi^2=1395.21$, $p=0.000$) of all studies included in the analysis. Hence, the results of the pooled analysis have to be taken with a certain degree of discretion.(19) Using the AMSTAR 2 tool, this meta-analysis was rated to be of critically low quality (see Appendix A).

4.1.4 Cost Implication

Implementing a nationwide vision screening program necessitates a strong commitment in terms of planning and budget allocation. Eye screening among infants may require professional care and appropriate facilities, which might involve higher costs. Hence, despite the importance of more comprehensive vision screening procedures, their implementation can be difficult in LMIC due to lack of financial and human resources.(20)

4.1.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

In developing countries, poor education, lower socioeconomic status, and inefficient healthcare delivery systems result in delayed diagnosis and suboptimal care. The complexity of multidisciplinary care required with retinoblastoma is seldom possible due to the lack of access to care, scarcity of human resources, unavailability of essential medications, lack of cancer registries, inadequate infrastructure, and lack of support from the government and other organizations. All of these factors could influence service delivery and the success of any screening or early detection program.(21)

4.1.6 Recommendations from Other Groups

Most CPGs recommended that some form of vision screening was necessary, unless or until evidence to the contrary was identified, based on the following premises: (a) vision is an important health consideration; (b) vision screening can detect latent or early symptomatic stages of a vision condition; and (c) early diagnosis of vision conditions often results in a better prognosis.(22) Table 5 and Table 6 summarize these recommendations.

Table 5. Recommendations from international CPGs

Group	Recommendation	Strength of recommendation and Certainty of evidence
National Health Service England (2021) (23)	The NIPE program screens babies (ideally) within 72 hours of birth (NIPE newborn screening examination) and again at 6–8 weeks of age (NIPE infant examination) for conditions relating to the eyes.	No evidence category provided
	The red reflex should be assessed. Babies with screen positive eye results following the NIPE newborn screening examination should be urgently referred via the NIPE pathway to an ophthalmologist within 2 weeks of the screening examination. Babies with screen positive eye results following infant screening examination should be referred promptly and seen by a consultant ophthalmologist or pediatric ophthalmology service by 11 weeks of age.	No evidence category provided
Canadian Association of Optometrists and Canadian Ophthalmological Society (2019) (24)	Routine age-appropriate screening as recommended by Rourke and ABCDaire (RRT, cover/uncover test, and visual acuity) of infants and children by a primary health care provider or pediatrician should continue.	No evidence category provided
	If an infant or child is identified with an abnormality, they should be referred to the appropriate eye care professional.	No evidence category provided
American Academy of Ophthalmology (2017) (25)	All children at elevated risk for retinoblastoma above the population risk require serial dilated fundus examination by an ophthalmologist with experience in retinoblastoma.	Grade D: directly based on category IV evidence (expert committee reports or opinions or clinical experiences of respected authorities, or both)
	We recommend screening for at-risk children from birth up to the age of 7 years.	Grade C: directly based on category III evidence (non-experimental descriptive studies)
American Optometric Association (2017) (26)	Infants should receive an in-person comprehensive eye and vision assessment between 6 and 12 months of age for the prevention and/or early diagnosis and treatment of sight-threatening eye conditions and to evaluate visual development.	Grade B: based on prospective cohort studies and a diagnostic study; high level of confidence; strong recommendation
US Preventive Services Task Force (2017) (27)	The United States Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening in children younger than 3 years.	I statement: insufficient evidence
Canadian Pediatric Society (2009) (28)	Red reflex examination should be performed from birth to 3 months of age. Failure to visualize a normal red reflex warrants immediate referral to an ophthalmologist	Level of evidence rating BII: fair evidence

Group	Recommendation	Strength of recommendation and Certainty of evidence
Canadian Retinoblastoma Society (2009) (29)	All infants and children in whom someone has observed a white pupil (either in person or in a photograph) should have a full dilated-eye examination including RRT within 72 hours by an ophthalmologist or medical practitioner who is fully aware of the importance of leukocoria as a sign of retinoblastoma.	Consensus
	Any child with strabismus or suspected strabismus should be seen by the child's pediatrician or family doctor. The RRT should be applied and urgent referral (within 72 hours) to an ophthalmologist should be done in the presence of an abnormal red reflex.	Consensus
American Academy of Pediatricians (2008) (11)	Children should have an assessment for eye problems in the newborn period and then at all subsequent routine health supervision visits.	No evidence category provided
	Mandatory red reflex examination of all infants should be performed within the first 2 months of life by a pediatrician or by a trained primary care ophthalmic clinician.	No evidence category provided
	Infants and children at high risk of eye problems should be referred for specialized eye examination by an ophthalmologist experienced in treating children.	No evidence category provided
National Children's Vision Screening Project Australia (2008) (22)	Screening programs for universal red reflex examination in newborns by trained personnel are proposed.	No evidence category provided
	Experts recommended that a vision check during the neonatal period was crucial, to detect treatable diseases with recognizable early pre-symptomatic stages.	Expert opinion
	A vision check between 3 and 6 months was recommended to detect any condition missed at the newborn check, and to assess visual behavior.	Expert opinion
World Health Organization (2007) (6)	Programs recommended for early diagnosis (target population being children with white reflex and convergent strabismus) but not for screening.	No evidence category provided

Table 6. Recommendations from local CPGs

Group	Recommendation	Strength of recommendation and Certainty of evidence
Philippine Society of Pediatric Ophthalmology and Strabismus and Philippine Academy of Ophthalmology (2015) (30)	Regular eye and vision screening examination of children from infancy until maturity of their visual system is recommended. This test can be administered by a primary care provider, nurse, midwife, optometrist, a community health worker, a school teacher or anyone trained to check vision and examine eyes.	No evidence category provided
	All high-risk infants should be referred to an ophthalmologist for comprehensive eye examination.	Level III: based on descriptive studies, case reports, and reports of expert committees/ organizations
Philippine Pediatric Society (2004) (31)	Examination of the red reflex or Bruckner test can easily be performed by pediatricians from the newborn period and then at all subsequent health supervision visits. Strabismus can readily be detected using the corneal reflex test and the cross-cover test	No evidence category provided

Group	Recommendation	Strength of recommendation and Certainty of evidence
	It is encouraged that patients at high risk for retinoblastoma such as 1) those with a family history of the disease or 2) those in whom retinoblastoma is suspected based on a family history of surgical eye removal and 3) all children found with leukocoria and strabismus should be referred immediately to an ophthalmologist familiar with retinoblastoma.	Level III: based on descriptive studies, case reports, and reports of expert committees/ organizations

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4.2 EBV DNA and/or Nasopharyngoscopy in Screening for Nasopharyngeal Cancer

RECOMMENDATIONS

1. Among asymptomatic apparently healthy adults, we suggest against screening for nasopharyngeal cancer using an EBV DNA test and/or nasopharyngoscopy.
(weak recommendation, low certainty evidence)
2. Among asymptomatic apparently healthy adults with a first-degree relative with a known nasopharyngeal cancer, we suggest screening for nasopharyngeal cancer using EBV DNA test and/or nasopharyngoscopy.
(weak recommendation, very low certainty evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Nasopharyngeal cancer is a priority health problem.
- Guidelines did not specify an age range for screening, but ages 30–60 were considered based on the available evidence and the panelists' experience with the disease.
- The benefits of screening outweighed the risks.
- EBV blood test and/or nasopharyngoscopy are accurate tests, but EBV blood tests are limited in accessibility. Among the EBV blood tests, EBV DNA is specified due to its higher diagnostic accuracy relative to the other tests and its availability in the laboratories that offer EBV testing.
- Screening using EBV DNA test and/or nasopharyngoscopy was not cost-effective, acceptable, or feasible, with uncertain on patient values and preferences.

4.2.1 Burden of disease

Disease Frequency

Nasopharyngeal cancer (NPCA) is quite rare; in most parts of the world, including the United States, there is less than one case for every 100,000 people each year.(1) However, it is endemic in Africa, Southern China, and Southeast Asia where the incidence can be as high as 17.8–41.4 per 100,000.(2,3) In the Philippines, NPCA is the 15th leading site of malignancy for both sexes, with 3,006 incident cases in 2020.(4) The estimated prevalence is 7.64 per 100,000 in 2020, which is a marked increase from the estimate of 1.2 per 100,000 in 2010. NPCA also ranked as the 13th leading cause of cancer-related mortality in 2020.(4,5)

NPCA is more common among males with an approximate ratio of 2–3:1.(6) It has a bimodal age distribution where majority of cases occur at around 40–60 years of age, and a small peak is observed in adolescents and young adults.(2)

The WHO 2017 classification defines the histological subtypes as nonkeratinizing squamous cell carcinoma (differentiated and undifferentiated), keratinizing squamous cell carcinoma, and the basaloid squamous cell carcinoma. The nonkeratinizing type of NPCA is the most common type in endemic and non-endemic areas, and is associated with Epstein-Barr virus (EBV) infection.(7) Various environmental factors have also been found to play a role. The most important are dietary (in particular consumption of certain salted fish, other salt-preserved and fermented foods), and smoking.(2,8–10)

Natural Course of the Disease

Early-stage NPCA (i.e., Stage I or II disease) is basically curable with a 10-year survival rate of up to 90% or higher. Unfortunately, most diagnosed NPCA patients (>80%) have Stage III or IV disease. Late diagnosis may be due to the deep location of the suspected tumor and the non-specificity of the initial symptoms, leading to poor prognosis and decreased survival.(11) For patients with Stage III or IV NPCA, the 2-year survival rate is only 20–30% despite aggressive concurrent chemoradiation therapy, and lesions often develop distant metastases despite local control.(12,13) Screening strategies for early-stage NPCA diagnosis and administration of treatment are therefore needed to reduce disease-specific morbidity and mortality.(2,13–16)

Management of the Disease

In most cases, a biopsy of the primary lesion done under local anesthetic using endoscopic procedures can be performed in outpatient clinics. However, most patients also use a neck CT scan or a neck MRI to properly localize the lesion. To clinically stage a patient, a CT scan of the chest and abdomen and a whole-body bone scan are usually done. Alternatively, a whole-body PET/CT scan with IV contrast may be requested. A meta-analysis of 18 studies showed the superiority of this scan in detecting locoregional nodal and distant metastases in NPCA.(17)

Patients with T1N0M0 NPCA should be treated with definitive radiation therapy alone, including elective radiation therapy to the neck. An advanced radiation technique like intensity modulated radiation therapy is preferred due to its ability to encompass all areas of cancer spread, which can be located in close proximity to the brainstem, cochleae, and optic nerves. For locoregionally advanced disease, concurrent chemoradiation with platinum-based chemotherapy with induction or adjuvant chemotherapy is the usual line of treatment. For patients who present with metastatic disease, systemic treatment is usually given in the form of chemotherapy, targeted treatment, or immunotherapy.(17)

Economic Impact of the Disease

A cost-effectiveness study on NPCA screening with EBV-DNA and/or serology in high incidence populations in the United States used a decision analytic model to compare 10 one-time screening strategies with no screening for people aged 50 years. Screening performance and the stage distribution of undiagnosed NPCA were derived from a systematic review of prospective screening trials. Screening was reported to be cost-effective in up to 14.5% of high incidence populations. Combinations of serologic and/or plasma polymerase chain reaction (PCR) screening were noted to be cost-effective,

serology and nasopharyngeal PCR being the most cost-effective combination. The estimated reduction in NPCA mortality was similar across screening strategies. For a hypothetical cohort of patients in China, 10-year survival improved from 71.0% (95% CI 68.8% to 73.0%) without screening to a median of 86.3% (range 83.5–88.2%) with screening. This corresponded to a median 10-year reduction in NPCA mortality of 52.9% (range 43.1–59.3%).(18)

In a Hong Kong study that used EBV-DNA for screening, the cost to detect one case was \$28,600.00.(19) Another study done in China that used VCA-IgA and EBNA1-IgA reported that it costed \$4,386.00 to detect one case.(20)

There were no direct studies investigating the economic impact of NPCA screening here in the Philippines since the practice is not standard here. However, a local study by the Philippine Costs in Oncology (PESO) Study and the ASEAN Costs in Oncology (ACTION) Study involving individuals who were diagnosed and treated for NPCA in the Philippines described the economic impact of cancer on the Filipino cancer patient.(21) This study highlighted that the combined Month 3 and Month 12 out-of-pocket expenditure during cancer treatment was PHP 181,789.00 in a sample whose combined household income was mostly less than PHP 51,500.00 per annum. Half of the patients recruited to participate in the studies were the primary income generators in their family. Belonging to higher income groups was significantly associated with a lower risk of financial catastrophe, while having health insurance did not significantly decrease for financial catastrophe in both higher and lower income families.

Social Impact of the Disease

There were no direct studies exploring the social and emotional impact of the disease in NPCA patients. In a local prospective cohort study that investigated quality of life scores in newly-diagnosed cancer patients (n=535), 89 patients (16.64%) represented cases of head and neck cancers (HNCs) among which 56 patients scored borderline for anxiety and depression, while two were high-risk as evaluated by the EQ-5D tool.(22) Another local cross-sectional study measured the risk of anxiety and depression among cancer patients (n=381) in outpatient clinics using the Hospital Anxiety and Depression Scale-Pilipino Version (HADS-P) scale. Nearly a third of these patients were HNC patients (33.07%), and most were borderline cases for anxiety but not for depression, according to the scale. Majority of these HNC patients were Stage III and had completed their treatment.(23)

4.2.2 Benefits and Harms of Screening Tests

EBV DNA and EBV serology (i.e., EA-IgA, VCA-IgA, EBNA1-IgA and Rta-IgG) have mainly been used for screening NPCA in endemic areas.(19,24,25) As of the present, there is no gold standard and consensus on which EBV blood test is best used to screen for NPCA. However, upon review, most studies used EBV DNA, EBNA1-IgA and VCA-IgA. Many also combined these blood tests for better outcomes. Nasopharyngoscopy has been traditionally used together with or after a positive EBV blood test as part of two- or a three-stage screening protocol and not as a sole screening tool. See Appendix B.

General Population

A. EBV Serology

Only one prospective cluster RCT ($n=80,049$; low certainty of evidence) used EBV serology in screening for NPCA.(20) However, this study used two kinds of serology at the same time to increase the diagnostic accuracy. This prospective, cluster RCT for NPCA screening (PRO-NPC-001) was conducted in 2008 in three selected towns of Zhongshan City and in 13 preselected towns of Suhui City in Southern China ($n=80,049$).

Serum samples for EBNA1-IgA and anti-VCA IgA were taken, and indirect mirror examination of the nasopharynx and/or lymph node palpation (IMLP) were also performed. Though analysis using a regression model, the values of the titers were used to categorize patients according to risk: high-risk (Logit $P \geq 0.98$), medium-risk (Logit $P \geq 0.65$) and low-risk (Logit $P < 0.65$).⁽²⁰⁾ A patient was also classified as high-risk even without a high EBV serology if there were abnormalities in the IMLP. Those who were high- or medium-risk at initial screening were invited to retest annually for 3 years. Those who were high-risk on retesting were referred for nasopharyngoscopy.

The values that will be quoted here are part of the interim analysis reported.

NPCA Incidence

A higher incidence of NPCA was reported in the screening arm (RR 1.64, 95% CI 1.23 to 2.18).⁽²⁰⁾

Early Diagnostic Rates

The proportion of early-stage cancers (Stage I and Stage II) were significantly higher in the screening arm (RR 0.81, 95% CI 0.79 to 0.86).⁽²⁰⁾

NPCA-Specific Mortality

NPCA-specific mortality was significantly less in the screening arm (RR 0.22, 95% CI 0.09 to 0.49).⁽²⁰⁾

All-Cause Mortality

All-cause mortality was likewise significantly less in the screening arm (HR 0.12, 95% CI 0.03 to 0.49).⁽²⁰⁾

B. EBV-DNA

A prospective cohort study on NPCA screening was done in Hong Kong among Chinese participants aged 40–62 years ($n=20,174$) from July 2013 until February 2016.⁽¹⁹⁾ A sample of 20 mL venous blood was obtained from each participant upon enrollment. Plasma EBV DNA was analyzed using real-time PCR assay that targeted the BamHI-W fragment of the EBV genome. This study used the lower detection limit of the machine, which was at 20 EBV genomes per milliliter of plasma. In participants with positive results, another sample was taken after 4 weeks. These patients were then referred for nasopharyngoscopy and MRI of the nasopharynx.

Upon enrollment, 1,112 participants (5.5%) had detectable EBV DNA in plasma and received follow-up analysis of EBV DNA in plasma, and 309 of these participants had persistently positive results. Histologically proven undifferentiated NPCA was confirmed in 34 (11%) of the 300 participants who underwent assessment. NPCA developed in only one participant with negative EBV DNA in plasma samples within 1 year of testing. The stage upon diagnosis and the survival were then compared with a historical cohort.

Early Diagnostic Rates

When compared to the historical cohort of all NPCA patients diagnosed in a cancer center, there were more early-stage cancers (Stage I and II) diagnosed in the screening arm (RR 0.70, 95% CI 0.69 to 0.72).(19)

Three-Year Progression Free Survival

A significantly higher proportion of participants with NPCA that was identified by screening had Stage I or Stage II disease than in historical cohort (71% vs. 20%, $p<0.001$ by chi-square test).(19) The 3-year progression free survival of the participants with NPCA detected on screening was superior to that of the patients in the historical cohort (97% vs. 70%; HR 0.10; 95% CI: 0.05 to 0.18; $p<0.001$ by the log-rank test).(19) There was no long-term follow-up to determine overall survival and NPCA-specific mortality.

High-Risk Families

There have been a few NPCA screening programs conducted independently by oncology centers in Southeast Asia. However, the results of these programs cannot be pooled as they differed in the screening modality used and the frequency these programs were done. Included in this section are large-scale screening programs that included only first-degree adult relatives of patients who were diagnosed with NPCA:

A retrospective study in Hong Kong on NPCA screening among family members of NPCA patients ($n=1,199$) was carried out between 1994–2005.(26) The participants underwent annual physical examination, focused history taking, nasopharyngoscopy, and EBV serology tests (VCA-IgA and EBNA1-IgA) at the same time. Eighteen participants developed NPCA in the screening program. The sensitivity and specificity of EBV serology for the program were 0.89 and 0.87, respectively. The screening-detected NPCA patients had significantly higher proportion of Stage I disease (0.41 vs. <0.01) and better disease-free survival compared with patients with symptomatic NPCA referred during the same period. However, there was no long-term follow-up to determine overall survival.(26)

A case-control study in Taiwan included unaffected participants from 358 families with NPCA ($n=2,557$) from 1996–2010.(27,28) This study investigated the ability of anti-EBV IgA antibodies (EBNA1-IgA, VCA-IgA and EA-IgA) to pick up early NPCA cases. These serologic markers were measured annually with a focused history, physical examination, and a low threshold to perform nasopharyngoscopy should any of the markers be positive. Twenty-one NPCA cases developed during the study and these were compared with 84 sex-matched controls selected from the Taiwanese Registry. In this study, EBNA1 IgA had the best performance and was able to detect 80% of high-risk individuals during

follow-up. However, approximately 40% of high-risk individuals who did not develop NPCA also tested positive.(27,28)

Another large prospective cohort study was conducted in Hong Kong from 2013–2016 and included Chinese participants (n=20,174), a subgroup of which had a family history of NPCA (n=1,003). This program used plasma EBV DNA; those with positive results underwent nasopharyngoscopy and MRI. At baseline, there were 102 participants who were EBV positive, and 29 were persistently positive on the second blood draw after 4 weeks. Among those with family history of NPCA, eight confirmed NPCA were diagnosed with a sensitivity of 0.89 and a specificity of 0.98.(19)

A multicenter prospective cohort study done in Singapore from 2004–2013 (n=524) investigated the effectiveness of NPCA screening by clinical follow-up and EBV testing. The cohort was evaluated with complete head and neck examination and nasopharyngoscopy done every 6 months. Blood was tested annually for VCA-IgA, EA-IgA, and serum EBV-DNA. Nasopharyngeal biopsy was performed when any irregularity in the nasopharynx was observed or when any of the EBV markers were elevated. Five participants were identified to have NPCA, giving a prevalence of 199 per 100,000 person-years of screening. Four of the five NPCA cases had asymptomatic T1 disease, at an earlier stage compared to NPCA patients diagnosed in the hospitals during the same time ($p=0.0297$). (29)

4.2.3 Diagnostic Performance of Screening Tests

Numerous individual studies have investigated the diagnostic value of EBV-DNA, EA-IgA, VCA-IgA, EBNA1-IgA and Rta-IgG detection for NPCA, but variable sensitivities and specificities have been reported (see Appendix B). Currently, there is no consensus on which is the best test for early diagnosis of NPCA. There were no direct studies investigating the sensitivity and specificity of an EBV blood test combined with nasopharyngoscopy.

A recent meta-analysis by Liu and colleagues published online last 10 March 2021 compared the diagnostic performance of these EBV blood tests.(30) This meta-analysis included 47 studies (17 EBV-DNA, 15 EA-IgA, 35 VC-IgA, 16 EBNA1-IgA and 16 Rta-IgG). The sensitivity, specificity, PLR, and NLR of the following EBV blood tests in the diagnosis of NPCA were evaluated. The pooled sensitivity and specificity of some EBV blood tests are as follows (Table 7).

Based on these values, EBV-DNA, VCA-IgA, EBNA1-IgA and Rta-IgG detection have high sensitivity and specificity in the early diagnosis of NPCA. The study concluded that based on the pooled values, EBV-DNA has the highest diagnosis accuracy. A lot of the studies included were in Chinese and so their method on how the screening was done could not be thoroughly evaluated.

Table 7. Pooled result of EBV-DNA, EA-IgA, VCA-IgA, EBNA1-IgA and Rta-IgG in the diagnosis of NPCA (30)

Method	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)	Pooled DOR (95% CI)
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EBV-DNA	0.76 (0.73, 0.77)	0.96 (0.95, 0.97)	14.66 (9.97, 21.55)	0.19 (0.13, 0.28)	84 (50.04, 139.88)
EA-IgA	0.55 (0.54, 0.57)	0.96 (0.96, 0.97)	12.91 (9.55, 17.45)	0.35 (0.29, 0.43)	39.57 (26.44, 59.23)
VCA-IgA	0.85 (0.84, 0.85)	0.89 (0.88, 0.89)	6.73 (5.38, 8.43)	0.17 (0.12, 0.23)	43.03 (31.51, 58.76)
EBNA1-IgA	0.86 (0.85, 0.88)	0.87 (0.88, 0.90)	7.55 (5.79, 9.87)	0.16 (0.13, 0.19)	50.95 (34.35, 75.57)
Rta-IgG	0.70 (0.69, 0.71)	0.94 (0.94, 0.95)	9.84 (8.40, 11.54)	0.25 (0.21, 0.31)	40.59 (32.09, 51.35)

PLR positive likelihood ratio, NLR negative likelihood ratio, DOR diagnostic odds ratio

4.2.4 Cost Implication

In the Philippines, only plasma EBV-DNA is available in some private hospitals and in Hi-Precision Diagnostics (Table 8). In an online search, we were able to determine that an EBV VCA-IgA kit costs PHP 79.20, while an EBV IgM rapid cassette costs PHP 110.00 at Alibaba.com.

Table 8 and Table 9 show the approximate cost of NPCA screening in the Philippines. The unit cost of screening can be as low as PHP 17,549.00 (EBV-DNA, nasopharyngoscopy, histopathology and neck CT scan) in a government hospital, and as high as PHP 48,049.00 (EBV-DNA, nasopharyngoscopy, histopathology, neck MRI) in the private setting. These costs do not include IV sedation fees by an anesthesiologist (if warranted), additional immunohistochemical stains, and additional scans to look for distant metastases if diagnosed with NPCA. These also do not include the cost for a re-test for EBV using EBV-DNA or EBV serology to exclude a transient EBV infection, as some screening studies had implemented. Some will repeat the EBV blood test 4–12 weeks after, while others would go straight to nasopharyngoscopy and imaging after a positive blood test.

Table 8. Cost of screening and confirmatory test in NPCA screening in the Philippines

Parameter	Type of institution	Screening Intervention		Confirmatory Test
		EBV Blood Test	Nasopharyngoscopy ^a	Nasopharyngeal Mass Biopsy ^b
Unit cost of screening intervention	Government	Plasma EBV-DNA is not available in the 3 public hospitals (UP-PGH, Jose Reyes, East Avenue) we asked in Luzon. This test is also not available in Chong Hua Hospital and Southern Philippines Medical Center.	PHP 0–1,500.00 (As long as with PhilHealth coverage, under local anesthesia and will be done in the service OPD center)	1. Nasopharyngoscopy: PHP 0–1,500.00 +++ 2. Histopathology: PHP 500.00 +++ (not shouldered by PhilHealth) (As long as with PhilHealth coverage, under local anesthesia and will be done in the service OPD center)

Parameter	Type of institution	Screening Intervention		Confirmatory Test
		EBV Blood Test	Nasopharyngoscopy ^a	Nasopharyngeal Mass Biopsy ^b
	Private	PHP 10,049.00–15,819.00: private hospitals in Metro Manila PHP 30,000.00: Hi-Precision diagnostics	PHP 20,000.00+++ (Includes the use of endoscopy unit, PPE, professional fee; fee will increase if the patient needs to be sedated ^c)	1. Nasopharyngoscopy: PHP 20,000.00 +++ 2. Histopathology: PHP 3,000.00 +++ (Includes the use of endoscopy unit, PPE, professional fee; fee will increase if the patient needs to be sedated ^c)
	Others	EBV serology (VCA-IgA, EBNA1-IgA and Rta-IgG) is not available in any private or government hospital we asked in the Philippines.		

PHP Philippine peso; UP PGH Philippine General Hospital

^a The PhilHealth case rate for “nasal endoscopy” (as stated in PhilHealth) or nasopharyngoscopy without biopsy is P10,540.00 (Php 5,040.00 for the professional fee and Php 5,400.00 for the Health Care Institutional Fee).

^b The PhilHealth case rate for “nasal endoscopy” (as stated in PhilHealth) or nasopharyngoscopy WITH biopsy is P12,120.00 (Php 6,720.00 for the professional fee and Php 9,600.00 for the Health Care Institutional Fee).

^c “Pay Price” for nasopharyngoscopy is based on interview from ENT colleagues.

Table 9. Additional Costs Associated with NPCA Screening*

Procedure	Cost (PHP)
Repeat EBV DNA to rule out transient infection	10,049.00–30,000.00
Nasopharyngoscopy	0–20,000.00 +++
CT scan of the Neck with IV contrast	7,000.00–10,680.00
MRI of the neck with IV contrast	15,000.00 +++
Histopathologic diagnosis including processing	0–3,000.00 +++
Additional stains if with equivocal findings (CK, LCA)	2,000–4,000.00 +++
Cost of radiation to the head and neck	0–150,000.00 +++
Cost of chemotherapy if with high-risk features	0–45,000 +++ (3 cycles of cisplatin or carboplatin)

PHP Philippine peso

* This table does not yet include the cost of additional scans to determine presence of distant metastases in the event of a positive screen.

4.2.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

Social

We found no study discussing the acceptability of NPCA screening. However, some patients might not agree to a nasopharyngoscopy because it is an invasive procedure. In some patients who are anxious, IV sedation might be warranted.

Patients undergoing nasopharyngoscopy may have a potential risk of bleeding, but one study has reported that nasopharyngoscopy had no adverse influence on the local tumor.(31) For the EBV blood test, no adverse effects such as psychological trauma, overdiagnosis and over-treatment because of false positive results were found.

Health Systems

The availability of plasma EBV-DNA is only limited to private hospitals and laboratories in the National Capital Region (NCR), and there are no locally available EBV IgA test kits. To implement NPCA screening, hospitals will need to buy IgA test kits for EBV serology or a PCR machine for EBV-DNA. This might be difficult to implement in primary or secondary hospitals that lack the manpower and expertise to perform these tests.

Additionally, the Philippine Society of Otolaryngology-Head and Neck Surgery only has about 900 members, who are concentrated in major cities Luzon. As present, not all provinces have an ENT surgeon in their locality. For a population of 111 million as of October 2021, the ratio is 1 ENT surgeon for every 123,333 Filipinos. Because of this shortage, ENT surgeons might not be readily available to do the nasopharyngoscopy and/or biopsy should a patient screen positive for the EBV blood test.

4.2.6 Recommendations from Other Groups

No published guidelines on NPCA screening were found in United States Preventive Services Task Force, Canadian Task Force on Preventive Health, National Institute for Health and Clinical Excellence, American Society of Clinical Oncology, European Society of Medical Oncology, and National Comprehensive Cancer Network. The American Cancer Society cited that current screening studies for NPCA do not provide solid evidence of a benefit associated with screening for NPCA.

On free text search, we found a guideline from Hong Kong written in 2018 that recommended to consider screening among patients with a first degree relative with NPCA (Table 10). No systematic review was attached to this recommendation and efforts were placed in contacting the authors but there was no reply.

Table 10. Recommendation of Hong Kong Cancer Expert Working Group on NPCA screening

Group	Recommendation	Strength of recommendation and Certainty of evidence
Cancer Expert Working Group on Cancer Prevention and Screening, Government of Hong Kong Special Administrative Region (May 2018) (32)	For persons at average risk: There is insufficient evidence to recommend a population-based NPCA screening program using IgA against specific Epstein-Barr virus (EBV) viral antigens and EBV DNA test. For persons at high risk: Family members of NPC patients may consider seeking advice from doctors before making an informed decision about screening.	None provided, only gave some references

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4.3 Liver Ultrasound and/or AFP in Screening for Hepatocellular Carcinoma

RECOMMENDATIONS

1. Among asymptomatic, apparently healthy adults, we suggest against the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma.
(weak recommendation, low certainty evidence)
2. Among patients at risk* to develop hepatocellular carcinoma who have or have not progressed to cirrhosis, we recommend the use of ultrasound with AFP every 6 months to screen for hepatocellular carcinoma.
(strong recommendation, moderate certainty evidence)

*Risk factors:

- Hepatitis B and/or C infection
- Metabolic diseases
- Non-alcohol/alcohol liver diseases
- A family history of liver cancer
- Prolonged heavy alcohol consumption
- Men > 40 years old

Considerations

The consensus panel considered the following when formulating this recommendation:

- HCC is a priority health problem.
- The benefits of screening with US and AFP and the tests' diagnostic accuracy outweighed potential harms despite the low certainty of evidence.
- Screening with US and AFP had low-to-moderate certainty of evidence for cost-effectiveness, and was deemed to entail moderate costs.
- Screening with US and AFP had poor acceptability and feasibility, and uncertain equity, with possible important uncertainty or variability regarding patient values and preferences.
- With screening, the number of transplant-eligible patients is expected to increase. However, there are limited facilities that could perform liver transplant.
- There are other treatment modalities for HCC aside from liver transplantation, such as surgical resection, ablation, embolization, and systemic treatments.
- Patients with cirrhosis may be asymptomatic, and diagnosis of cirrhosis would entail similar procedures (i.e., US and AFP).

4.3.1 Burden of disease

Disease Frequency

Hepatocellular carcinoma (HCC) is the 4th leading cause of cancer-related deaths and the 6th most common cancer in the world.(1) In 2020, the incidence rate among men in Southeast Asia was 21.2 per 100,000 population, while it was 13.7 per 100,000 for women.(2)

Management of the Disease

Curative interventions are applicable only at the very early stage of HCC. It is therefore critical to catch HCC at its earliest stage to offer patients a better chance for survival with ablative intervention(s). Screening individuals at risk for developing HCC is an important strategy that will increase the probability of early detection and longer survival.(3–7)

Ultrasonography (US) is a non-invasive imaging procedure that uses soundwaves instead of ionizing radiation (such as those used for X-rays) to produce images of organs inside the abdomen or pelvis. Meanwhile, AFP is a tumor marker which can be quantified in the blood. Among adults, AFP comes from cancers in the liver, testicles, or ovaries. Semiannual US and/or AFP determination has been recommended as a non-invasive surveillance strategy among at-risk individuals in a number of HCC CPGs.(8)

4.3.2 Benefits and Harms of Screening Tests

HCC Mortality and Survival

Based on one RCT with a high risk of bias, screening every 6 months using US and AFP among patients predisposed to develop HCC was associated with a 40% lower risk of HCC-related mortality (95% CI 8% to 61%) compared to unscreened individuals.(9) There was no significant difference between the screened group and the unscreened group in terms of the number of cancers detected. However, there is a significantly higher proportion of HCC detected at an early stage in the screened group. See Appendix C.

Although early detection can lead to longer survival, how much of the benefit is due to earlier diagnosis (lead time bias) is unclear. Almost two thirds of HCC patients are expected to survive for at least 1 year with screening.(9) More than half of HCC patients will still be alive after 3 years if HCC is detected early with surveillance compared to <8% without surveillance. Without surveillance, no HCC patient is expected to live for >3 years. Surveillance improves 4-year survival in more than half of patients and 5-year survival in >40% of patients (Table 11).

Table 11. Survival outcomes and diagnostic yield of US and AFP surveillance (9)

Outcome	Screened Group (N=9,373)	Usual Care Group (N=9,443)	RR (95% CI)
HCC Mortality	32	54	0.60 (0.39, 0.92)
1-year survival	65.9%	31.2%	
2-year survival	59.9%	7.2%	
3-year survival	52.6%	7.2%	
4-year survival	52.6%	0	
5-year survival	46.4%	0	
Cancers Detected	86	67	1.29 (0.94, 1.78)
Stage 1 HCC (Subclinical or Early stage)	52	0	82.07 (5.16, 1305.59)
Small HCC	39	0	
Resectable tumors	40	5	8.06 (3.18, 20.41)

HCC hepatocellular carcinoma; RR risk ratio

Harms Associated with HCC Screening

Although US and AFP as a screening tool for HCC causes minimal discomfort and no real physical harm, there are risks associated with the performance of confirmatory tests for patients with positive screening results.(10) Confirmatory US and contrast-enhanced CT scan carry a 10% risk of mild adverse events.(11) Needle track seeding of cancer cells is a potential risk associated with biopsy of hepatic tumors, which can be as high as 0.9% per annum.(12)

A presumptive diagnosis of HCC can also result in psychological distress among patients.(3,13) On the other hand, false negative results from screening can also be devastating for patients who will eventually be diagnosed with HCC at a much later stage.(3) Cancer screening (particularly for breast, lung, colorectal, prostate, and cervical malignancies) has been shown to be associated with low level of psychological distress.(14) However, there are no studies evaluating psychological distress among patients who have undergone HCC screening, much less among those given a presumptive HCC diagnosis after screening. As there is considerable false positive rate associated with HCC screening,(15) it will be prudent to look into this often-neglected harm that may be inflicted on patients.

4.3.3 Diagnostic Performance of Screening Tests

We identified an RCT (n=9,373; very low certainty of evidence) reporting the accuracy of US alone or combined with AFP in HCC surveillance among patients with Hepatitis B.(15) AFP surveillance used a locally-developed enzyme-linked immunoassay kit with a detection cutoff of 20 µg/L. HCC diagnosis was confirmed histologically or through long-term follow up. A total of 20,243 screening tests were performed for this study. The sensitivity, false positive rate, and positive predictive value (PPV) for US alone were 0.84, 0.03, and 0.07, while for US and AFP, the values were 0.92, 0.08, and 0.03, respectively (Table 12). See Appendix C.

Table 12. Accuracy parameters and cost for US and/or AFP in HCC screening among Hepatitis B patients in Shanghai, PRC (15)

Parameters	US Alone	AFP Alone	US + AFP
Sensitivity	84%	69%	92%
False Positive Rate	2.9%	5%	7.5%
PPV	6.6%	3.3%	3%
Cost per HCC detected	USD 1,982	USD 3,029	USD 3,639

HCC *hepatocellular carcinoma*; PPV *positive predictive value*; US *ultrasound*; USD *United States dollar*

The major limitations of this study were the sequential steps between screening tests (AFP and US) and biopsy for those who tested positive in at least one screening method, and the non-performance of confirmatory examination(s) among patients who had negative US and AFP screening tests. These could have introduced verification bias.

4.3.4 Cost Implication

We did not find any study on cost-benefit analysis of HCC screening among the general population. In an informal survey of four stand-alone laboratories in Manila, the local cost of liver US (single organ) ranged from PHP 600.00–700.00, and quantitative AFP determination ranged from PHP 850.00–2,000.00. In an online search, we were able to determine that rapid qualitative AFP test kits cost PHP 10.00–30.00 each at alibaba.com, and about PHP 70.00 at homehealth-uk.com. The cost of the test kit is exclusive of the cost of foreign exchange transaction, delivery charges, applicable duties and taxes, other supplies, waste disposal, and personnel salary.

The cost of saving lives through screening will include the cost of detection (screening and confirmatory testing) and of treatment (see Table 12 and Table 13). The costs related to harms associated with screening, opportunity costs incurred in the course of screening, confirmation, treatment, rehabilitation, and palliation, morbidities as well as mortalities have to be taken into consideration. These costs may be shouldered by the patient, the family, and/or society. It has to be emphasized that cost will also vary with the prevailing rates in the locality, as well as with the inflation rate over time.

It will cost much more to save lives with screening because of the added expenditures related to treatment. The cost estimates of screening individuals who have liver cirrhosis in France and the United States are given in Table 13. A Markov model was used in the economic evaluation of two strategies of surveillance of patients with cirrhosis: the first is using biannual US, and the second is with actual or real-life monitoring. Prevailing unit costs in 2012 for France, and from 2010–2016 for the United States were used. The incremental cost of lives saved is the difference between the combined costs of HCC diagnosis and treatment without the benefit of screening, and the cost HCC screening, confirmatory testing, and treatment if surveillance is carried out. Incremental cost effectiveness ratio (ICER) for each life year gained with semiannual monitoring in France was nearly USD 1,800.00 while it was almost USD 32,500.00 in the United States. This disparity was largely due to the unit prices being four to ten times higher in the latter.(16)

Table 13. Cost of HCC surveillance, diagnosis, and treatment among patients with cirrhosis in France and the United States (16)

Setting	France		United States	
<i>Surveillance Strategy</i>	Semiannual US	Real Life Monitoring	Semiannual US	Real Life Monitoring
Cost per HCC Case (USD)	87,476	86,829	93,795	81,829
<i>Cost Difference (USD)</i>	648		11,965	
<i>Estimated LYG (year)</i>	0.37		0.37	
<i>ICER per LYG (USD)</i>	1,754		32,415	

US ultrasound; HCC Hepatocellular Carcinoma; LYG Life Year Gained; ICER Incremental Cost-Effectiveness Ratio; USD United States dollar

Cost estimates in France are based on 2012 French National Claims database; that for the US on Medicare Outpatient Prospective Payment System data from 2010 to 2016
 Benefit accrued from early diagnosis and access to first-line curative treatment: Radiofrequency Ablation had the best value for money compared to Liver Resection and Liver Transplantation
 Unit cost of procedures and visit to doctors 4–10x higher in the United States

Among patients at risk to develop HCC in the United Kingdom, surveillance using semiannual US and AFP was estimated to more than triple the number of patients with operable tumors at the time of diagnosis and reduce HCC mortality by nearly 50% compared to no screening, at a lifetime cost of USD 78,600 per HCC detected.(17) The great per capita cost of the program was primarily driven by interventions related to treatment. In particular, surveillance is projected to significantly increase the proportion of HCC patients who will be eligible to undergo liver transplantation.

In the overall context of a health system with finite resources, opportunity costs of programs have to be considered. It is not enough to evaluate the program efficacy, benefits, harms, and costs. It is also necessary to assess the other programs that will be displaced and their attendant benefit, harms, and costs that will be foregone.(18)

4.3.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

Ethical

The combination of US and AFP is more likely to be a cost-effective HCC screening strategy among patients with cirrhosis secondary to Hepatitis B compared to patients with cirrhosis secondary to alcoholic liver disease.(17) Particular attention has to be given to chronic viral hepatitis patients who have progressed to cirrhosis because the proportion of patients who will develop HCC in this patient population can be as high as 40%.⁽¹⁹⁾ Risk factors that increase the likelihood of HCC have to be considered when selecting subjects who are eligible to undergo surveillance. Table 14 summarizes the risk associated with some of these predisposing factors.⁽²⁰⁾

Table 14. Annualized probability of HCC for the different risk factors associated with the condition (20)

Cirrhosis Status	Risk Factor	Annualized HCC Risk
Patients with Cirrhosis	Hepatitis C	2–7%
	Hepatitis B	3–5%
	Genetic Hemochromatosis	NA
	Primary Biliary Cirrhosis	2–3%
	Nonalcoholic Steatohepatitis	NA
	Alpha 1 Antitrypsin Deficiency	NA
	Autoimmune Hepatitis	NA
Non-Cirrhotic Hepatitis B Carriers (HBs Ag +)	Asian Male, > 40 years of age	0.4–0.6%
	Asian Female, > 50 years of age	0.3–0.6%
	Africans, > 20 years of age	NA
	Family History of HCC	NA

HCC *Hepatocellular Carcinoma*

To determine if the survival benefits of US and/or AFP screening among Hepatitis B patients were consistent with the reported survival benefits of screening among patients with cirrhosis and those with Hepatitis C, we looked for relevant studies that considered these populations of interest. In a systematic review and meta-analysis of 47 mostly retrospective studies (n=15,158) that examined HCC detection, treatment, and survival among patients with cirrhosis using US and/or AFP, surveillance was associated with longer HCC-related survival rate.(7) Surveillance was also associated with early diagnosis, receipt of curative treatment, and longer survival. However, the overall quality of this evidence is very low because of the retrospective design and the insufficient follow-up duration in most studies, as well as failure to adjust survival based on liver function or lead time bias.

In an Australian cohort of HCC patients (n=272) with mixed etiologies (41% from Hepatitis C, 39% from alcohol-related liver disease, and 22% from Hepatitis B), participation in HCC screening was significantly associated with lower mortality and receipt of curative intervention.(21) Similarly, in an Italian mixed cohort of chronic Hepatitis B and Hepatitis C patients (n=8,900), surveillance increased the proportion of HCC patients with potentially curable disease and improved HCC-related survival.(19)

The accuracy of US is highly dependent on the expertise of the technician and the reader.(3,22) It has been shown that in settings where there is paucity of expert sonologists, the addition of AFP in the screening modality improves HCC detection rate.(23,24) US may also be less accurate among obese individuals and patients with nodular cirrhosis.(22) The technical specifications of US machines are also important parameters in HCC surveillance. Tzartzeva and colleagues demonstrated increasing US sensitivity when they compared surveillance studies done prior to 1990 to those done after 2000.(25)

Evaluating the rate of AFP rise instead of relying on the most recent AFP level may improve the accuracy of AFP as an adjunct in HCC screening.(26) There also be racial differences with respect to the level and prognostic value of AFP.(27)

In HCC screening programs, the availability and accessibility of therapeutic intervention(s) have to be ensured to realize the survival benefit associated with HCC surveillance.(28) However, surveillance with US and/or AFP may not result in HCC-related survival benefits among patients with cirrhosis (29) much less among those with advanced liver disease or decompensated cirrhosis (Child-Pugh B or worse) (30,31) because of the patients' poor response to treatment.

Social

We found no study on patient preferences with respect to HCC screening. However, in a review of stated preferences in breast, cervical, and colorectal cancer surveillance, important determinants of patient choice were identified to be efficacy, process, and costs of the screening methods.(32)

4.3.6 Recommendations from Other Groups

We found no guideline recommending HCC screening in the general population, but several guidelines recommend screening of patients with risk factors. While the exact criteria for the population at risk to develop HCC differ slightly depending on the geographic region, it is generally accepted that groups with Hepatitis B and/or C infection, those with cirrhosis of any cause, individuals with a family history of liver cancer, those with prolonged heavy alcohol consumption, and men older than 40 years are at an increased risk of developing HCC.(33) For these groups, many CPGs recommend HCC surveillance using US and/or AFP. A review of surveillance recommendations (8) revealed the following guidelines from various professional groups (Table 15).

Table 15. Summary of key recommendations from different groups (8)

Group	Recommendation
Asia Pacific Association for the Study of the Liver	US and AFP every 6 months
Korean Liver Cancer Association – National Cancer Center	US and AFP every 6 months
American Association for the Study of Liver Diseases	US and/or AFP every 6 months
Liver Imaging and Reporting Data System	US and/or AFP every 6 months
European Association for the Study of the Liver	US surveillance every 6 months

US *ultrasound*

In general, CPGs from the Americas and Europe recommend semiannual US surveillance of patients at risk for HCC, while CPGs from Asia recommend semiannual screening with US and AFP. (23,34–36)

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4.4 HPV Testing, Cytology, Co-Testing, or VIA in Screening for Cervical Cancer

RECOMMENDATIONS

1. Among women aged 21 to 29 years, we recommend against screening for cervical cancer with cervical cytology or any alternative screening tests. (*strong recommendation, low certainty evidence*)
2. Among women aged 30 to 65 years, we recommend screening for cervical cancer every 3 years with cervical cytology alone or every 5 years with high-risk HPV testing alone. (*strong recommendation, low certainty evidence*)
3. Among women aged 30 to 65 years, we recommend against screening for cervical cancer every 5 years with high-risk HPV testing in combination with cytology (co-testing). (*strong recommendation, very low certainty evidence*)
4. Among asymptomatic women aged 30 to 65 years old, we recommend screening for cervical cancer every 3 years using visual inspection with acetic acid, as an alternative to Pap smear. (*strong recommendation, moderate certainty evidence*)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Cervical cancer is a priority health problem
- The panelists favored screening using HPV testing, cytology, or co-testing as it was deemed to have moderate benefit with small harm and very low certainty of evidence. Majority of the panelists still favored screening due to these judgments.
- Screening using HPV testing, cytology, or co-testing was deemed to have high diagnostic accuracy
- Screening using HPV testing, cytology, or co-testing was deemed to entail large costs with a low to moderate certainty of evidence on the required resources. Majority of the panelists still favored screening.
- Screening using HPV testing, cytology, or co-testing was deemed to be equitable, acceptable, and feasible with possibly important uncertainty or variability in terms of patient values and preferences

Remarks

- Despite the low level of evidence, the panelists recommended against screening for women aged 21–29 years old due to evidence presented on the decreased prevalence of disease in this age group, the higher rates of regression and clearance in this age group, as well as considerations on acceptability.

- A strong recommendation was given for screening with hrHPV testing alone among women aged 30–65 years despite the low level of evidence and low accessibility of hrHPV testing due to its high diagnostic accuracy. The option of cervical cytology alone is also presented; hence, screening would not be hindered among this age group.
- There is a strong recommendation against screening with hrHPV testing and cervical cytology (co-testing) among women aged 30–65 years old despite of the limitations due to hrHPV testing detailed above because of the limited marginal benefit, additional costs, and potential harms to the patient when conducting both tests.

4.4.1 Burden of disease

Disease Frequency

The global disease burden of cervical cancer is high, with an age-standardized mortality rate of 7.9 per 100,000 population.(1) However, there is a wide disparity in the incidence and mortality of cervical cancer among developed and undeveloped countries, with 85% of cases and deaths occurring in LMIC.(2) In the Philippines, 7,897 new cases and 4,052 deaths were recorded in 2020 (1), and the age-standardized mortality rate was 7.3 per 100,000 in 2012.(3) Possible reasons for the consistently high mortality rate include diagnosis at an advanced stage, and the lack of availability and high treatment costs.(4) Although a preventable disease, screening and vaccination programs are not widely available in developing countries. As of 2020, only 44% of women in LMIC have been screened for cervical cancer compared to more than 60% of women in high-income countries.(5)

Human Papillomavirus (HPV) infection is common among women under 30 years old, particularly in those between 20–24 years old. HPV infection is usually cleared in this age group as opposed to women older than 30 years old.(6)

Management of the Disease

Around 60% of cervical intraepithelial neoplasia grade 1 (CIN1) will spontaneously regress after 1 year; hence, the American Society for Colposcopy and Cervical Pathology recommended observation.(7,8) In all nonpregnant patients with a diagnosis of histologic high-grade squamous intraepithelial lesion (HSIL) or CIN3, treatment with loop electrosurgical excision procedure (LEEP) or cryotherapy is recommended. Nonpregnant patients with histologic HSIL (CIN2) are usually recommended to get treatment unless the patient is desirous of pregnancy, which outweighs the risk for cervical cancer.(8) For Stage IA1, IA2, IB2 and IIA, patients may undergo hysterectomy and adjuvant chemoradiotherapy; those with poor prognostic factors such as positive margins, positive lymph nodes, and parametrial involvement may undergo adjuvant chemotherapy and radiation. For FIGO IB2, IIB and IIIB, patients may undergo concurrent chemoradiotherapy, or neoadjuvant chemotherapy followed by adjuvant treatment.(9)

4.4.2 Benefits and Harms of Screening Tests

Cytology and Primary HPV testing

A cluster RCT conducted in India investigated the effect of HPV testing using the Hybrid Capture II assay, cytology, and visual inspection with acetic acid (VIA) in 52 clusters among women 30–59 years old (n=131,476).⁽¹⁰⁾ Participants were randomized into four groups with 12 clusters each [HPV testing (n=34,126), cytology (n=32,058), VIA (n=34,074), and control (n=31,488)] with an 8-year follow-up. See Appendix D.

There were more cases of CIN2+ detected with cytology or HPV testing (Table 16). There was also a 53% reduction in the detection of cervical cancer (Stage II and above) in the HPV testing group. Moreover, 34 deaths due to cervical cancer were noted in the HPV testing arm and 64 deaths in the control group, showing decreased risk of cervical-cancer related mortality. However, the study did not show any reduction in advanced cervical cancer (Stage II and above) or death using cytology or VIA testing. The age-standardized rate of invasive cancer among those with negative results on cytologic testing or VIA was more than four times than that of HPV-negative women, highlighting the high negative predictive value (NPV) with HPV testing.

Table 16. Effect of HPV and cytology testing on cervical cancer detection, CIN detection and death (10)

Outcome	Test	Effect Measure (95% CI)	Interpretation
Incidence of CIN2+	Cytology	RR 8.60 (6.49, 11.40)	More cases detected with cytology
	Primary HPV testing	RR 6.65 (5.01, 8.83)	More cases detected with HPV testing
Incidence of all cervical cancer	Cytology	HR 1.34 (0.99, 1.82)	Not significant
	Primary HPV testing	HR 1.05 (0.77, 1.43)	Not significant
Incidence of stage II and above cervical cancer	Cytology	HR 0.75 (0.51, 1.10)	Not significant
	Primary HPV testing	HR 0.47 (0.32, 0.69)	Decreased incidence of stage II and above cervical cancer on the HPV testing group
Cervical cancer-related mortality	Cytology	HR 0.89 (0.62, 1.27)	Not significant
	Primary HPV testing	HR 0.52 (0.33, 0.83)	Decreased death on the HPV testing group

HPV human papillomavirus; HR hazard ratio; RR risk ratio

In a model commissioned by the United States Preventive Services Task Force comparing the risks and benefits of various screening strategies, various screening strategies resulted in reduction in cervical cancer and deaths, and gain in life-years.⁽¹¹⁾ Moving from cytology testing from age 21 to primary high-risk HPV testing at 30 years was the most efficient, based on the model. Strategies involving co-testing were not deemed efficient.

Cytology and Co-Testing

There were no randomized studies retrieved investigating the effect of HPV co-testing on mortality and detection of CIN and invasive cancer compared to a no-screening approach. Indirect evidence from five major RCTs comparing HPV-based screening to cytology alone were found (Table 17). In these trials, women aged 20–80 years old were recruited to participate (n=10,154–45,174).^(12–19) Most trials were from Europe

(SWEDESCREEN, ARTISTIC, POBASCAM, and NTTC Phase I) (12–18), while the only study conducted in Asia was done in China.(19) All trials used conventional cytology as the control except for NTTC Phase 1 (16) and Chan et al. (19) which used liquid-based cytology. Trials also differed in the frequency of screening (every 3–5 years) as well as types of tests used in detecting HPV. Majority of the trials were deemed at risk for bias due to low follow-up rates. See Appendix D.

Table 17. Effect of HPV co-testing compared to cytology testing on cervical cancer detection, CIN detection and death

Outcome	Round	RR (95% CI)	Interpretation	No of studies, sample size (n)
Incidence of CIN2+	1	1.60 (1.23, 2.08)	More cases detected with co-testing	5 studies (n=138,174)
	2	0.69 (0.51, 0.93)	Less cases detected with co-testing	5 studies (n=124,271)
	C	1.23 (1.05, 1.44)	More cases detected with co-testing	5 studies (n=138,174)
Incidence CIN3+	1	1.30 (0.98, 1.72)	Not significant	5 studies (n=138,174)
	2	0.67 (0.54, 0.83)	Less cases detected with co-testing	5 studies (n=124,271)
	C	1.05 (0.89, 1.23)	Not significant	5 studies (n=138,174)
Incidence of cervical cancer	1	0.97 (0.21, 4.56)	Not significant	2 studies (n=64,618)
	2	0.51 (0.08, 3.13)	Not significant	2 studies (n=53,540)
	C	0.70 (0.40, 1.23)	Not significant	3 studies (n=77,142)

RR risk ratio

Adverse Events

The cluster RCT by Sankarayanan et al. reported mild adverse events in 123 women, and a severe adverse event in a woman who experienced bleeding after undergoing LEEP, resulting in eventual hysterectomy among those screened with HPV, cytology or VIA and subsequently treated.(10)

In the ARTISTIC trial, a sample of women from both the intervention (received both HPV and cytology results) and screening group (received cytology results only) answered the General Health Questionnaire (GHQ-28), the Sexual Rating Scale (SRS), and the Spielberger State-Trait Anxiety Inventory.(14) Although there was no difference in distress and anxiety after receiving the results, women in the intervention group reported lower sexual satisfaction. Observational comparisons also showed that women in the intervention arm that were hrHPV+ with normal cytology were at higher odds for psychological distress (OR 1.70, 95% CI 1.33 to 2.17).

NTTC Phase I, POBASCAM, SWEDESCREEN and ARTISTIC trials also reported false positive rates of co-testing compared to cytology (Table 18), which were summarized by Melnikow.(20) See Appendix D.

Table 18. False positive rates for CIN2+ as reported in clinical trials

Round	Study group	NTTC Phase 1	POBASCAM	SWEDESCREEN	ARTISTIC
1	Intervention	2,702/22,042 (12.3%)	1,149/19,742 (5.8%)	NR	3,566/17,933 (19.9%)
	Control	771/21,972 (3.5%)	513/19,913 (2.6%)	72/6,192 (1.2%)	653/5,991 (10.9%)
2	Intervention	NR	610/9,572 (6.4%)	NR	1,178/10,512 (11.2%)
	Control	NR	612/9,450 (6.5%)	NR	176/3,832 (4.6%)

Relevant Subgroups

Due to the high prevalence of transient HPV infections between women aged 21–29 years, United States Preventive Services Task Force recommended the use of cytology alone for this age group.(21) In trials that compared HPV testing and cytology, higher detection rates were observed among women less than 30 or 35 years old when cytology was used.(16,22–24) Modeling studies also showed that switching from cytology to primary HPV testing at ages 25, 27 and 30 produced minimal differences in life-years gained (LYG). Moreover, testing with primary HPV at 25 years old increased the number of colposcopies done.(15) Thus, primary HPV testing may be commenced at 30 years old.(21) See Appendix D.

Patients at high risk for cervical cancer (immunocompromised patients and exposure to diethylstilbestrol [DES]) were not included in the guidelines and most studies.

4.4.3 Diagnostic Performance of Screening Tests

A Cochrane review showed that HPV testing may detect more cases of CIN2 and CIN3 due to its higher sensitivity compared to cytology.(25) This comes at the cost of more unnecessary referrals for procedures such as colposcopy due to false-positives. A negative HPV test may be more reassuring than a negative cytologic exam since the latter has a higher chance of false-negativity, which may translate to delayed treatment. Although no RCTs comparing HPV co-testing and primary HPV testing are available, some studies show that there is limited added benefit with the combination approach.(16,26,27)

Two high-quality RCTs demonstrated the diagnostic accuracy of a Pap smear, HPV DNA test, and co-testing. One study was conducted among women aged 30–69 years old (n=10,154) who sought cervical cancer screening in Canada with either Pap smear or HPV test, using the Hybrid Capture 2 test and biopsy as the gold standard.(28) In another study, Pap smear was compared to co-testing with Pap smear and HPV test on a subgroup of the intervention arm of an RCT (n=6,257) to determine sensitivity and specificity.(13) Table 19 summarizes the diagnostic accuracy among the three different tests. See Appendix D.

Table 19. Diagnostic accuracy of the three screening tests based

	Mayrand et al (CIN2-3) (28)	Naucler et al (CIN2+) (13)

	Pap smear (95% CI)	HPV (95% CI)	Co-testing (95% CI)	Pap smear (95% CI)	HPV (95% CI)	Co-testing (95% CI)
Sensitivity	55.4% (33.6, 77.2)	94.6% (84.2, 100)	100%	71.3% (60.6, 80.5)	95.4% (88.6, 98.7)	100% (95.8, 100)
Specificity	96.8% (96.3, 97.3)	94.1% (93.4, 94.8)	92.5%	98.6% (98.3, 98.9)	94.2% (93.5, 94.7)	NR

CI confidence interval; HPV human papillomavirus

4.4.4 Cost Implication

HPV testing and co-testing are more costly compared to cytology-based testing. In addition, false-positives from HPV testing may result in more referrals for colposcopy.(29)

A local cost-utility analysis was performed using a semi-Markov model evaluating screening (VIA and Pap smear) alone or in combination with vaccination against HPV infection using various coverage implementations.(30) Pap smear was not deemed to be cost-effective due to its high cost.(30)

A cost-effectiveness analysis in Thailand was conducted on different screening strategies (cytologic testing every 3 years from 21–65 years of age with either repeat cytology or hrHPV triage for atypical squamous cells of undetermined significance; cytologic testing every 3 years for women aged 21–29 years followed by co-testing; or primary hrHPV testing alone for women aged 30–65 years). Cytology in women who were 21–29 years old, followed by low-cost HPV screening every 5 years or cytology every 3 years, was the most feasible strategy based on benefits, harms and costs.(31) Table 20 shows the cost of testing and treatment for preinvasive lesion.

Table 20. Estimated annual cost of screening for cervical cancer

Parameter	Screening intervention		
	Pap Smear	Primary HPV Testing	Co-Testing
Unit cost of screening intervention (PHP per year)	PHP 225 ^a PHP 500 ^b	PHP 5,400 ^b	PHP 225 ^a PHP 500 ^b
Unit cost of treatment (PHP per year) ^c	Colposcopy PHP 10,000–15,000 Cryotherapy PHP 1,500 LEEP PHP 12,644.50 Cold knife conization PHP 8,100.36 Simple hysterectomy PHP 41,362.67		

PHP Philippine peso

^a Price based form PGH; ^b Price based from Hi-Precision Diagnostics; ^c Values based on the 2015 cost-utility study conducted in the Philippines (29)

4.4.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

Eighty-seven percent of new cervical cancer cases and 91% of all cervical cancer-related deaths occur in LMIC, highlighting the global disparity of this disease.(32) This imbalance in cases is due to the lack of infrastructure and available screening tests in developing nations precluding the implementation of nationwide screening programs.(33) In a systematic review on the barriers of cervical cancer screening in LMIC, lack of knowledge

and understanding on the roles of these tests was identified as a barrier to uptake of cervical screening.(34) Factors which may enable cervical cancer screening include level of education, living in an urban area, and employment outside of home.

4.4.6 Recommendations from Other Groups

Table 21 summarizes key recommendations from various groups on screening for cervical cancer.

Table 21. Summary of key recommendations from different groups

Guideline	Recommendation
American Association of Obstetricians and Gynecologists (2021) (35)	Adopted United States Preventive Services Task Force recommendation
American Cancer Society (2020) (36)	The ACS recommends that individuals with a cervix initiate cervical cancer screening at age 25 y and undergo primary HPV testing every 5 y through age 65 y (preferred). If primary HPV testing is not available, individuals aged 25-65 y should be screened with cotesting (HPV testing in combination with cytology) every 5 y or cytology alone every 3 y (acceptable) (strong recommendation).
US Preventive Services Task Force (2018) (21)	Recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21 to 29 years. Recommends screening every 3 years with cervical cytology alone, every 5 years with hrHPV testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting) in women aged 30 to 65 years.
Department of Health (2009) (4)	Women 25-55 years old will undergo VIA (with acetic acid wash) cervical cancer screen at least once every 5-7 years in areas with no Pap smear capability, otherwise Pap smear will be used; Acetic acid wash (3-5%) will be used as the primary screening method at local health units (rural health units; health centers), district hospitals and provincial hospitals with no Pap smear capability; VIA will be used as a triage method before Pap smear at district, provincial and regional hospitals with Pap smear capability; Positive or suspicious lesion noted upon screening will be referred immediately; and Referral centers for cervical cancer diagnostic tests and treatment will be established in tertiary facilities.

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4.5 ENT Screening and Dental Check-Up in Screening for Oral Cancer

RECOMMENDATION

1. Among asymptomatic apparently healthy adults aged 35 years and older, we suggest screening for oral cancer once every 3 years by trained health workers.
(no consensus, low certainty evidence)
2. Among adults aged 35 years and older who are smokers and/or alcohol drinkers, we recommend screening for oral cancer **using visual and tactile inspection** once every 3 years by trained health workers.
(strong recommendation, moderate certainty evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Oral cancer is a priority health problem.
- Majority of panelists favored annual ENT screening and dental check-up due to the large benefit and good diagnostic accuracy despite the moderate costs and low certainty of evidence.

Remarks

- The panelists were unable to reach consensus for the first recommendation. Those who were for the screening cited its simplicity and lack of risk to the patient, while those against the screening were concerned with the low impact of screening among low-risk patients and the potentially increased burden on the health system (i.e., confirmatory testing).

4.5.1 Burden of disease

Oral cancer is one of the most common HNCs in the Philippines, most often in the form of squamous cell carcinoma.(1) Over 7,400 new HNCs were identified in 2015 alone, making up 6% of incident malignancies in the country for that year.(2,3)

The Philippines has experienced a decreasing trend in incidence of oral cancer over the years, from 5.3 per 100,000 in males and 6.2 per 100,000 in females between 1980–1982 to 3.4 per 100,000 in males and 2.9 per 100,000 in females between 1998–2002.(4,5) The age-adjusted mortality rate of oral cancer in the local setting is 4.41 per 100,000 population.(4) Tobacco and alcohol use are the most common risk factors for the development of disease (1), but quid and smoking are the most common risk factors in the Philippines, according to a narrative review on oral cancer in Asia.(5,6) It is of note that these epidemiological data were confined to two areas only in the Philippines.

The relatively low incidence rates of oral cancer seemed to result in the little attention given to oral cancer in the national cancer program, although the Philippine Cancer Control Program provided preventive measures for tobacco use under the lung cancer control program.(7) Specialists, however, believed that primary care physicians and dentists should include periodic oral cancer screenings for smokers, alcohol drinkers, and individuals with suspected oral cancer lesions.(8)

4.5.2 Benefits and Harms of Screening Tests

There was no evidence found on oral cancer screening using adjuncts such as toluidine blue and fluorescent light versus no screening program.

A Cochrane review (9) that included a RCT with six publications (10–15) was used to examine the evidence on benefits and harms of a screening program for oral cancer. The trial began in October 1995 and included four cycles of screening at 3-year intervals. The first round ended in May 1998, and the second in June 2002. The final round occurred in October 2004 and final screening in 2009. All participants (n=191,873) were apparently healthy individuals aged ≥35 years living in 13 rural clusters in Trivandrum City, Kerala, India. Each cluster had a mean of 14,759 eligible individuals. Those who were bedridden, had open tuberculosis or other debilitating diseases, or who had previously been diagnosed with oral cancer were not eligible for this study.

The screening was carried out by health workers who were non-medical university graduates, trained and provided with visual aids and descriptions of oral lesions. In the screening arm, eligible participants underwent the following: (a) an interview to gather demographic, social, and personal habits, as well as the use of paan, tobacco, alcohol, and food supplements; (b) advice on tobacco and alcohol cessation if appropriate; (c) oral visual inspection with flashlight; and (d) palpation of oral sites and neck to assess enlarged lymph nodes. Sites assessed were labial and buccal mucosa, retromolar area, gingiva, anterior tongue, floor of mouth, and hard palate.

Participants who tested positive in the screening (i.e., those with referable lesions: white lesions, ulcerated or nodular lesions, verrucous lesions, red lesions, oral submucous fibrosis) were directed to a dentist or physician for confirmation. It was unclear if these physicians had been fully trained to recognize mouth cancer or possibly malignant condition. Oral biopsies were taken from patients who had homogenous or non-homogeneous leukoplakias, oral submucous fibrosis, or oral malignancies. Whenever feasible, surgical removal of leukoplakia was performed. All PMDs were evaluated on a regular basis.

The RCT reported quantitative data on oral cancer incidence, oral cancer mortality, stage at diagnosis after 15-years follow-up, and survival rate (Appendix E). There were no available data for all-cause mortality. Efficiency of screening was also analyzed based on hypothetical trajectory from mortality rates.

Oral Cancer Mortality among All Adults at 15 Years

There were 279 individuals in the screening group and 244 in the control group who were diagnosed with oral cancer from 1996–2010. Over a 15-year follow-up, 138 of 279 subjects with oral cancer in the intervention group and 154 of the 244 cases in the control group died.(12) The screening arm had a 12% lower death rate than the no-screening arm, although this difference was not statistically significant.

Oral Cancer Mortality among All Adults at 9 Years

Short-term follow-up showed a much lower risk of mortality (32%) in individuals who were screened (n=205) compared to those who were not screened (n=158) and all who were diagnosed with oral cancer from 1996–2004.(11)

Oral Cancer Mortality among High-Risk Individuals at 15 Years

Benefit was more apparent when death from oral cancer was compared among high-risk individuals or those who were tobacco and/or alcohol users who were screened (n=254) or not screened (n=232) for oral cancer (RR 0.80, 95% CI 0.69 to 0.94).(12)

Oral Cancer Mortality among High-Risk Individuals at 9 Years

The risk of oral cancer mortality decreased further among screened high-risk individuals than those who were not screened and who diagnosed with oral cancer from 1996–2004 (RR 0.68, 95% CI 0.54 to 0.86).(11)

Five-Year Survival Rate

A significantly higher 5-year survival rate was recorded in the intervention group than in the control group (n=523; 50% vs. 34%, $p=0.009$).(11,12)

Oral Cancer Incidence

Among the participants in the screening group (n=96,517), 6.3% were identified to have referable lesions.(12) Out of 5,586, 59% had gone for confirmatory evaluation by dentists or physicians in the special clinics. Of those diagnosed with potentially malignant disorder, 499 (21.4%) underwent biopsies and 22 of them had confirmed squamous cell carcinoma. Of those diagnosed with suspicious growths, 166 had squamous cell carcinoma or verrucous carcinoma.

Proportion of Cancers at Stage III or Worse

Oral malignancies were classified based on the International Union Against Cancer TNM (tumor, node, metastasis) staging method. Unlike the two mentioned outcomes examined at 15 years, there was a statistically significant benefit of shifting the stage.(13) There was lower proportion of cancers at Stage III or higher among those who were screened (52.6%) than those who were not or had delayed screening (65.2%) (RR 0.81, 95% CI 0.70 to 0.93).(13)

Quality of Life and Harmful Effects of Screening

There were no available data on quality of life and psychological effects among screened participants, particularly among those who were assessed to have suspicious lesions and referred to specialists for biopsies. There were no cases of severe adverse events such

as mortality, vaso-vagal attack, anaphylactic response, hemorrhage, hospitalization, infection, severe pain, or other adverse reactions (cosmetic or functional disabilities) as a result of screening, biopsies, or removal of lesions.(12)

Efficiency of Screening

In two hypothetical strategies for selection of individuals based on the hazard of oral cancer mortality, a risk-based selection of individuals for screening provided greater sensitivity for oral cancer mortality.(14) Restricting the screening to high-risk population (43.4%) resulted to 974 oral cancer deaths averted in the next 9 years per 1 million screened.(14) On the other hand, screening all adult population showed 490 oral cancer deaths averted in the next 9 years per 1 million screened.

4.5.3 Diagnostic Performance of Screening Tests

Visual examination was found to have a sensitivity of 0.67 in detecting oral cancer.(12) There was insufficient information to deduce the program's specificity or PPVs in the trials across the 4 cycles of the screening program. However, in the study published in 2003, the screening program consisting of visual and tactile inspection performed by trained non-medical university graduates compared with a reference test of clinical confirmation by specialists had a sensitivity of 0.82 and a specificity of 0.85.(11)

4.5.4 Cost Implication

In a low-resource country like India, the benefit of the screening program was 269.31 life-years saved per 100,000 for all individuals and 1,437.64 life-years for those at high risk.(15) The incremental cost per life-year saved was USD 835.00 for all individuals, which decreased to USD 156.00 for individuals with high risk for oral cancer.(15)

Visual examination for oral cancer screening was found to be cost-effective.(15) Over the duration of a 9-year screening program, visual examination may be performed for less than USD 6.00 per individual who is eligible for screening while considering the cost of diagnostic tests, treatment required and the associated patients' time, which was based on daily minimum wage of USD 5.00.(15)

4.5.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

There were no local studies available that tackled issues on equity and acceptability of an oral cancer screening test or program. However, in a study on Filipinos' interest in oral cancer, it was found that residents in the tobacco-producing regions of the Philippines had sought information on oral cancer.(16) Due to the insufficient epidemiological studies, this finding is difficult to interpret. Nevertheless, it provides some information on health-seeking behavior among the residents in these areas. The study also noted that the Philippine Dental Association provided general public education programs on oral health, particularly during National Oral Health Month. However, the Association has not provided a comprehensive oral cancer screening and has not yet collaborated with the Philippine

Cancer Society.(16) To date, there is no national program for oral cancer screening in the Philippines.(7)

4.5.6 Recommendations from Other Groups

The American Dental Association, as part of a good practice statement for evaluation of potentially malignant disorders, suggested that clinicians should perform an intraoral and extraoral conventional visual and tactile examination on all adult patients.(17)

The National Comprehensive Cancer Network® had no specific recommendations about screening for oral cancers.(18) While the United States Preventive Services Task Force had no recommendation on screening for oral cancers among asymptomatic adults aged ≥18 years who were seen by primary care providers, this was due to the belief that there was insufficient evidence to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults.(19)

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4.6 Fecal Immunochemical Test in Screening for Colorectal Cancer

RECOMMENDATIONS

Among average risk and apparently healthy adults, there is insufficient evidence to suggest screening for colorectal cancer using fecal immunochemical test over fecal occult blood test.

(no recommendation, insufficient evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- CRC is a priority health problem.
- Majority of panelists favored screening using FIT due to the large benefit, small harm, and diagnostic accuracy of the test.
- Screening using FIT was perceived as acceptable and feasible, would probably increase equity, and is with possible important uncertainty or variability in terms of patient values and preferences.
- Other Asian populations use FIT for screening CRC.

Remarks

- The evidence examined was indirect as the studies compared FIT with no screening.

4.6.1 Burden of disease

Disease Frequency

Colorectal cancer (CRC) is currently the third leading site of malignancy for both sexes in the Philippines.(1) Incidence for CRC has been escalating from 9,625 cases in 2015 to 17,364 in 2020.(1,2) The estimated 5-year prevalence across all ages was 23.65 per 100,000 for colon cancer and 13.30 per 100,000 for rectal cancer. The age-standardized incidence rates were 23.7 per 100,000 for men and 15.1 per 100,000 for women. In 2020, CRC accounted for 9.8% of cancer-related deaths across all cancer sites.(1–3)

Management of the Disease

CRC is diagnosed via biopsy through scoping procedures like colonoscopy or sigmoidoscopy. Once cancer is confirmed, tumors are removed and further management including chemotherapy or chemoradiotherapy is done depending on the patient's stage.

4.6.2 Benefits and Harms of Screening Tests

CRC-Specific Mortality

No studies on the all-cause mortality benefit for fecal immunochemical test (FIT) were available. Biennial screening with FIT using either OC-Sensor or HM Jack done 1–3 times was associated with lower CRC-specific mortality after a 6-year follow-up (adjusted RR 0.90, 95% CI 0.84 to 0.95). (4,5) See Appendix F.

Adverse Events – Serious Bleeding

There were no available studies that examined the serious harms of stool testing using FIT or the fecal occult blood test (FOBT) since these are considered non-invasive tests, although diagnostic inaccuracy or eventual harm from follow-up tests like scoping procedures are possible. One of the adverse events from colonoscopy following an abnormal stool test (FIT or FOBT) is serious bleeding. The pooled estimate was 17.5 events per 10,000 (95% CI 7.6 to 27.5).(4)

Adverse Events – Perforation

The pooled estimate of perforations from colonoscopy following an abnormal stool test is 5.4 events per 10,000 procedures (95% CI 3.4 to 7.4).(4)

4.6.3 Diagnostic Performance of Screening Tests

Diagnostic Performance of FIT in diagnosing CRC

Based on nine studies (n=34,352) that utilized FIT (OC Sensor) and used colonoscopy as reference standard with the manufacturer-recommended cutoff of 20 ug Hb/g feces, pooled sensitivity was 0.74 (95% CI 0.64 to 0.83; I²=31.6%) and pooled specificity was 0.94 (95% CI 0.93 to 0.96; I²=96.6%).(4,5) See Appendix F.

Diagnostic Performance of FOBT in diagnosing CRC

The previous edition of the Periodic Health Examination reported that the sensitivity of FOBT ranged from 0.50–0.79 (95% CI 0.01 to 0.99) and specificity ranged from 0.87–0.98 (95% CI 0.86 to 0.99). These are based on five prospective studies (n=19,742) with colonoscopy and cancer registry as reference standard.(6)

4.6.4 Cost Implication

CRC is considered preventable with early screening. However, screening for CRC was not included in the Z package established by PhilHealth in 2016, which aimed to fully subsidize the treatment cost of enrolled cancer patients.(3)

In 2018, a cost-utility analysis (CUA) and budget impact analysis (BIA) was conducted by Wong et al. to determine the feasibility of a screening benefit package.(7) Four different screening modalities were used for the microsimulation model: (a) FOBT confirmed by colonoscopy every 10 years; (b) FIT confirmed by colonoscopy every 10 years; (c) FIT confirmed by flexible sigmoidoscopy and colonoscopy screening every 10 years; and lastly (d) no screening. All modalities were noted to be cost-effective, considering that the

ICERs fell below the 1 GDP per capita threshold. Based on the BIA, the most cost-effective strategy was FIT followed by colonoscopy every 10 years. The findings of this CUA also showed that either FOBT or FIT followed by colonoscopy were reasonable screening strategies for CRC. The budget impact of both interventions was PHP 9 billion with moderate compliance, or PHP 1 billion assuming low compliance in the first year of national program implementation.(7)

Below is the table on the cost of screening interventions and confirmatory test (colonoscopy) in both low resource and high resource settings (Table 22).

Table 22. Unit cost of screening interventions and confirmatory test for low resource and high resource settings

	Screening intervention		Confirmatory Test
	<i>Annual FIT</i>	<i>Annual FOBT</i>	<i>Colonoscopy</i>
<i>Low Resource Setting</i>	PHP 215-305	PHP 70	Waived (c/o Philhealth)
<i>High Resource Setting</i>	PHP 950-1000	PHP 190	PHP 20,000-25,000

FIT *fecal immunochemical test*; FOBT *fecal occult blood test*; PHP *Philippine peso*

4.6.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

In most developing Asian countries (including the Philippines), awareness and knowledge of CRC symptoms and risk factors is low, resulting in low CRC screening in this region.(8,9) Demographic and socioeconomic characteristics, as well as access to healthcare and health services have been identified as contributors to screening disparities and inequities among different racial/ethnic groups.(9) Physician's recommendation has also been identified as a positive predictor of screening behavior of patients, but this is often offset by financial and access barriers, especially in an out-of-pocket economy like the Philippines.(10)

Due to the non-invasive nature of screening tests like FIT and FOBT, patients generally prefer them and are willing to repeat these procedures for screening compared to scoping procedures. Understandably, pain is significantly associated with unwillingness to repeat scoping modalities like the flexible sigmoidoscopy.(11) Based on the CUA by Wong et al., FOBT was the more cost-effective strategy with the least budget impact when applied as a benefit package.(7) However, FIT is recommended due to its accuracy and specificity for human blood (unaffected by iron supplements that may be taken by some individuals). FIT is notably preferred as well because of its convenience and ease of administration.

Currently, PhilHealth is considering covering screening through the National Health Insurance Act.(7) FIT is usually available in both private and public hospitals and some laboratories.

Overcoming the low awareness and knowledge on the benefits of CRC screening and to consequently increase its participation rates entail promoting the physician's role and conducting continuous health education activities for the target population.(12) These, together with adequate funding, can have positive impact on CRC screening in the country.

4.6.6 Recommendations from Other Groups

Two international guidelines (4,13) and one local guideline (14) recommended first-line CRC screening annually using FIT starting at the age of 50 years old (Table 23). Although the United States Preventive Services Task Force highly recommended screening all adults aged 50–75 years old (Grade A), the recent update also recommended screening patient as early as 45 years old (Grade B).

Table 23. Key recommendations from clinical practice guidelines

Group	Recommendation	Strength of recommendation and certainty of evidence
US Preventive Services Task Force (2021) (4)	Annual FIT for average risk individuals ≥ 50 years old	Strong recommendation, Low Certainty of Evidence
American Cancer Society (2018) (13)	Annual FIT for average risk individuals ≥ 50 years old	Strong recommendation
Philippine Society of Gastroenterology and Philippine Society of Digestive Endoscopy (2017) (14)	Annual Fecal occult blood tests, preferably using FIT, is the recommended first line screening test for CRC in average risk individuals 50 years old and above	Strong recommendation, High level of evidence

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4.7 Mammogram, Breast Ultrasound, or Clinical Breast Examination in Screening for Breast Cancer

RECOMMENDATIONS

1. Among apparently healthy asymptomatic women aged 50 to 69 years, we recommend screening for breast cancer every one to two years using mammography.
(strong recommendation, low certainty evidence)

2. Among apparently healthy asymptomatic women aged 50 years and older, we recommend performing biennial clinical breast examination to screen for breast cancer.
(strong recommendation, moderate certainty evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Breast cancer is a priority health problem
- The panelists favored screening because of the diagnostic accuracy of screening and due to the benefits outweighing the harms, despite the low certainty of evidence on the benefits and harms, the moderate costs of screening.
- Screening using a mammogram, breast ultrasound, or a clinical breast examination is acceptable and feasible, although not equitable with important uncertainty or variability regarding patient values and preferences.
- It is emphasized that the clinical breast examination (which is performed by a trained health worker) is different from a self-breast examination that could be done by a patient.

Remarks

For draft recommendation 1, the tradeoffs (i.e., pain, radiation exposure, cost of mammogram, psychological stress with the benefit of decreased breast cancer mortality) were in favor of screening despite the low level of evidence.

4.7.1 Burden of disease

Disease Frequency

According to estimates of the WHO, breast cancer is the most common malignancy in the Philippines in 2020 with a 5-year prevalence of 85,206 cases.(1) In the Philippines, breast cancer has an age-standardized incidence rate of 52.7 per 100,000, and is the 3rd leading cause of cancer-related deaths (10.7%). Additionally, Filipino women with breast cancer have an estimated 5-year survival rate of 57%, which is much lower compared to that in developed countries (European countries, 79%).(1,2)

Management of the Disease

Early detection and treatment are the most effective means to reduce mortality and morbidity from breast cancer. Across many countries, there are observed declines in mortality despite stable incidence rates, which suggest an improvement in breast cancer diagnostics and care. The treatment of early breast cancer includes surgery, radiation therapy, systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or a combination of these. Palliative treatment is also given to patients with metastatic disease. However, most patients in the Philippines may have difficulty accessing these services due to the inability of affording the costs of diagnosis and treatment, alongside other socioeconomic factors that further impede their ability to access healthcare services.(3)

4.7.2 Benefits and Harms of Screening Tests

Data on the benefits and harms of a mammogram and/or clinical breast examination (CBE) were found from a systematic review of 10 trials (randomized and quasi-randomized), which was of moderate-to-high quality.(4) A prospective RCT on CBE compared to usual care was found. However, no RCTs involving breast US compared to no screening were identified. Available studies have suggested US as supplementary to mammography in the evaluation of high-risk women or those with higher breast density.

A. Mammography

Breast Cancer Mortality

Based on data from eight RCTs (n=615,023), screening with mammography and/or CBE was shown to decrease the risk of breast cancer mortality among cases identified during the study's screening period (short-case accrual – median follow-up 23 years) (RR 0.85, 95% CI 0.78 to 0.93).(5–9) Decreases were also observed overall when all cases identified during the follow-up period were included (long-case accrual – median follow-up of 18 years) (RR 0.81, 95% CI 0.70 to 0.92).(5,6,10–12) However, there was inconsistency in the effects across trials.

Short-case accrual

According to data from eight RCTs, mammography and/or CBE reduced the risk of breast cancer mortality compared to usual care for a median follow-up of 23 years (Appendix G). The absolute effect ranged from 30–104 fewer deaths per 100,000 in the screening arm, depending on different baseline risks (low to high: 200–690 per 100,000). The number needed to screen (NNS) to prevent one additional death attributed to breast cancer ranged from 3,333 (95% CI 2,273 to 7,143) to 962 (95% CI 658 to 2,083) based on low to high baseline risks. GRADE assessment of low quality was given due to very serious risk of bias across studies.

Subgroup analysis by age (40–49 years, 50–59 years, 60–69 years, 70–74 years)

The number of women included for analyses was unknown. Analysis showed a decrease in the risk of breast cancer mortality among women aged 60–69 years old (RR 0.70; 95%

CI 0.56 to 0.88) (Appendix G). A test for subgroup differences was not statistically significant ($I^2= 0\%$; $p=0.39$).

Long-case accrual (10 RCTs)

Data from 10 RCTs showed that screening with mammography and/or CBE reduced the risk of breast cancer mortality compared with usual care for a median follow-up of 18 years. The absolute effect ranged from 44–209 fewer deaths per 100,000 in the screening arm, depending on different baseline risks (low to high: 230–1,100 per hundred thousand). The NNS to prevent one additional death attributed to breast cancer ranged from 2,273 (95% CI 1,149 to 5,556) to 478 (95% CI 303 to 1,136) based on low to high baseline risks (Appendix G). GRADE assessment of very low quality was given because the risk of bias and inconsistency across studies were each deemed very serious concerns in this body of evidence.

A decrease in breast cancer mortality was observed among women aged 50–59 years old (RR 0.82, 95% CI 0.68 to 0.99), and in the 60–69 years old subgroup (RR 0.65, 95% CI 0.50 to 0.85) (Appendix G). However, a test for subgroup differences was not statistically significant ($I^2=29\%$; $p=0.24$).

All-Cause Mortality

Based on eight RCTs (5–7,13), no statistical differences were observed between mammography and/or CBE and usual care for all-cause mortality (RR 0.99, 95% CI 0.98 to 1.01) for a median follow-up of 16 years. GRADE assessment of low quality was given due to very serious risk of bias issues across studies (Appendix G).

When examined by age in subgroups, no differences were detected ($I^2=0\%$; $p=0.62$) (Appendix G).

Overdiagnosis

Estimates of overdiagnosis varied widely between various studies, from almost none to up to 54%.^(14–18) Three RCTs reported on overdiagnosis. No quantitative syntheses of the data were carried out due to inconsistencies of data presentation and incomplete reporting.^(18–20) Among women aged 40–49 years, 55% of identified invasive and in situ cancers were estimated to be over-diagnosed, and 48% of identified invasive cancers were estimated to be over-diagnosed in 20 years after screening. In 5 years after screening, 25% of identified invasive and in situ cancers were estimated to be over-diagnosed among women aged 50–59 years, and 16% of identified invasive cancers were estimated to be over-diagnosed (Appendix G).

False-positive mammography and biopsy

Using data from the 2011–2012 Canadian Partnership Against Cancers (Table 24) (4), rates of false positive screens with resulting biopsies were calculated. False positive mammography and biopsy rates tended to be greater in women of younger age. Among 1,000 women screened over 7 years, 294 will receive a false positive result and 43 will undergo a biopsy in women aged 40–49 years, while 219 will receive a false positive result and 30 will undergo a biopsy in the aged 70–74 subgroup. Among women aged 40–49

years, 508 experienced a false positive result to prevent one cancer death, and 74 experienced a biopsy on a false positive result per one breast cancer death prevented. Overall, false positives and biopsies on false positives per 1,000 women screened for 1 year decreased with increasing age.

Table 24. False-positives and biopsies on false-positives

Outcome	Age range, year			
	40–49	50–59	60–69	70–74
<i>Per 1000 women screened</i>				
FP mammography	294	294	256	219
Biopsies on FP	43	37	35	30
<i>Per 1 breast cancer death prevented</i>				
FP mammography (based on 3 cycles of screening)	508	392 (M)	278	141
Biopsies on FP (based on 3 cycles of screening)	74	50 (M)	38	19

FP *false-positive*

M = calculated using the moderate baseline risk for this age group

*Three cycles of screening for which women are screened every 2-3 years, for a total of 6-9 years of a screening period. Calculation: Initial screening cycle + 2 (subsequent screening cycle) to estimate harms occurring with 7 years of screening

B. Clinical Breast Examination

Breast Cancer Mortality

A prospective cluster RCT on CBE compared to usual care showed a non-significant 15% reduction in breast cancer mortality in the overall study population (95% CI 0.71 to 1.01) (Appendix G).(21) Women in the screening arm received four screening rounds of biennial CBE conducted by trained female primary health workers. A post hoc subset analysis showed that there was a nearly 30% relative reduction in breast cancer mortality in women aged ≥ 50 years (RR 0.71, 95% CI 0.54 to 0.94), but no significant reduction in women < 50 years old (RR 0.93, 95% CI 0.79 to 1.09).(21)

All-Cause Mortality

There was a reduction in all-cause mortality among all ages, but was not statistically significant (RR 0.95, 95% CI 0.81 to 1.10) (Appendix G). GRADE assessment of low quality was given due to serious issues on risk of bias and imprecision (Appendix G).

4.7.3 Diagnostic Performance of Screening Tests

The sensitivity of mammography ranged from 0.77–0.95, and the specificity was between 0.94–0.97.(22) Screening mammography for Filipino women showed a sensitivity of 0.83 (95% CI 0.75 to 0.89) and a specificity of 0.932 (95% CI 0.93 to 0.94).(23) Some factors such as age and increased breast density were found to reduce the sensitivity and specificity of mammograms for detecting breast cancer. Additionally, there was lower sensitivity in women ≤ 40 years old. A Breast Cancer Surveillance Consortium study of more than 300,000 women found that sensitivity decreased from 0.87 in the lowest breast density category to 0.63 in the highest, and specificity decreased from 0.96 to 0.90 as breast density increased.(24) Any suspicious abnormalities identified in mammography were recommended for biopsy in the absence of clinical contraindication.(25)

A well-performed CBE has similar specificity with mammography (0.93–0.97) but lower sensitivity (0.40–0.69). However, it has been shown that CBE sensitivity is higher in younger women (40–49 years old), in Asian women, and when it is applied as a stand-alone screening modality.(26)

4.7.4 Cost Implication

Cost-effectiveness studies showed that screening with mammography was cost-effective compared to no screening (Table 25).(27–29)

Table 25. Estimated annual cost of screening for breast cancer using breast ultrasound/mammogram

Parameter	Screening modality	Confirmatory Test
	Mammogram (in PHP)	Biopsy (FNAB, Core-needle or Excision; in PHP)
Unit cost of screening intervention	2,500	10,000
Other direct costs associated with the implementation of the proposed screening intervention	Initial and follow-up consultations 300 x 2 = 600	Initial and follow-up consultations 300 x 2 = 600
Annual Screening cost per patient	3,100	PHP 10,600 PHP 13,700 (with mammogram)

FNAB *fine-needle aspiration biopsy*; PHP *Philippine peso*

4.7.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

A systematic review that included 22 individual studies on women's values and preferences concerning breast cancer screening and diagnostic services showed that women were willing to accept the psychological and physical burden of breast cancer screening and a significant risk of overdiagnosis and false-positive mammography findings, in return for the benefit of earlier diagnosis.(30) The willingness to accept overdiagnosis was related to socio-demographic factors: those with a higher educational status accepted significantly higher levels of overdiagnosis than those with a lower educational status.(31) Furthermore, women over 50 accepted significantly less overdiagnosis than younger women.

A cross-sectional study that explored Filipino women's knowledge of and perception towards breast cancer screening showed that more than half of the Filipino women participants were not aware of breast self-examination, CBE and mammography.(32) Financial concerns were highlighted as a major barrier to obtaining more expensive screening procedures, such as mammograms. Participants also reported a number of negative psychological impacts associated with screening procedures (e.g., fear and pain) and myths about screening (e.g., feeling OK, therefore screening is not needed). Designing and implementing effective educational programs that increase women's awareness about breast cancer and promote screening uptake are important steps to reduce the burden affected by breast cancer among women in low-resources settings.

4.7.6 Recommendations from Other Groups

The United States Preventive Services Task Force 2016 guidelines recommended biennial screening mammography for women aged 50–74 years (*Grade B Recommendation*).⁽³³⁾ The American Cancer Society 2015 recommended that annual mammography screening for women begins at age 45 (*Strong Recommendation*).⁽¹⁴⁾ A younger age of 40 years to start annual screening mammography was recommended by the National Cancer Comprehensive Network 2021 (*Category I Recommendation*)⁽³⁴⁾ (Table 26).

Table 26. Key recommendations from clinical practice guidelines

Group	Recommendation	Strength of recommendation and certainty of evidence
National Comprehensive Cancer Network (2021) (34)	Women with an average risk between ages of 25 and 39 are recommended to have a clinical encounter (breast cancer risk assessment, risk reduction counseling, CBE every 1 to 3 years, report changes in their breasts to their health care provider).	Category 2A
	Women with an average risk of 40 years and older are recommended to have annual clinical encounters (ongoing breast cancer risk assessment, risk reduction counseling, CBE, report any changes in their breast) and annual screening mammography with the consideration of tomosynthesis	Category I recommendation (for annual screening mammogram)
US Preventive Services Task Force (2016) (22)	Women with an average risk between ages of 25 and 39 are recommended to have a clinical encounter (breast cancer risk assessment, risk reduction counseling, CBE every 1 to 3 years, report changes in their breasts to their health care provider).	Category 2A
	The decision to start screening mammography in women before age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between 40 and 49 years of age.	Grade C recommendation
	For women aged 75 years or older, current evidence is insufficient to assess the balance of benefits and harms of screening mammography	I statement
American Cancer Society (2015) (14)	Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years	Strong recommendation
	Women aged 45 to 54 years should be screened annually, transitioning to biennial screening at 55 years of age with the option to continue annual screening	Qualified recommendation
	Women between the ages of 40 and 44 years should have the opportunity to begin annual screening	Qualified recommendation
	Healthy women should continue screening mammography as long as they have a life expectancy of 10 years or longer.	Qualified recommendation
	ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age.	Qualified recommendation

Some Asian countries, such as South Korea, Japan, and Singapore, have initiated population-based screening programs. In South Korea, women were screened with mammography every 2 years starting at age 40.⁽³⁵⁾ The Ministry of Health of Singapore recommended that biennial mammography screening should be implemented for women between 50–69 years.⁽³⁶⁾ According to Hamashima et al., Japanese women between 40–74 years of age should be screened by mammography without clinical breast examination for population-based screening.⁽³⁷⁾ However, in most Asian countries, there were no national population-based breast cancer screening programs.

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4.8 PSA Determination and/or Digital Rectal Exam in Screening for Prostate Cancer

RECOMMENDATION

Among asymptomatic males with age from 50 to 64 years old, we suggest shared decision making before biennial screening with PSA and digital rectal exam for prostate cancer.

(weak recommendation, low certainty evidence)

Considerations

The consensus panel considered the following when formulating this recommendation:

- Prostate cancer is a priority health problem
- Screening with PSA and DRE was favored, with small-to-moderate benefit, small harm, and low-to-moderate costs.
- Screening with PSA and DRE was equitable, acceptable, and feasible with possible important uncertainty or variability with patient values and preferences.
- There is a great risk for overtreatment, and the panelists emphasized the importance of informing the patient of this risk prior to screening.

Remarks

- “Shared decision-making” was added to the recommendation statement after an initial two rounds of voting on the direction of the recommendation.

4.8.1 Burden of disease

Disease Frequency

Prostate cancer is the 5th leading cause of cancer in the Philippines with an estimated incidence of 8,242 cases in 2020.(1) It has the 2nd highest estimated 5-year prevalence at 26,942 cases, and is the 9th leading cause of death among cancers of various sites. Among Filipinos abroad and locally, the incidence rates are lower than those of Caucasians, but are one of the highest among Asian groups.(2) In the Surveillance, Epidemiology, and End Results program data from 2014–2018, about 72.5% of prostate cancers were among those aged 55–74 years old.(3)

Natural Course of the Disease

The development of prostate cancer is hypothesized to result from an accumulation of genetic and epigenetic alterations. It may take three or four decades before the disease is diagnosed, and this evolution is heavily influenced by hormonal factors. The most common presenting symptoms are hesitancy, nocturia, incomplete urinary bladder emptying, and diminished urinary stream. The Gleason Grading System is used to describe the degree of differentiation on biopsy and has prognostic significance.(4) The 5-year survival of prostate cancer is 100% in both local and regional disease, while it is 50.6% in those with distant disease.(3,5)

Management of the Disease

Confirmatory tests via prostate biopsy dictate further management.(6) Localized disease can be managed by EBRT, brachytherapy, surgery, and observation. Metastatic disease is managed with hormonal therapy including novel hormonal therapy, EBRT, chemotherapy, and immunotherapy.

Economic Impact of the Disease

Disability-adjusted life years (DALYs) provide a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death. Prostate cancer was estimated to cause 7.1 million (95% UI 6.1 million–8.4 million) DALYs globally in 2017.(7) Of these, 88% were attributed to Years of Life Lost (YLLs) and 12% from Years Lost Due to Disability (YLD).

There is no published data on the cost-of-illness of prostate cancer in the Philippines. However, an Iranian study demonstrated that the cost of prostate cancer treatment increased as cancer stage increased (Table 27).(8)

Table 27. Comparison of costs according to stage of prostate cancer

Stage of Prostate Cancer	Direct medical costs (USD)	Direct nonmedical costs (USD)	Indirect costs (USD)
Low-risk metastatic prostate cancer	102.79	97.06	23.85
Local nonmetastatic prostate cancer	2,673.43	339.71	83.49
Locoregional nonmetastatic prostate cancer	2,210.51	485.29	119.27
Non-resistant metastatic prostate cancer	4,133.15	776.47	238.54
Resistant prostate cancer	7,747.89	1,067.65	357.81

USD United States dollar

Social Impact of the Disease

Several options in the management of early-stage prostate cancer and the lack of agreement gathered from second opinions of patients have been shown to add distress to patients. Erectile dysfunction from prostate cancer treatment has been associated with role limitations due to emotional problems, depression, self-esteem, and marital satisfaction.(9) Urinary incontinence from the prostate cancer or the treatments also increased mental distress, social restrictions and social isolation.

4.8.2 Benefits and Harms of Screening Tests

Benefits of Screening

A. PSA +/- DRE vs. No Screening

Prostate Cancer-Specific Mortality and All-Cause Mortality

Three RCTs included in the analysis had different pre-biopsy thresholds for prostate-specific antigen (PSA) values and had different screening intervals. These RCTs showed no significant difference in prostate cancer-specific mortality (RR 0.92, 95% CI 0.8 to 1.07) and all-cause mortality (RR 0.99, 95% CI 0.97 to 1.02) when screening was compared with no screening.(10–12) The highest risk reduction in prostate cancer-

specific mortality was seen in a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC) in Sweden. These patients were screened every 2 years for 20 years and had a PSA screening threshold of 2.5–3.0 ng/mL (RR 0.58, 95% CI 0.46 to 0.72).(13)

Only two RCTs had data on subgroups by age, and these studies showed that the greatest benefit from screening with PSA was observed in ages <65 years old (see Appendix H).(10,12)

Only one RCT conducted PSA screening at yearly intervals, and there was no significant difference in prostate cancer-specific and all-cause mortality.(14) The centers in the ERSPC trial had different cutoff values per center, ranging from 2.5–4 ng/ml. The lowest hazard ratio for prostate cancer-specific mortality was seen in the center with cutoff values of 2.5–3.0 ng/ml.

There is no available individual patient level data from the above RCTs to analyze outcomes of screening of high-risk patients in relation to mortality. One RCT compared screening of *BRCA1/2* germline pathogenic mutation carriers with controls who tested negative for *BRCA1/2* mutation. The results showed that those with *BRCA2* mutations were associated with a higher incidence of prostate cancer, a younger age at diagnosis, and clinically significant tumors.(15)

B. Digital Rectal Examination

There are no direct evidence showing the effectiveness of standalone digital rectal examination (DRE) compared to no screening for prostate cancer in improving clinical outcomes.(16,17)

Harms of Screening

False Positive Results

Different PSA thresholds have been used in the RCTs reviewed. Lower thresholds of PSA allowed for the diagnosis of more prostate cancer cases, but false positive rates also increased from 11.3% to 19.8% when cutoffs were 4 ng/ml and 3 ng/ml, respectively.(18) False positive results trigger additional testing and possible biopsy.

Complications and Adverse Effects of Biopsy

In a systematic review, the most frequent complications with prostate biopsy were blood in semen (93%), blood in urine (66%), pain (44%), shivers (19%) and fever (18%). There were 1.4% (95% CI 0.8 to 2.4%) admitted to the hospital due to sepsis.(19)

Adverse Effects of Treatment

A. Prostatectomy

Radical prostatectomy decreased the risk of death from prostate cancer to 195 deaths per 1,000 from 316 deaths per 1,000 in watchful waiting on 10 years of follow-up (HR 0.57, 95% CI 0.44 to 0.73).(20) When compared to active monitoring, there was probably no difference (HR 0.63, 95% CI 0.21 to 1.89). At 10 years, the risk of death is 9 deaths per 1,000 in radical prostatectomy, and 15 deaths per 1,000 in active monitoring.(20)

Radical prostatectomy in localized prostate cancer decreased the risk of death from any cause compared to watchful waiting (HR 0.79, 95% CI 0.7 to 0.9). Translated to overall mortality at 29 years, there were 764 deaths per 1,000 in the radical prostatectomy group compared to 839 deaths per 1,000 in the watchful waiting group. However, there were no differences when radical prostatectomy was compared to active monitoring (HR 0.93, 95% CI 0.65 to 1.33). This matches the 101 deaths per 1,000 in the radical prostatectomy group vs. 108 deaths per 1,000 in the active monitoring group.(20)

B. Radiation Treatment

In a pooled analysis of three RCTs, more patients had urinary incontinence with radical prostatectomy (22.5%), while 8.9% experienced urinary incontinence in the conservative management arm (RR 2.53, 95% CI 1.81 to 3.55).(21–23) In two RCTs, 5.08% of patients had urinary incontinence with radiation treatment and 7.76% with conservative management (RR 0.63, 95% CI 0.38 to 1.05).(22,24)

Erectile dysfunction occurred more often among those who had radical prostatectomy (65%) compared to patients who had conservative management (42%).(21–23) One RCT reported that erectile dysfunction in radiation therapy occurred in 36.2% compared to 39.8% in those who had conservative management, although this difference was not statistically significant (RR 0.91, 95% CI 0.77 to 1.08).(25)

4.8.3 Diagnostic Performance of Screening Tests

A. PSA +/- DRE vs. No Screening

The first round of prostate cancer screening in Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) showed a sensitivity of 0.88 and specificity of 0.48 when the PSA cutoff was >4 ng/mL. When combined with abnormal DRE, the sensitivity was 0.93 and the specificity was 0.91.(26)

The Finnish subset of the ERSPC showed a sensitivity of 0.93 and a specificity of 0.92 for the first round of screening based on the PSA cutoff of >4 ng/mL or 3–4 ng/mL+ with abnormal DRE findings.(27) The study reported the following are the numbers needed to invite and the numbers needed to detect to prevent one case of prostate cancer-specific mortality with prostate cancer screening at a cut-off of >4 ng/mL done every 4 years for three rounds (Table 28).(28)

Table 28. Number needed to treat and number needed to detect for prostate cancer (28)

	NNI (95% CI)	NND (95% CI)
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9-year follow-up	1,410	48
11-year follow-up	979	35
13-year follow-up	781(490–1,929)	27 (17–66)

NNI number needed to invite; NND number needed to detect

In comparing screening of *BRCA1/2* germline pathogenic mutation carriers with controls who were tested at a PSA cut-off of 3 ng/mL for 3 years, a higher PPV for prostate cancer was found among *BRCA2* carriers (PPV 0.37, 95% CI 0.25 to 0.48) compared to controls (PPV 0.24%, 95% CI 0.09 to 0.40).(15) For *BRCA1* carriers, it was 0.33 (95% CI 0.22 to 0.44) compared to 0.21 (95% CI 0.11 to 0.32) among controls.

Biopsy among *BRCA2* patients had a PPV of 0.41 (95% CI 0.29 to 0.53) compared to 0.33 (95% CI 0.13 to 0.53) in controls. Among the *BRCA1* carriers, the PPV was 0.39 (95% CI 0.27 to 0.51) compared to 0.25 (95% CI 0.13 to 0.37) among controls.(15)

B. Digital Rectal Exam

In a systematic review that included seven studies of DRE screening in the primary care screening, the pooled sensitivity, specificity, PPV and NPV were 0.51 (95% CI 0.36 to 0.67), 0.59 (95% CI 0.41 to 0.76), 0.41 (95% CI 0.31 to 0.52) and 0.64 (95% CI 0.58 to 0.7), respectively.(16)

C. Abnormal DRE vs. Normal DRE, DRE vs. PSA, DRE + PSA

In a multivariable analysis adjusted for age and intra-study PSA, the retrospective study of the PLCO trial showed that a suspicious DRE performed by urologists was associated with increased detection of clinically significant prostate cancer (HR 2.21, 95% CI 1.99 to 2.44) and prostate cancer-specific mortality (HR 2.54, 95% CI 1.41 to 4.56). Abnormal PSA was associated with a five-fold increase in detection of clinically significant prostate cancer (HR 5.48, 95% CI 5.05 to 5.96) and prostate-cancer specific mortality (HR 5.23, 95% CI 3.11 to 8.79) as compared to abnormal DRE.(29)

In the PLCO study, only 15.4% of patients had suspicious DRE and abnormal PSA.(29) Another retrospective study reported that 67% of patients were referred for abnormal DRE with normal PSA, and 35% of these patients were diagnosed with prostate cancer.(30) These two studies may suggest a role of DRE as a complement to PSA screening.

4.8.4 Cost Implication

There are no local cost-effectiveness evaluations of prostate cancer screening. An online search and query in hospitals and among doctors yielded the following cost estimates (Table 29).

Modeling from ERSPC Trial was done in one of the three RCTs included in prostate cancer-specific mortality analysis. It showed that the most cost-effective approach was screening between ages 55–59 at 2-year intervals, which cost \$72,791.00 per Quality-Adjusted Life Years (QALY).(31) These values are close to usual reference values for QALYs, which are USD 50,000 or USD 100,000 (Table 30).

Table 29. Cost estimates for prostate cancer screening

Parameter	Costs of DRE (in PHP)	Costs of PSA (in PHP)
<i>Unit cost of screening intervention</i>	Consultation Fee Private Hospital: 1,000.00 ^a Government Hospital: 400.00 ^b	Private Hospital: 7,850.00 ^a Private Laboratory: 2,945.00 ^c Government Hospital: 900.00 ^b
<i>Other direct costs associated with the implementation of the proposed screening intervention</i>	Standard Biopsy	Private Hospital: 30,000.00 ^d Government Hospital: 12,000.00 ^b
<i>Annual screening cost per patient</i>	Consultation Fee Private Hospital: 1,000.00 ^a Government Hospital: 400.00 ^b	Private Hospital: 7,850.00 ^a Private Laboratory: 2,945.00 ^c Government Hospital: 900.00 ^b

DRE digital rectal exam; PHP Philippine peso; PSA prostate-specific antigen

^aAsian Hospital and Medical Center; ^bSouthern Philippines Medical Center; ^cMyHealth; ^dSt. Luke's Medical Center**Table 30. Prostate cancer specific mortality reduction, overdiagnosis, LYG, and incremental cost-effectiveness for the most efficient screening strategies per 1,000 men^a**

Screening Strategy End age, year	Interval	Prostate Cancer Mortality Reduction % ^b	Overdiagnosis ^c	LYG	Total Net Cost (USD)	QALYs ^b gained	Cost/QALY ^b	Incremental cost effectiveness (USD) ^d
55	-	5	29.7	8.4	168,469	e	31,467	31,467
57	2	9	31.1	13.4	303,936	7.9	38,563	53,593
58	3	10	32.1	14.8	343,908	8.4	40,785	72,567
59	2	13	33.0	18.2	452,568	9.9	45,615	72,971
61	2	17	34.8	22.6	612,063	11.3	54,349	118,989
61	1	18	34.8	24.9	747,784	11.8	63,263	243,031
62	1	20	35.7	27.1	848,006	12.2	69,481	260,507
63	1	22	36.7	29.0	948,659	12.3	76,920	776,149

LYG life years gained; QALY quality adjusted life year; USD United States dollar

^a 2008 US dollars. The QALYs gained and costs are 3.5% discounted.^b Compared with no screening.^c as % of screen detected men^d The difference in costs compared with the previous least expensive strategy divided by the difference in QALYs between those strategies

4.8.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

In the Philippine setting, equal access to hospitals with PSA screening, biopsy, treatment facilities, and trained physicians to do quality DRE is a foreseen problem. Other barriers to prostate cancer screening that have been identified in a study among Filipino Hawaiian men include lack of awareness of the need for screening, fear of the diagnosis of cancer, financial issues, time constraints, embarrassment, and hesitation in seeking health care.(32) These are reflective of patients' values and preferences that must be considered.

The National Integrated Cancer Control Program states the PhilHealth will expand its benefit packages to include primary care screening. Recommendations for prostate cancer screening will require more resources in the implementation of the program. The Z Benefit Package of PhilHealth covers treatment of low- to intermediate-risk prostate cancer amounting to PHP 100,000.00. This amount covers cardiopulmonary risk assessment, surgery, radiation therapy or hormonal therapy. Screening for prostate

cancer allows detection at an earlier age, which will allow more patients to be qualified for the Z Package.(33)

4.8.6 Recommendations from Other Groups

The following are recommendations on screening for prostate cancer from CPGs (Table 31).

Table 31. Summary of key recommendations from other guidelines

Organization, Year	Recommendations	Grade
American Urological Association (2018) (34)	Recommends against PSA screening in men age <54 years. For men ages 55–69 years, decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55–69 years that are considering PSA screening and proceeding based on a man's values and preferences.	Evidence Strength C <i>Standard; Evidence Strength Grade B</i>
	To reduce the harms of screening, a routine screening interval of ≥2 years may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of 2 years preserve the majority of the benefits and reduce over diagnosis and false positives.	<i>Option; Evidence Strength Grade C</i>
	The Panel does not recommend routine PSA screening in men age ≥70 years, or any man with less than a 10- to 15-year life expectancy.	<i>Recommendation; Evidence Strength Grade C</i>
Canadian Task Force on Preventive Health Care (2014) (18)	For men aged <55 years of age, we recommend not screening for prostate cancer with the PSA test.	Strong recommendation; low-quality evidence.
	For men aged 55–69 years of age, we recommend not screening for prostate cancer with the PSA test.	Weak recommendation; moderate-quality evidence
	For men ≥70 years, we recommend not screening for prostate cancer with the PSA test.	Strong recommendation; low-quality evidence
EAU-EANM-ESTRO-ESUR-SIOG Guidelines (35)	Individual risk-adaptive strategy. Inform of risk and benefits. Males aged >50 years, aged >45 years with family history of prostate cancer, or African American males aged >45 years, only screen if good performance status and at least 10–15-year life expectancy.	
National Comprehensive Cancer Network (2021) (36)	Start discussion about risks and benefits : 1. For average-risk individuals 45–75 years old, baseline PSA and biopsy for PSA >3 ng/mL and/or suspicious DRE 2. For age >75 years, baseline PSA (category 2A) and biopsy for PSA >4 ng/mL and/or suspicious DRE. DRE should not be used as a standalone screening test Timing for testing for men with BRCA1 mutation, MLH1, MSH2, MSH6, PMS2 germline gene mutations is less clear Prostate cancer screening is recommended for those of African American ancestry or those with BRCA2 mutation starting at age 40 years	
US Preventive Services Task Force (2018) (37)	For men aged 55–69 years, the decision to be screened for prostate cancer should be an individual one	Grade C
	For men 70 y and older, do not screen for prostate cancer	Grade D

Organization, Year	Recommendations	Grade
	Clinicians should not screen men who do not express a preference for screening	Grade C
Department of Health Prostate Cancer CPG (2021)	Among Filipinos with single elevated PSA and normal DRE, we suggest watchful waiting with risk factor assessment and serial PSA monitoring over an immediate prostate biopsy.	

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4.9 Low-Dose CT in Screening for Lung Cancer

RECOMMENDATIONS

1. Among asymptomatic apparently healthy adults with low risk for lung cancer, we suggest against annual low-dose CT scan to screen for lung cancer.
(weak recommendation, very low certainty evidence)
2. Among asymptomatic apparently healthy adults with high risk* for lung cancer, we suggest annual low-dose CT scan to screen for lung cancer.
(weak recommendation, very low certainty evidence)

*Risk factors:

- Age >50 years with history of smoking
- Family history of lung cancer

Considerations

The consensus panel considered the following when formulating this recommendation:

- Lung cancer is a priority health problem.
- Screening with LDCT is favored and was judged to have moderate-to-large benefit, small harms, and be diagnostically accurate, although it may entail large costs.
- Screening with LDCT is equitable and acceptable, with variable feasibility. Panelists are split on the probability of important uncertainty or variability in terms of patient preferences.
- There was not enough data for persons with low baseline risk.

4.9.1 Burden of disease

Disease Frequency

According to WHO 2020 data, lung cancer accounted for 12.5% of the 153,751 newly diagnosed cancer cases in the Philippines.(1) Among males, lung cancer was the most common cancer and accounted for one third of all cases. Lung cancer was attributable to 18.4% of the total number of cancer-related deaths in the Philippines equating to 17,063 individuals.

An increasing trend of lung cancer incidence was observed from 2000–2008 based on data from the Lung Center of the Philippines Registry.(2) Older age consistently posed a higher risk of the disease, with most cases diagnosed beginning 40 years of age. About 50% of lung cancer cases in the registry data occurred during the 6th decade of life onwards. Male patients aged ≥ 60 years comprised the highest frequency at 40.9%, while females comprised only 25–29% of cases among patients aged ≥ 40 years. The NCR reported the highest lung cancer incidence at 43% annually.

In 2015, lung cancer in the Philippines was responsible for 38,594 DALYs, as per a discount rate of 3%, with an increasing trend seen among individuals aged 45–79 years old.(3) The DALY rate in the country was estimated to be 0.4 DALYs per 1,000 person-years. When calculated without the discount rate, the calculated burden of disease substantially increased to 50,977 DALYs. Individuals aged 70–79 years had the highest calculated burden of disease at 4.7 DALYs per 1,000-years.

Management of the Disease

Local guidelines on lung cancer diagnosis and management were recently formulated by the Department of Health (literature search up to April 2021). However, this CPG does not address questions related to screening of asymptomatic adults. For patients with non-small cell lung cancer (NSCLC) receiving treatment with curative intent, the CPG stated that there was insufficient evidence to recommend the use of low-dose CT scan (LDCT) over standard-dose CT scan.(4) PET-CT was also suggested to be used over CT scan for detecting mediastinal lymph node involvement among patients with Stage I–IIIA NSCLC. Adjuvant chemotherapy was not suggested after surgical resection for Stage IB NSCLC, while concurrent chemoradiotherapy was suggested for fit patients with unresectable Stage IIIA–IIIC NSCLC.

In the Pan-Asian adaptation of the European Society for Medical Oncology (ESMO) CPGs, it was recommended that systemic therapy be offered to all patients with advanced metastatic NSCLC, along with smoking cessation and consideration of the patient's preferences, age, comorbidities, and histological findings/molecular pathology.(5) For patients with locally-advanced unresectable tumors, contrast-enhanced CT scans of the chest, upper abdomen, and brain are recommended before initiating concurrent chemoradiotherapy.(6)

For localized small-cell lung cancer (SCLC) (T1–4, N0–3, M0), combined concurrent chemoradiotherapy, surgery followed by four cycles of adjuvant chemo/radiotherapy, or prophylactic cranial irradiation are considered depending on the patient's characteristics.(7) On the other hand, palliative chemotherapy is recommended for metastatic (Stage IV) SCLC.

4.9.2 Benefits and Harms of Screening Tests

No new eligible RCTs were found from our systematic search beyond our search date (Appendix I). Evidence on the diagnostic accuracy, benefits, and harms of LDCT for lung cancer screening was obtained from three high-quality systematic reviews (8–10) published in 2021 (Appendix I). All of these reviews recruited participants at high risk for lung cancer on the basis of age and smoking history. The most recent search was performed in the systematic review by the United States Preventive Services Task Force (10), which included nine RCTs (Appendix I) and non-randomized clinical trials to assess the diagnostic accuracy, benefits, and harms associated with LDCT screening. Table 32 and Table 33 summarize the outcomes of LDCT screening.

Table 32. Benefits and harms of LDCT screening for asymptomatic healthy individuals

Outcome	Subgroup	Studies (n)	Effect Estimate (95% CI)	Interpretation	Certainty of Evidence
Benefits of LDCT screening (from RCTs only)					
Lung cancer-related mortality	Overall	8 (87,876)	RR 0.87 (0.78, 0.98)	Favors LDCT	Moderate
	LDCT vs. NS	6 (31,106)	RR 0.80 (0.69, 0.92)	Favors LDCT	Moderate
	LDCT vs. CXR	2 (56,770)	RR 0.95 (0.82, 1.10)	Inconclusive	Moderate
All-cause mortality	Overall	8 (87,876)	RR 0.99 (0.94, 1.05)	Not significant	Moderate
	LDCT vs. NS	6 (31,106)	RR 0.98 (0.90, 1.07)	Not significant	Moderate
	LDCT vs. CXR	2 (56,770)	RR 1.04 (0.87, 1.26)	Inconclusive	Moderate
Diagnosis of early-stage tumors	Overall	9 (88,497)	RR 2.42 (1.71, 3.44)	Favors LDCT	Moderate
	LDCT vs. NS	6 (31,106)	RR 1.52 (1.04, 2.23)	Favors LDCT	Moderate
	LDCT vs. CXR	3 (57,391)	RR 2.73 (1.91, 3.90)	Favors LDCT	Moderate
Diagnosis of late-stage tumors	Overall	9 (88,497)	RR 0.75 (0.68, 0.83)	Favors LDCT	Moderate
	LDCT vs. NS	6 (31,106)	RR 0.67 (0.56, 0.80)	Favors LDCT	Moderate
	LDCT vs. CXR	3 (57,391)	RR 1.21 (0.38, 3.89)	Inconclusive	Moderate
Harms of LDCT screening					
Overdiagnosis	Overall	6 (82,108)	30% (6–55%)	Does not favor LDCT	Low
	LDCT vs. NS	5 (28,656)	38% (14–63%)	Does not favor LDCT	Low
	LDCT vs. CXR	1 (53,452)	4% (-10% to 18%)	Does not favor LDCT	Low
Radiation exposure	Single LDCT scan	9 studies	0.65–2.36 mSv	Does not favor LDCT	Very Low
	25-yr annual LDCT	1 study	20.8–32.5 mSv	Does not favor LDCT	Very Low
False-positive results	Baseline screening	27 studies	7.9–49.3%	Small to substantial false-positive rates	Very Low
	Screening rounds	27 studies	0.6–28.6%	Lower false-positive rates for subsequent screening rounds	Very Low
Complications following false-positive results	Needle biopsies and complications	9 studies	0.09–0.56%	Does not favor LDCT	Very Low
	Surgical procedures	6 studies	0.5–1.3%	Does not favor LDCT	Very Low
	Surgical resections	9 studies	0.1–0.5%	Does not favor LDCT	Very Low
	Deaths	3 studies	R0–0.007%	Does not favor LDCT	Very Low
	Complications	1 study	Any complication – 0.1% Major – 0.03% Intermediate – 0.05% Minor – 0.01%	Does not favor LDCT	Very Low
Psychological harms	Overall	7 studies	<i>Effect estimates not extracted from individual studies</i>	LDCT not associated with worse HRQOL, anxiety, distress. Higher anxiety for true-positives. Distress worse for indeterminate screening test results.	Very Low

CI confidence interval; LDCT low-dose CT scan; RCT randomized controlled trial; RR risk ratio

Table 33. Diagnostic accuracy of LDCT screening for asymptomatic healthy individuals.

Outcome	Subgroup	Studies (n)	Effect Estimate (range)	Certainty of Evidence
Sensitivity	RCTs	6 (48,500)	0.80 (0.59, 0.95)	Very Low
	Non-RCTs	7 (58,700)	0.93 (0.88, 1)	Low
Specificity	RCTs	6 (48,500)	0.76 (0.26, 0.99)	Very Low
	Non-RCTs	7 (58,700)	78.6% (34.0%, 99.7%)	Very Low
PPV	RCTs	6 (48,500)	21.3% (3.3%, 43.5%)	Very Low
	Non-RCTs	7 (58,700)	8.7% (3.5%, 20.9%)	Very Low
NPV	RCTs	6 (48,500)	99.2% (97.7%, 99.9%)	Low
	Non-RCTs	7 (58,700)	99.6% (99.2%, 100%)	Low
PLR	RCTs	6 (48,500)	3.40 (0.80, 118.8)	Very Low
	Non-RCTs	7 (58,700)	4.35 (1.33, 333.3)	Very Low
NLR	RCTs	6 (48,500)	0.26 (1.55, 0.05)	Very Low
	Non-RCTs	7 (58,700)	0.06 (0.36, 0.001)	Very Low

LDCT *low dose CT scan*; NLR *negative likelihood ratio*; PLR *positive likelihood ratio*

Lung Cancer-Related Mortality

Eight RCTs showed that LDCT significantly reduced lung cancer-related deaths (RR 0.87, 95% CI 0.78 to 0.98; $I^2=24\%$). This benefit was only observed for studies that compared LDCT with no screening (six RCTs; RR 0.80, 95% CI 0.69 to 0.92; $I^2=0\%$).⁽⁸⁾ The two RCTs (LSS, NLST trials) that compared LDCT against chest X-ray (CXR) showed no differences related to this outcome (RR 0.95, 95% CI 0.82 to 1.10; $I^2=11\%$).

The United States Preventive Services Task Force 2021 review included subgroup analyses for age, sex, race/ethnicity, smoking status, pack-years, and history of pulmonary conditions. No statistically significant differences (all p values > 0.05) were noted for all subgroups compared.⁽¹⁰⁾

All-Cause Mortality

Eight RCTs showed that LDCT did not significantly reduce all-cause mortality (RR 0.99, 95% CI 0.94 to 1.05; $I^2=27\%$).⁽⁸⁾ Although similar results were observed for LDCT versus no screening (six RCTs; RR 0.98, 95% CI 0.90 to 1.07; $I^2=27\%$) and LDCT vs. CXR (two RCTs; RR 1.04, 95% CI 0.87 to 1.26), substantial heterogeneity was noted in the LDCT versus CXR comparison ($I^2=63\%$). This may be due to the finding of one RCT (NLST trial), which was a greater reduction in all-cause mortality with LDCT screening (1,912 vs. 2,039 deaths; 1,141 per 100,000 person-years vs. 1,225 per 100,000 person-years; IRR 0.93, 95% CI 0.88 to 0.99).

Diagnosis of Early-Stage Tumors

Nine RCTs showed that LDCT was associated with significantly high early-stage (Stage I-II) tumor detection rates (RR 2.42, 95% CI 1.71–3.44; $I^2=81\%$).⁽⁸⁾ This effect in favor of LDCT was evident for studies with CXR as comparator (six RCTs; RR 1.52, 95% CI 1.04 to 2.23; $I^2=24\%$) and was more pronounced for studies that used no screening as control (RR 2.73, 95% CI 1.91 to 3.90; $I^2=63\%$). Although the computed I^2 values suggest substantial heterogeneity across studies, all studies except for the DEPISCAN trial ($n=625$) consistently yielded estimates in favor of LDCT. The overall certainty rating for

this body of evidence was downgraded to moderate due to high risk of performance and detection bias.

Diagnosis of Late-Stage Tumors

Pooled estimates from nine RCTs showed an effect favoring LDCT (RR 0.75, 95% CI 0.68–0.83; $I^2=0\%$) for the detection of late-stage tumors.(8) Results of the three trials comparing LDCT with CXR suggest that late-stage cancer detection rates are similar for these two modalities (RR 1.21, 95% CI 0.38 to 3.89; $I^2=27\%$). However, results are inconsistent; the DEPISCAN and LSS trials ($n=4,087$) showed no effect and imprecise results while the NLST trial ($n=54,517$) showed a clear advantage of LDCT. For the six RCTs comparing LDCT with no screening, significantly more late-stage cancer cases were detected with LDCT (RR 0.67, 95% CI 0.56 to 0.80; $I^2=0\%$).

Overdiagnosis

Five RCTs estimated that the percentage of over-diagnosed lung cancer cases was at 30% (95% CI 6% to 55%; $I^2=80\%$).⁽¹⁰⁾ This figure is higher for LDCT versus no screening at 38% (95% CI 14% to 63%; $I^2=65\%$). This pooled estimate is highly uncertain due to the risk of detection bias and widely inconsistent estimates reported across studies ($I^2=65\%$). When compared to CXR, LDCT did not result in significantly higher overdiagnosis rates based on the NLST trial (4%; 95% CI -10% to 18%).⁽¹⁰⁾

Radiation Exposure

Nine studies from the United States Preventive Services Task Force review documented that the associated radiation dose from a single LDCT scan ranged from 0.65–2.36 mSv (Appendix I).⁽¹⁰⁾ The cumulative radiation exposure received by a person from 25 years of annual LDCT screening was estimated to be 20.8–32.5 mSv. The lifetime risk of cancer resulting from 10 annual LDCTs was 2.6–8.1 major cancers for every 10,000 people screened.

False-Positive Results

False-positives were defined as any LDCT-positive finding that led to additional testing (such as repeat LDCT or biopsy) that did not ultimately result in a cancer diagnosis.⁽¹⁰⁾ The false-positive rates across 27 studies from the United States Preventive Services Task Force review ranged from 7.9–49.3% for baseline screening and 0.6–28.6% for subsequent screening rounds (Appendix I).

Further Testing and Complications Following a False-Positive Result

The proportion of patients who underwent additional invasive procedures for a false-positive result were as follows: 0.09–0.56% for needle biopsy (nine studies), 0.5–1.3% for surgical procedures (six studies; e.g., bronchoscopy, thoracotomy, etc.), and 0.1–0.5% for surgical resections (nine studies). In the NLST trial, complications occurred in 0.1% of screened individuals (major – 0.03%, intermediate – 0.05%, minor – 0.01%). LDCT-related deaths occurred in 0.007% of screened individuals (Appendix I).⁽¹⁰⁾

Psychological harms

Seven studies reviewed by the United States Preventive Services Task Force showed that LDCT screening did not significantly worsen general health-related quality of life, anxiety, and distress over a 2-year follow-up period. Higher anxiety was noted for individuals who tested positive for cancer, while distress was worse for those with indeterminate screening test results.(10)

4.9.3 Diagnostic Performance of Screening Tests

The sensitivity and specificity of LDCT were synthesized from 13 studies (six RCTs, seven non-randomized clinical trials; see Appendix I) in the United States Preventive Services Task Force 2021 review.(10) The overall methodological quality of this body of evidence was rated fair/moderate.

Mean values and ranges were reported for sensitivity, specificity, PPV, and NPV. Average sensitivity was 0.80 (0.59–0.95) for RCTs and 0.93 (0.88–1) for non-RCTs.(10) Only three studies reported >0.80 sensitivity. Average specificity was 0.76 (0.26–0.99) for RCTs and 0.79 (0.34–1) for non-RCTs; only three studies reported >0.75 specificity.(10) Average PPV was higher for RCTs at 0.21 (0.03–0.44) compared to non-RCTs, which was 0.09 (0.04–0.21). NPV estimates are similarly high regardless of study types considered (>0.99; 0.98–1).(10)

The imprecision in the diagnostic accuracy estimates was associated with the heterogeneity in participants included, the fair-to-moderate reliability among radiologists, and the number of screening rounds and screening intervals. The incomplete follow-up duration, especially for the non-randomized studies, may not have been adequate to detect false-positive and false-negative cases.

In terms of the impact of certain variables on diagnostic accuracy, United States Preventive Services Task Force found evidence from two studies (n=44,792) that for persons aged >65 years, LDCT is more sensitive (0.94 vs. 0.93), less specific (0.72 vs. 0.78), and has increased PPV (0.05 vs. 0.03).(10) Data from the other study in Japan found no impact of sex or smoking status on test accuracy. Three other retrospective studies (n=73,404) showed that using the Lung-RADS criteria increased specificity (0.73–0.87) while using larger nodule size thresholds (>5 mm diameter) increased PPV. RCTs that recorded significant reduction in lung cancer-related mortality also showed that the screening protocol used influenced test accuracy. The NELSON trial in Netherlands used a volumetric approach and added an indeterminate nodule result category, which resulted in moderate sensitivity (0.77) and high specificity (0.96). In contrast, the NLST trial that used a maximum diameter without an indeterminate result category had high sensitivity (0.93) and poor specificity (0.59).

4.9.4 Cost Implication

A systematic review of economic evaluations of LDCT screening for lung cancer from 2004–2017 was performed by Snowsill et al. in 2018 for the context of the United Kingdom. Based on their synthesis of 19 trial- and model-based analytic studies and five

systematic reviews, LDCT screening was reported to be more effective but also more expensive compared to no screening.(11) No conclusions in terms of cost-effectiveness were given as inconsistent results were reported across studies. Certainty of evidence was very low due to serious inconsistency, serious risk of bias (no sensitivity analyses, unsupported assumptions, incomplete costing), and serious indirectness (no Philippine study).

The factors that significantly increased cost-effectiveness of LDCT screening were the following: female sex; age and smoking history; lower cost of LDCT scans; low prevalence or risk of lung cancer in the target population; and higher effectiveness of LDCT (effects in reducing lung cancer mortality, prolonging survival beyond lead time, stage shift without significant overdiagnosis).(10)

Based on a PESO study in 2018, the mean combined Month 3 and Month 12 out-of-pocket health expenditures of Filipino cancer patients was PHP 181,789.00.(12) Indirect costs—transportation fees, meals, and outside caregiver salaries—have the highest share of Month 12 expenditures at PHP 70,510.20, followed by medication expenses at PHP 51,138.42. Hospitalization costs ranged from no expenses to PHP 9,885.57.(12) Treatment for lung cancer was associated with catastrophic financial burden. Chemotherapy alone cost within the range of PHP 50,000–120,000 per month. Medicines were estimated to cost monthly as much as PHP 100,000 or more (Table 34).(13)

Table 34. Costs of screening interventions for lung cancer

Parameter	Cost of CXR
<i>Unit cost of screening intervention</i>	CT scan of chest (PHP 5,500.00 = 1 x PHP 5,500.00) (14)
<i>Other direct costs associated with the implementation of the proposed screening intervention</i>	<p>Initial and follow-up outpatient consultations with primary care physicians or specialists (PHP 150.00 = 2 x PHP 75.00) (15)</p> <p>According to the Clinical Treatment Guidelines of the PCS, it is recommended for lung cancer suspects to undergo CT scan of chest, abdomen, and adrenal glands as it is considered to be the most useful and highly-sensitive among all modalities and confirmatory tests in determining the characteristics of lung cancer.(16)</p> <ol style="list-style-type: none"> 1. CT scan of abdomen (PHP 8,100.00 = 1 x PHP 8,100.00) (14) 2. CT scan of adrenal glands (PHP 8,450.00 = 1 x PHP 8,450.00) (14) <p>Costs related to professional fees, contrast material, may vary. Costs of linked treatments (e.g., bronchoscopy, thoracotomy, biopsy, surgery, etc.) are not yet accounted for.</p>
<i>Annual treatment cost per patient</i>	PHP 22,200.00
<i>Total number of users of the screening intervention</i>	Among all cancer sites, lung cancer ranked 2nd among the highest incidences comprising about 12.5% of the total cancer cases newly diagnosed in 2020 which amounted to 19,180 cases.(1)
<i>Estimated budget impact</i>	PHP 425,796,000.00 = 22,200.00 x 19,180

CXR chest X-ray; PHP Philippine peso

*As of November 26, 2020, \$1 = PHP 50.5

4.9.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

Ethical

Gender and social differences were also identified as significant factors influencing participation in lung cancer screening programs, particularly populations with higher socioeconomic status, and males.(17) The results of this review were also mirrored by another study in the USA that showed higher participation in higher income, older age, and insured groups with low baseline risk as compared to high lung cancer risk group (e.g., ever smokers, minorities).(18) Individuals with HIV-positive status and occupational exposure must also be considered as they have a disproportionately higher burden of lung cancer morbidity.(17,19) Strategies should be done to increase engagement among these subgroups to ensure equity.

Social

One study describing the online search behaviors of Filipinos related to lung cancer revealed that Filipinos had a steady interest in learning about its etiology, symptoms, and management in the last decade.(20) However, a formal qualitative study on the social, behavioral, and cultural determinants of participation in a lung cancer screening program in the Philippines still needs to be done, as well as the most efficient strategies to promote and improve lung cancer screening participation especially among high-risk groups.

A systematic review of factors influencing participation in LDCT screening among East Asian populations showed that females and persons with older age (>50 years) had significantly improved screening rates (for female: OR 1.32, 95% CI 1.15 to 1.52; for adults: OR 1.94, 95% CI 1.52 to 2.49).(21)

Health Systems

To reduce the high cost and risks of LDCT (i.e., false-positives), certain strategies were proposed by two reviews.(22,23) These include (a) using semi-automated volume measurement and use of doubling time as reference method to optimize risks and minimize false positive rates; (b) surveillance of subsolid nodules to reduce overdiagnosis and overtreatment; (c) maximizing bronchoscopy and identification of biomarkers; and (d) adapting a tailored approach with personalized risk stratification (e.g., longer interval between LDCT screening rounds for participants with lower risk).

4.9.6 Recommendations from Other Groups

As of March 2021, the United States Preventive Services Task Force recommends annual LDCT screening for adults 50–80 years with a 20 pack-year smoking history and currently smoke, or former smokers who have quit within the past 15 years (Table 35). The same recommendation in favor of LDCT is maintained by the Canadian Task Force on Preventive Health Care, but specifies a narrower age range (55–74 years) and a longer pack-year smoking history (>30 years). LDCT is strongly not recommended for all other populations who do not meet these criteria.(24)

Table 35. Summary of key recommendations from other groups

GUIDELINE	POPULATION	RECOMMENDATIONS
Canadian Task Force on Preventive Health Care (2016) (25)	Inclusion: Asymptomatic adults, 18 years of age and older, not suspected of having lung cancer on clinical grounds, with/without risk factors (e.g., smoking, exposure to substances) Exclusion: Age < 18 years, with suspected or previous diagnosis of lung cancer	Weak recommendation, low-quality evidence <ul style="list-style-type: none"> LDCT every year up to 3 consecutive years Among adults aged 55 to 74 years with at least a 30 pack-year smoking history, who smoke or quit smoking less than 15 years ago Screening should only be done in health care settings with access to expertise in early diagnosis and treatment of lung cancer Strong recommendation, very low-quality evidence <ul style="list-style-type: none"> Not screening all other adults, regardless of age, smoking history or other risk factors, for lung cancer with LDCT
US Preventive Services Task Force (2013; 2020; 2021) (24)	2013: Adults aged 55-80, with a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 y 2020: Adults aged 50-80, with at least 20 pack-year smoking history	Grade: B[†] The United States Preventive Services Task Force recommends annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

[†] Grade B: United States Preventive Services Task Force recommends the service; high certainty that the net benefit is moderate or there is more moderate certainty that the net benefit is moderate to substantial

[‡] Evidence last reviewed 2015;

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4.10 Upper Gastrointestinal Series or Upper Endoscopy in Screening for Gastric Cancer

RECOMMENDATION

1. Among apparently healthy adults aged 40 to 70 years without risk factors, we suggest against routine screening for gastric cancer using either upper endoscopy or upper gastrointestinal series.
(weak recommendation, very low certainty evidence)

2. Among apparently healthy adults with risk factors, we suggest shared decision making before doing active screening for gastric cancer using upper gastrointestinal series or upper endoscopy.
(weak recommendation, very low certainty evidence)

*Risk Factors:

- Age ≥40 years
- Family history of gastric cancer
- Documented history of precancerous lesions for gastric cancer (i.e., atrophic gastritis, intestinal metaplasia)
- History of *H. pylori* infection
- Obesity
- History of smoking
- History of high consumption of salted food

Considerations

The consensus panel considered the following when formulating this recommendation:

- Gastric cancer is a priority health problem
- Screening with upper GI series or upper endoscopy is favored as there is perceived tradeoff between the large benefit and the good diagnostic accuracy of the tests with the moderate harm and moderate cost of the tests.
- The certainty of evidence of benefits and harms was judged to be very low, while the certainty of the evidence for resource requirement was deemed moderate.
- Screening with upper GI series or upper endoscopy is feasible with reduced equity, variable acceptability, and possibly important uncertainty or variability with patient values and preferences.
- Data used as bases for the recommendations came from countries with high incidence for gastric cancer.

4.10.1 Burden of disease

Disease Frequency

Cancer is a leading cause of death in the Philippines, second only to ischemic heart disease.(1)

A decline was observed in the age-standardized incidence rate for gastric cancer (from 11.8% to 7.5%) during 1980–2002, which was largely attributed to changes in food preservation such as refrigeration rather than salting or smoking.(2) Gastric cancer has since dropped to the 13th most common cancer overall in the Philippines by 2020, with an incidence rate of 2.2% and a 5-year prevalence of 4.13 per 100,000 population.(3)

Globally, gastric cancer ranks 6th among all-cancer incidence and is the 4th leading cause of death.(4) Eastern Asia (particularly South Korea, Mongolia, and Japan) has the highest prevalence of gastric cancer, while some South American and Eastern European countries (i.e., Chile, Costa Rica, Kyrgyzstan, Lithuania, and Singapore) belong to the intermediate-risk group. Despite their numbers, cost-benefit analysis showed that screening by endoscopy is most cost-effective among high- and intermediate-risk countries. The Philippines, the United States of America (7 per 100,000), and Australia (8.3 per 100,000) are considered low-risk countries.

The 5-year survival rate of gastric cancer depends on the type and stage of the cancer. Localized cancer has survivability of 70%, while those with regional and distant spread have significantly lower survival rates at 32% and 6%, respectively.(5) Among residents of Metro Manila, the 5-year relative survival rate was 27%, which is slightly lower than that of Filipino-Americans (31%).(2) Mortality due to gastric cancer reached 1,954 in 2018 and had an age-adjusted death rate of 2.89 per 100,000 population, making it 38th among the causes of death in the Philippines and 157th in the world.(6)

Gastric cancer is a multifactorial disease that involves both genetic and environmental risk factors. These include (in descending order) intestinal metaplasia, *H. Pylori* infection, a family history of gastric cancer, high salt intake, cigarette smoking, obesity, and alcohol.(7,8) Additional risk factors include non-white origin, history of gastric surgery for benign disease >15 years, age >45 years old, and male sex.(7,9)

Management of the Disease

Korea and Japan have been implementing national screening programs for gastric cancer due to their high incidence rates; hence, survival rates in these countries have improved. The high cost of screening and, to a certain extent, the fear of finding out has precluded early detection in most of our elderly population.

Apart from countries where gastric cancer is highly prevalent, many generally lack national guidelines or recommendations for screening of gastric cancer.(10) Aside from the high cost of screening, there is no evidence that screening for gastric cancer would result in a decrease in mortality in areas with relatively low incidence of the disease, such as in the United States of America, Australia, and Europe.(11)

Endoscopic US, CT scan, and endoscopic biopsies are some of the diagnostic procedures performed for confirmation.(12,13) These can be followed by endoscopic mucosal resection or endoscopic submucosal dissection, which can also be considered as adequate therapy for lesions ≤ 2 cm in diameter. Gastrectomy and lymphadenectomy are recommended for gastric cancers that are poorly differentiated, invasive, and with possible lymph node metastases. Patients may undergo chemotherapy and/or radiotherapy, and targeted biologicals depending on the stage, type of gastric carcinoma, and biomarkers present. Genetic risk assessment is also sometimes done in countries with high risk of gastric cancer.

Any gastric cancer treatment involves surgery along with a long recovery period. Risks from surgery and concomitant chemotherapy or radiography include pain, bleeding, diet restrictions, hair loss, nausea, diarrhea, weakness, and hyperpigmentation, to name a few.(14)

4.10.2 Benefits and Harms of Screening Tests

There were no RCTs that compared active screening (i.e., using either upper endoscopy or upper gastrointestinal series) with no screening among apparently healthy and/or asymptomatic adults on mortality and other patient-important outcomes. It was noted in the literature search that RCTs were difficult to implement particularly in countries like Korea and Japan where gastric cancer screening has been introduced in their national programs.(15) See Appendix J.

Table 36. All-cause mortality and adverse events from upper endoscopy screening and treatment of gastric cancer

Outcomes	No. of Studies (no. of participants)	Effect estimate (95% CI)	Level of Certainty
Gastric cancer-related mortality	1 SRMA with 10 studies: 4 nested case control, 6 cohort Eastern China, n=342,013 (15)	pooled RR 0.60 (0.49, 0.73) $I^2=66.7\%$, $p<0.001$	Low
All-cause mortality	1 cohort (n=20,066) (16)	HR 0.80 (0.72, 0.89) for <2 yrs HR 0.83 (0.76, 0.91) for 2–5 yrs	Low
	1 case control (n=13,985) (17)	OR 0.58 (0.56, 0.61), $p<0.001$	
	1 cohort (n=4,394) (18)	SMR 0.71 (0.63, 0.81)	
Adverse events due to screening	1 RCT (n=9,142) (19)	0.07%, $p<0.0001$	Low

HR hazard ratio; OR odds ratio; RCT randomized controlled trial; RR risk ratio; SMR specific mortality rate; SRMA systematic review and meta-analysis

A. Upper Endoscopy

A systematic review and meta-analysis pooled together nonrandomized studies (i.e., six cohort studies and four nested case-control studies) that looked into the comparison of at least one endoscopic screening (including mass screening or opportunistic screening) followed by entry or no entry into surveillance among adults aged >18 years without diagnosis of gastric cancer in the general population for outcomes of mortality and incidence of gastric cancer after endoscopic screening. These studies were compared with the following: no screening, other screening methods (e.g., radiographic screening), or expected numbers in the general population.(15)

Gastric Cancer-Specific Mortality

A systematic review by Zhang et al. (3 case-control studies, 7 cohort studies, n=342,013) found a significant reduction in gastric cancer-specific mortality (pooled RR 0.60, 95% CI 0.49 to 0.73).(15) In a subgroup analysis, endoscopic screening was significantly associated with a reduction in gastric cancer-specific mortality compared to those belonging to the never screened group (RR 0.58, 95% CI 0.48 to 0.70, $p<0.001$, $I^2=42.5\%$).^(17,20–24) In another subgroup analysis, gastric cancer-specific mortality was reduced among those screened (RR 0.56, 95% CI 0.48 to 0.65, $p<0.001$, $I^2=34.8\%$)^(17,20–27) but not in the screening followed by surveillance group (included one study).⁽¹⁸⁾

The review also showed that endoscopic screening provided protection in both men (RR 0.62, 95% CI 0.48 to 0.81, $p=0.001$, $I^2=76\%$) and women (RR 0.58, 95% CI 0.44 to 0.78, $p<0.001$, $I^2=44.4\%$).^(17,18,20,22,26,27)

Significant reduction in gastric cancer-specific mortality was observed upon comparison by study design, particularly among those in the nested case-control study (RR 0.60, 95% CI 0.47 to 0.76, $p<0.001$, $I^2=61.1\%$)^(17,20–22) and in the cohort study (RR 0.57, 95% CI 0.39 to 0.83, $p=0.003$, $I^2=70.8\%$).^(18,23–27)

An associated significant decrease in gastric cancer specific mortality was seen in studies done in Japan (RR 0.51, 95% CI 0.38 to 0.69, $p<0.001$, $I^2=37.8\%$)^(20,21,23,25–27) and in Korea (RR 0.53, 95% CI 0.51 to 0.56; $p<0.001$, $I^2=0.0$)^(17,24). Endoscopic screening in China was associated with a 15% non-statistically significant reduction in gastric cancer mortality (RR 0.85, 95% CI 0.61 to 1.18, $p=0.326$, $I^2=57.0\%$).^(18,22)

All-Cause Mortality

A large case-control study that matched 54,418 pairs of newly diagnosed gastric cancer cases with never-screened individuals found an odds ratio of 0.83 (95% CI 0.81 to 0.85), with the odds ratios increasing directly with age but not with economic status.⁽¹⁷⁾ Similarly, a cohort study that compared all-cause mortality among newly-diagnosed cases and their time from endoscopic screening found hazards ratios similar to the first study for <2 years and 2–5 years screening period with HR of 0.80 (95% CI 0.72 to 0.89) and 0.83 (95% CI 0.76 to 0.91), respectively.⁽¹⁶⁾

Unlike gastric cancer-related mortality rate, mortality from all causes was reduced by almost 30% in the 11-year study in China.⁽¹⁸⁾ This may be because only healthy individuals were included in the study and may have subsequently led to an increased health consciousness among the participants.

Adverse Events

A 10-year study of medical records on upper gastrointestinal endoscopic procedures showed that iatrogenic perforation from diagnostic endoscopy was 0.002% (3/149,792).⁽²⁸⁾ A single retrospective study in Japan that compared the detection rate of gastrointestinal endoscopy and radiography also monitored for adverse reactions. Six

patients out of 9,142 (0.06%) experienced nasal bleeding (n=2), Mallory-Weiss syndrome (n=2) or lidocaine allergy (n=1). No serious adverse reactions, i.e., anaphylactic shock, respiratory depression or fatality were reported.(19)

B. Upper Gastrointestinal Series

A systematic review of four case-control studies and four cohort studies evaluated the effect of gastric cancer by photofluorography on mortality was found.(10) One case-control study was conducted in Venezuela, while the rest were from Japan. The subgroup of case-control studies conducted in Japan demonstrated a 40–60% reduction in gastric cancer-related mortality, while the study done in Venezuela did not show any detectable reduction in this outcome.(29) In that subgroup of three case-control studies, the odds ratios for ever-screened versus never-screened subjects were 0.39% (95% CI 0.29 to 0.52) for men and 0.50 (95% CI 0.34 to 0.72) for women in reducing gastric cancer mortality.(30–32)

Among the cohort studies, one study lacked statistical power and did not show any significant difference in the relative risk of mortality.(33) Another cohort revealed significantly reduced mortality in men (RR 0.54, 95% CI 0.41 to 0.70) but not in women (RR 0.74, 95% CI 0.51 to 1.07).(34) Two cohorts, one with a 13-year follow-up, found a 40% reduction in mortality among screened versus unscreened subjects (RR 0.60, 95% CI 0.43 to 0.83 and RR 0.52, 95% CI 0.36 to 0.75), respectively.(35,36)

4.10.3 Diagnostic Performance of Screening Tests

A. Upper Endoscopy

In two prospective, fair-quality studies, one used biopsy as a reference standard (n=18,021) and the other study compared upper endoscopy with the national cancer registry as a reference standard (n=924,822) (see Appendix J). These studies showed that the pooled sensitivity of upper endoscopy was 0.70 (95% CI 0.68 to 0.71) and the specificity was 0.96 (95% CI 0.96 to 0.96) for detecting gastric cancer.(37,38) Both studies included participants aged >40 years, excluding only those with history of gastric cancer, missing information, or whose screening method was unclear. One study divided the group based on screening history (i.e., prevalence, and incidence screening), while the other subgroups were stratified according to sex, age, and health insurance type.

Previous studies also reported the superiority of upper endoscopy over upper GI series, and have generally accepted upper endoscopy with biopsy as the gold standard for the diagnosis and clinicopathological evaluation for gastric cancer.(37)

In a population-based study in Korea from 2002–2004 (n=2,690,731), 66.0% underwent upper GI series screening while 34% had endoscopy where the latter was chosen by mostly younger men and insurance beneficiaries. The gastric cancer detection rate of upper GI series was significantly lower (0.68 per 1,000 screenings) than that of endoscopy (2.61 per 1,000 screenings).(37) Another study done concurrently in the same span had 1,503,646 participants undergoing upper GI series (n=1,067,378) and

endoscopy (n=436,268). The probability of finding a true positive using upper GI series was 836 per 100,000 while that for endoscopy was 2,386 per 100,000, with a 2.9-fold higher detection for endoscopy.(39) Following this, a nested case control study analyzed 54,418 patients who died of gastric cancer and were matched with 217,672 controls (n=272,090). The study determined the proportion of screen-detected cancer using upper GI series, endoscopy, or both, wherein screen-detected cancer by endoscopy was higher (72.3%) than that for upper GI series (50.4%).(17)

Researchers in Japan compared the detection rates of endoscopy, X-ray, and photofluorography for 3 years in a mass screening program (n=106,246). They found that detection ratio for endoscopy by the third year was 0.87%, approximately 2.7 and 4.6 times higher than X-ray (0.32%) and photofluorography (0.19%), respectively. (40)

B. Upper Gastrointestinal Series

One review with eight studies, majority of which were done by the Japanese, reported that the sensitivity of upper GI series ranged from 0.57–0.89, while specificity ranged from 0.81–0.92.(10) A study done in Korea showed that upper GI series had a sensitivity and specificity of 0.37 and 0.96, respectively. The differences in sensitivities and specificities might have been affected by the screening intervals, which was biennially in Korea and annually in Japan.(37)

Pooled estimates from a systematic review of 10 observational studies and 2 large studies from Korea and Japan (n=3,797,996), showed a sensitivity of 0.61 (95% CI 0.60 to 0.62), a specificity of 0.90 (95% CI 0.90 to 0.903), and a PPV of 0.01 (95% CI 0.01 to 0.01). The authors concluded that identifying false-negative cases was crucial in quantifying these indices and suggested that follow-up those who screened negative could be done to ascertain the cancer cases that may arise among them.(37,41,42)

In the systematic review of 10 studies showed sensitivities ranging from 0.66–0.90 and specificities ranging from 0.77–0.92. While the range of overall diagnostic accuracy estimates are wide, the studies show acceptable diagnostic accuracy.(42)

4.10.4 Cost Implication

A study in Japan concluded that while endoscopy costed more than ordinary upper GI series, the overall cost of identifying one case of gastric cancer with endoscopy was much less than the other two methods, and was more cost-effective overall.(40)

Cost-effectiveness studies among Filipino Americans in the U.S. (specifically among patients aged 50 years, irrespective of sex, and subsequent endoscopy only when indicated) showed that one-time endoscopic screening bundled with colonoscopy for colorectal cancer screening was the most cost-effective. Among Asian Americans, Filipino Americans had the highest ICER, but these were still cost-effective at the predetermined willingness-to-pay threshold. The ICER for males was higher (USD 88,190) than females (USD 83,732). Biennial endoscopic surveillance was less effective, caused more harm, and was costlier.(43) When bundled as part of an aggregated group

of Asian Americans, one-time endoscopic screening bundled with colonoscopy was also found to be cost-effective at the predetermined willingness-to-pay threshold of USD 100,000/QALY, with an ICER of USD 71,451/QALY.(44)

A systematic review of 17 studies showed that screening with annual surveillance (if indicated) generated lower ICERs compared with biennial screening (five studies: United States, Europe, Singapore) and that endoscopic screening was more cost-effective compared with upper GI series (six studies: Korean, Japan, Singapore). The review concluded that systematic screening and surveillance strategies were paramount to reducing gastric cancer morbidity, mortality, and societal costs, given that early detection was directly associated with improved mortality.(45) Moreover, they mentioned that high-quality decision analysis can best serve low- to intermediate-incidence and resource-limited countries (such as the Philippines) to define high-risk groups who may benefit the most from gastric cancer screening and preneoplasia surveillance.

There is an apparent wide range of price for endoscopy in the Philippines varying from institution to institution, possibly due to newer imaging devices (Table 37). The cost of an upper GI series seems to be cheaper and more stable.

Table 37. Unit costs of screening intervention and confirmatory testing

Screening intervention		Confirmatory Test
<i>Upper Endoscopy</i>	<i>Upper GI series (radiography)</i>	<i>Histopathology</i>
PHP 6,000–15,000 (without anesthesia) PHP 25,000–45,000 (private, with anesthesia)	PHP 1,600–2,500 (with dye; RMC) PHP 2,500–5,000 (private)	PHP 2,650–15,000

PHP *Philippine peso*; GI *gastrointestinal*

Table 38 presents confirmatory tests and treatments for gastric cancer and their corresponding costs. Subsequent confirmatory tests like histopathology, and appropriate therapeutic interventions should be considered as part of the cost impact to the patient. There are no PhilHealth Z packages for cancer of the stomach, nor for the surgery, subsequent chemotherapy, neoadjuvant therapy, and the surveillance that proceeds after.

Table 38. Costs of confirmatory test and treatments associated with gastric cancer*

Procedure	Cost
Endoscopic Biopsy	PHP 2,000–5,000
CT scan (chest and abdomen)	PHP 15,000–30,000

PHP *Philippine peso*

*range taken from government and private hospitals in Metro Manila and CALABARZON

4.10.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

A recent retrospective study assessed the feasibility of including endoscopic screening in a comprehensive health checkup (n=13,120), evaluating both gastrointestinal endoscopy and radiography. Gastric cancer detection rate was higher in the endoscopy group

(34/9,142 or 0.48%) than in the gastroscopy group (3/3,978 or 0.08%) ($p=0.003$).⁽¹⁹⁾ The population was individuals ≥ 20 years of age undergoing a comprehensive health checkup. Propensity-score matched analysis was done to minimize confounders and selection bias.

The price of endoscopy starts at a minimum of PHP 6,000. It is higher if patients opt for anesthesia while it is a bit lower for charity rates. There are 13 hospitals in the NCR and 6 in the rest of the Philippines that offer these services. No health facilities offer this procedure in Central and Northern Luzon.⁽⁴⁶⁾ The disparity in availability of services and their highly variable rates are a few of the apparent inequities in access to cancer screening and care. Other factors include lower income, level of education, age, and areas of residence.

Most people in LMIC like the Philippines pay for healthcare out of their own pockets. A study showed that out-of-pocket spending for catastrophic conditions like cancer is increasing, and that financial protection remains low in the Philippines.⁽⁴⁷⁾ More than 40% of families experienced financial toxicity, with about 25% falling into the lowest income bracket.⁽⁴⁸⁾

A lot of Filipinos with cancer use complementary and alternative medicine, usually herbal and dietary supplements (HDS).⁽⁴⁸⁾ A study done by the Cancer Institute of UP PGH showed that about 89% (338/380) of patients with cancer use HDS for their illness; 63% initiated use after cancer diagnosis and 42.3% continued along with systemic intervention.⁽⁴⁹⁾ Approximately 25% delayed conventional treatment in favor of HDS.

4.10.6 Recommendations from Other Groups

Low-risk countries such as North America and Europe do not recommend screening for gastric cancer, except for those with genetic or familial high-risk assessments and those of Asian descent. The recommended surveillance is every 3 years for those at risk.⁽⁹⁾ The National Cancer Institute did not find evidence that screening would decrease mortality in gastric cancer.⁽¹¹⁾

Intermediate-risk countries (IR 10–20 per 100,000 population) like China and Taiwan, screening was recommended for those with gastric cancer-associated genetic syndromes such as Peutz-Jegher syndrome. Screening and surveillance of family members are also recommended.

High-risk countries (IR <20 per 100,000 population) such as Japan and Korea recommend population-based, opportunistic screening as studies have shown that the benefits outweigh the harms, especially for individuals aged 40 and above, or those who are younger if they have a strong family history.

Table 39. Summary of key recommendations from clinical practice guidelines

Group	Recommendation	Strength of recommendation and certainty of evidence
National Health Commission of Peoples Republic of China (2018) (13)	Screening is recommended for gastric cancer patients over 40 years old, with family history of gastric cancer and pre-gastric cancer related diseases or risk factors. Patients younger than 40 but with GA-associated genetic syndromes, ie Juvenile Polyposis and Peutz-Jegher syndromes should also be screened.	None mentioned
National Comprehensive Cancer Network (2021) (12)	Esophagogastroduodenoscopy (EGD with extended duodenoscopy) may be considered as a screening strategy in select individuals who have genetic or familial high-risk assessment or those of Asian descent.	Level of evidence : LOW Consensus : Intervention is Appropriate
British Society of Gastroenterology (9)	Endoscopic screening should be considered in individuals aged >= 50 years with multiple risk factors for Gastric adenocarcinoma (GAD) (male, smokers, pernicious anemia)- in particular, in those with a first-degree relative with GA Do not recommend screening for GAD in the UK population	Evidence Level: Low Grade of Recommendation : Weak Level of Agreement : 100% Evidence Level : Low Grade of Recommendation : Strong Level of Agreement : 100%
National Cancer Center, Division of Cancer Screening Assessment and Management (2018) (50)	Endoscopic and radiographic screenings are recommended for population-based and opportunistic screenings as its benefits outweigh its harms. (For individuals ages 50 and above)	Grade of Recommendation : B (moderate) Level of Evidence : 2+ (Medium quality with low risk of bias, confounding and moderate probability that relation is causal. Overall consistency is needed)
European Society of Gastrointestinal Endoscopy (2020) (51)	In high-risk populations, endoscopic screening for gastric cancer should be considered for individuals aged more than 40 years. Its use in countries/regions with intermediate risk may be considered on the basis of local settings and availability of endoscopic resources.	
National Cancer Screening Programme (17)	NCSP recommends biennial gastric cancer screening for men and women aged 40 years or older, by either upper gastrointestinal series or upper endoscopy.	None stated

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5. RESEARCH IMPLICATIONS

Many neoplastic diseases covered in this CPG lacked direct evidence on the screening methods specified in the clinical question: EBV blood test versus nasopharyngoscopy among the general population and high-risk persons (NPCA); US and AFP in the general population (HCC); HPV co-testing and primary HPV testing (cervical cancer); toluidine blue or fluorescent light versus no screening (oral cancer); FIT versus FOBT (CRC); breast US versus no screening (breast cancer); DRE versus no screening (prostate cancer); LDCT versus no screening for the low-risk population (lung cancer); and active screening using either upper endoscopy or upper gastrointestinal series versus no screening (gastric cancer). Retinoblastoma lacked a screening test capable of detecting disease in the preclinical phase, and the evidence for the RRT was only for the diagnosis of ocular abnormalities in general. It was suggested during the CP meeting that future CPGs on retinoblastoma could look into the use of indirect fundoscopy as a tool for early diagnosis. In terms of benefits and harms, there were no studies that covered overall survival and NPCA-specific mortality for NPCA, and all-cause mortality for oral cancer and CRC. Studies on psychological distress were also lacking for HCC and oral cancer.

Conducting studies on some cases, such as for gastric cancer, present a challenge as high-incidence countries have long-established screening programs for these cancers, making it difficult to recruit participants. The non-invasiveness of FIT and FOBT as stool exams also deter the conduct of further large-scale studies to directly compare the two screening tests. For retinoblastoma, it would be unethical to conduct clinical trials for this subset of the population, as it would entail withholding an intervention from children with active cancer. Additionally, while there have been cost-effectiveness studies and acceptability studies done for many of the neoplasms covered above, many of these studies were conducted in Western settings or in countries with incomparable disease burden. Hence, these may not be applicable to the Philippine setting.

Many research questions emerged from collating the evidence for this CPG and during the CP discussions. Filling in these gaps can provide a clearer picture of the impact of screening programs using previously mentioned tests and may influence the recommendations for updating this guideline.

6. DISSEMINATION AND IMPLEMENTATION

A full copy of this document will be sent to the Department of Health for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC) and health maintenance organizations (HMOs) and NGOs involved in a periodic health examination. The recommendations and the evidence summaries will be posted in the PHEX web based application.

All strong recommendations in this guideline can be used for monitoring and auditing practices in institutions. This can be converted to key performance indicators and it can also be used in creating clinical pathways.

The DOH planned to develop a simplified version of this CPG and made it available in the format that will be ready for reproduction and dissemination to the patients in different health care settings. It will also be available for interested parties who might visit the DOH website.

7. APPLICABILITY ISSUES

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. Comprehensive history taking, physical examination, and monitoring are essential parts of evaluating risk factors and the probability of developing diseases. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those part of the workforce.

8. UPDATING OF THE GUIDELINES

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. The CPGs will be updated every 3-5 years or earlier if new significant evidence becomes available.

9. APPENDICES

Search Strategy, Characteristics of Included Studies, Forest Plots, GRADE Evidence, and Cost-effectiveness Studies for the Research Questions

1.Screening for Retinoblastoma

SEARCH STRATEGY

Date of search: 29 July 2021

Name of database: PubMed

CPG search

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms]) (((((((screening) OR ("ophthalmologic examination")) OR ("ophthalmic examination")) OR ("ocular examination")) OR ("eye examination")) OR (funduscopy)) OR (ophthalmoscopy)) OR ("red reflex")) OR ("early diagnosis")) OR ("early detection")	7,613 5,340,896
2	#1 AND #2	2,650
3	(guideline[Publication Type]) OR (practice guideline[Publication Type])	35,985
4	#3 AND #4	4

Screening & mortality

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms]) (((((((screening) OR ("ophthalmologic examination")) OR ("ophthalmic examination")) OR ("ocular examination")) OR ("eye examination")) OR (funduscopy)) OR (ophthalmoscopy)) OR ("red reflex")) OR ("early diagnosis")) OR ("early detection")	7,613 5,340,896
2	#1 AND #2	2,650
3	(((((("meta analysis"[Publication Type]) OR ("systematic review"[Publication Type])) OR ("review"[Publication Type])) OR ("randomized controlled trial"[Publication Type])) OR ("clinical trial"[Publication Type])) OR ("clinical study"[Publication Type])) OR ("observational study"[Publication Type])	3,962,560
4	#3 AND #4	386
5	((mortality) OR (death)) OR (survival)	2,959,460
6	#5 AND #6	107

Screening & blindness

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms]) (((((((screening) OR ("ophthalmologic examination")) OR ("ophthalmic examination")) OR ("ocular examination")) OR ("eye examination")) OR (funduscopy)) OR (ophthalmoscopy)) OR ("red reflex")) OR ("early diagnosis")) OR ("early detection")	7,613 5,340,896
2	#1 AND #2	2,650
3	(((((("meta analysis"[Publication Type]) OR ("systematic review"[Publication Type])) OR ("review"[Publication Type])) OR ("randomized controlled trial"[Publication Type])) OR ("clinical trial"[Publication Type])) OR ("clinical study"[Publication Type])) OR ("observational study"[Publication Type])	3,962,560
4	#3 AND #4	386
5	((blindness) OR ("loss of vision")) OR ("vision loss")) OR ("visual loss")) OR ("visual disturbance")	70,163
6	#5 AND #6	11

Screening & diagnostic accuracy

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms]) ((((((screening) OR ("ophthalmologic examination")) OR ("ophthalmic examination")) OR ("ocular examination")) OR ("eye examination")) OR (funduscopy)) OR (ophthalmoscopy)) OR ("red reflex") OR ("early diagnosis")) OR ("early detection")	7,613 5,340,896
2	#1 AND #2	2,650
3	(((((meta analysis"[Publication Type]) OR ("systematic review"[Publication Type])) OR ("review"[Publication Type]))) OR ("randomized controlled trial"[Publication Type])) OR ("clinical trial"[Publication Type])) OR ("clinical study"[Publication Type])) OR ("observational study"[Publication Type])	3,962,560
4	#3 AND #4	386
5	((((sensitivity) OR (specificity)) OR (accuracy)) OR ("likelihood ratio")) OR ("predictive value")	5,663,262
6	#5 AND #6	58

Screening & cost-effectiveness

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms]) (((((((screening) OR ("ophthalmologic examination")) OR ("ophthalmic examination")) OR ("ocular examination")) OR ("eye examination")) OR (funduscopy)) OR (ophthalmoscopy)) OR ("red reflex") OR ("early diagnosis")) OR ("early detection")	7,613 5,340,896
2	#1 AND #2	2,650
4	((("economic analysis") OR ("cost-effectiveness")) OR ("cost-benefit")) OR ("cost-minimization")) OR ("cost-utility")	128,597
5	#3 AND #4	4

Treatment & mortality

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms])	7,613
2	Therapy[MeSH Subheading]	7,419,045
3	#1 AND #2	3,088
4	((("meta analysis"[Publication Type]) OR ("systematic review"[Publication Type])) OR ("review"[Publication Type])) OR ("randomized controlled trial"[Publication Type]) OR ("clinical trial"[Publication Type])) OR ("clinical study"[Publication Type]) OR ("observational study"[Publication Type])	3,962,560
5	#3 AND #4	471
6	((mortality) OR (death)) OR (survival)	2,959,460
7	#5 AND #6	132

Treatment & adverse effects

#	Search terms	Results
1	(eye cancer, retinoblastoma[MeSH Terms]) OR (familial retinoblastoma[MeSH Terms])	7,613
2	Therapy[MeSH Subheading]	7,419,045
3	#1 AND #2	3,088
4	((("meta analysis"[Publication Type]) OR ("systematic review"[Publication Type])) OR ("review"[Publication Type])) OR ("randomized controlled trial"[Publication Type]) OR ("clinical trial"[Publication Type])) OR ("clinical study"[Publication Type]) OR ("observational study"[Publication Type])	3,962,560
5	#3 AND #4	471
6	Adverse Effects[MeSH Subheading]	2,296,317
7	#5 AND #6	68

NEWCASTLE-OTTAWA SCALE SCORES FOR THE INCLUDED OBSERVATIONAL STUDIES

Quality assessment criteria	Mattosinho et al.	Rodrigues et al.	Rotschild et al.	Yousef et al.
Selection				
Representativeness of the exposed cohort	1	1	0	0
Selection of the non-exposed cohort	0	0	1	1
Ascertainment of exposure	1	1	1	1
Demonstration that outcome of interest was not present at start of study	1	1	1	1
Comparability				
Comparability of cohorts on the basis of the design or analysis controlled for confounders	0	0	0	0
Outcome				
Assessment of outcome	1	1	1	1
Was follow-up long enough for outcomes to occur	1	1	1	1
Adequacy of follow-up of cohorts	1	1	1	1
TOTAL	6*	6*	6*	6*

*High risk

AMSTAR-2 SCORE FOR THE META-ANALYSIS BY TAKSANDE ET AL.

Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	No
Did the review authors use a comprehensive literature search strategy?	Partial yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	No*
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Partial yes
Did the review authors report on the sources of funding for the studies included in the review?	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No*
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

*Critical weakness

2. Screening for Nasopharyngeal Cancer

SEARCH STRATEGY

Date of search: 23 July 2021

Name of database: PubMed

EBV Blood Test for NPCA Screening

Search terms	Yield
("Nasopharyngeal Cancer"[All Fields] OR "Nasopharyngeal Carcinoma"[All Fields]) AND ((("diagnos*" [All Fields] OR "screen*" [All Fields]) AND (((herpesvirus 4, human"[MeSH Terms] OR "human herpesvirus 4"[All Fields] OR "ebv"[All Fields]) AND ("dna"[MeSH Terms] OR "dna"[All Fields])) OR "ebv antibod*[All Fields]))	567

EBV Blood Test and Nasopharyngoscopy for NPCA Screening

Search terms	Yield
((("Nasopharyngeal Cancer"[All Fields] OR "Nasopharyngeal Carcinoma"[All Fields]) AND ((("diagnos*" [All Fields] OR "screen*" [All Fields]) AND (((herpesvirus 4, human"[MeSH Terms] OR "human herpesvirus 4"[All Fields] OR "ebv"[All Fields]) AND ("dna"[MeSH Terms] OR "dna"[All Fields])) OR "ebv antibod*[All Fields]))) OR ((("Nasopharyngeal Carcinoma"[Title/Abstract] OR "Nasopharyngeal Cancer"[Title/Abstract]) AND ((("Nasopharyngoscopy"[Title/Abstract] OR "rhinoscopy"[Title/Abstract] OR "nasopharyngeal examination"[Title/Abstract] OR "endoscopy"[Title/Abstract] OR "visualization"[Title/Abstract]) AND ("screen*[Title/Abstract] OR "diagnos*[Title/Abstract])))	679

Nasopharyngoscopy for NPCA Screening

Search terms	Yield
("Nasopharyngeal Carcinoma"[Title/Abstract] OR "Nasopharyngeal Cancer"[Title/Abstract]) AND ((("Nasopharyngoscopy"[Title/Abstract] OR "rhinoscopy"[Title/Abstract] OR "nasopharyngeal examination"[Title/Abstract] OR "endoscopy"[Title/Abstract] OR "visualization"[Title/Abstract]) AND ("screen*[Title/Abstract] OR "diagnos*[Title/Abstract]))	124*

*no good quality studies using nasopharyngoscopy alone in the NPCA screening

GRADE SUMMARY OF EVIDENCE

Nasopharyngeal cancer screening using EBV serology compared to no screening for asymptomatic populations

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no screening	With NPCA screening		Risk with no screening	Risk difference with NPCA screening
Nasopharyngeal cancer incidence (EBNA1-IgA and anti-VCA IgA)											
80,049 (1 RCT)	very serious ^a	not serious	not serious	not serious	none	Low	99/50636 (0.2%)	62/29413 (0.2%)	RR 1.64 (1.23, 2.18)	196 per 100,000	125 more per 100,000 (from 45 more to 231 more)
Early Diagnostic Rates(EBNA1-IgA and anti-VCA IgA)											
80,049 (1 RCT)	very serious ^a	not serious	not serious	not serious	none	Low	19/50636 (0.0%)	49/29413 (0.2%)	RR 0.81 (0.79, 0.86)	38 per 100,000	7 fewer per 100,000 (from 8 fewer to 5 fewer)
NPCA Specific Mortality (EBNA1-IgA and anti-VCA IgA)											
80,049 (1 RCT)	not serious	not serious	not serious	not serious	none	High	23/50636 (0.0%)	2/29413 (0.0%)	RR 0.22 (0.09, 0.49)	45 per 100,000	35 fewer per 100,000 (from 41 fewer to 23 fewer)
All-Cause Mortality (EBNA1-IgA and anti-VCA IgA)											
80,049 (1 RCT)	not serious	not serious	not serious	not serious	none	High	23/50636 (0.0%)	2/29413 (0.0%)	HR 0.12 (0.03, 0.49)	45 per 100,000	40 fewer per 100,000 (from 44 fewer to 23 fewer)

CI confidence interval; HR hazard ratio; RR risk ratio

a. No allocation concealment and blinding

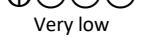
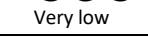
Nasopharyngeal cancer screening using EBV-DNA compared to no screening for asymptomatic populations

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no screening	With NPCA screening		Risk with no screening	Risk difference with NPCA screening
Nasopharyngeal Cancer Incidence (EBV-DNA)											
21,452 (1 OS)	very serious ^a	not serious	not serious	not serious	none	 Very low	This study compared those screened with EBV-DNA (N=20,174) vs a historical sex- and aged-matched cohort (N=1278). In the screening cohort, there were 1112 participants that tested at positive with EBV-DNA at baseline and 308 had persistently positive results. There were 34 patients who developed NPCA in those who had a positive EBV-DNA and 1 patient developed NPCA in those who tested negative for EBV-DNA, giving a 97.1% sensitivity, 98.6% specificity, 11.0% PPV and 99.99% NPV. The historical cohort consisted of consecutively diagnosed NPCA patients in a hospital, all these did not undergo screening.				
Early Diagnostic Rates (EBV-DNA)											
1,312 (1 OS)	very serious ^a	not serious	not serious	not serious	none	 Very low	255/1278 (20.0%)	24/34 (70.6%)	RR 0.70 (0.69, 0.72)	19,953 per 100,000	5,986 fewer per 100,000 (from 6,185 fewer to 5,587 fewer)
Progression-Free Survival (EBV-DNA)											
1,312 (1 OS)	not serious	not serious	not serious	not serious	none	 Low	520/1278 (40.7%)	9/34 (26.5%)	HR 0.10 (0.05, 0.18)	40,689 per 100,000	35,599 fewer per 100,000 (from 38,111 fewer to 31,714 fewer)

CI confidence interval; HR hazard ratio; OS observational study; RR risk ratio

a. No allocation concealment and blinding

Diagnostic Accuracy of the Different EBV Screening Blood Tests

Certainty assessment							Summary of findings			
Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Effect Estimate	Relative effect (95% CI)	Interpretation	Basis
EBV DNA										
Sensitivity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	76%	73-77%	Moderate	17 OS
Specificity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	96%	95-97%	High	17 OS
Eg-IgA										
Sensitivity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	55%	54-57%	Low	15 OS
Specificity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	96%	96-97%	High	15 OS
VCA-IgA										
Sensitivity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	85%	84-85%	High	35 OS
Specificity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	89%	88-89%	High	35 OS
EBNA1-IgA										
Sensitivity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	86%	85-88%	High	16 OS
Specificity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	87%	88-90%	High	16 OS
Rta-IgG										
Sensitivity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	70%	69-71%	Moderate	16 OS
Specificity	very serious ^a	very serious ^b	not serious	not serious	none	 Very low	94%	94-95%	High	16 OS

CI confidence interval; OS observational studies

a. No/unsure allocation concealment and blinding, some studies were in Chinese.

- b. Different time frames on when the next EBV blood test is taken and for how long; some studies also coupled the EBV blood test with physical examination and/or imaging, some studies were in Chinese so frequency of the EBV blood tests could not be determined

3. Screening for Hepatocellular Carcinoma

SEARCH STRATEGY

Date of Search: 31 July 2021

Name of database: PubMed

#	Search terms	Yield
1	("Carcinoma, Hepatocellular"[Mesh]) OR (((("liver cancer"[All Fields]) OR ("liver carcinoma"[All Fields])) OR ("hepatic carcinoma"[All Fields])) OR ("hepatic cancer"[All Fields])) OR ("hepatocellular carcinoma"[All Fields]))	141,043
2	("Early Detection of Cancer"[Mesh]) OR (("screening"[All Fields]) OR ("surveillance"[All Fields]))	916,838
3	("Ultrasonography"[Mesh]) OR (((("ultrasound"[All Fields]) OR ("ultrasonography"[All Fields])) OR ("sonogram"[All Fields]))	638,468
4	("alpha-Fetoproteins"[Mesh]) OR (((("alpha fetoprotein"[All Fields]) OR ("alpha foetoprotein"[All Fields])) OR ("afp"[All Fields])))	29,890
	((("Carcinoma, Hepatocellular"[Mesh]) OR (((("liver cancer"[All Fields]) OR ("liver carcinoma"[All Fields])) OR ("hepatic carcinoma"[All Fields])) OR ("hepatic cancer"[All Fields])) OR ("hepatocellular carcinoma"[All Fields]))) AND (((("Early Detection of Cancer"[Mesh]) OR (("screening"[All Fields]) OR ("surveillance"[All Fields]))) AND (((("Ultrasonography"[Mesh])	2,156
5	OR (((("ultrasound"[All Fields]) OR ("ultrasonography"[All Fields])) OR ("sonogram"[All Fields]))) OR (((("alpha-Fetoproteins"[Mesh]) OR (((("alpha fetoprotein"[All Fields]) OR ("alpha foetoprotein"[All Fields])) OR ("afp"[All Fields])))))	24
6	((("Carcinoma, Hepatocellular"[Mesh]) OR (((("liver cancer"[All Fields]) OR ("liver carcinoma"[All Fields])) OR ("hepatic carcinoma"[All Fields])) OR ("hepatic cancer"[All Fields])) OR ("hepatocellular carcinoma"[All Fields]))) AND (((("Early Detection of Cancer"[Mesh]) OR (("screening"[All Fields]) OR ("surveillance"[All Fields]))) AND (((("Ultrasonography"[Mesh])	42
	OR (((("ultrasound"[All Fields]) OR ("ultrasonography"[All Fields])) OR ("sonogram"[All Fields]))) OR (((("alpha-Fetoproteins"[Mesh]) OR (((("alpha fetoprotein"[All Fields]) OR ("alpha foetoprotein"[All Fields])) OR ("afp"[All Fields])))))	
	Randomized Controlled Trial	
7	((("Carcinoma, Hepatocellular"[Mesh]) OR (((("liver cancer"[All Fields]) OR ("liver carcinoma"[All Fields])) OR ("hepatic carcinoma"[All Fields])) OR ("hepatic cancer"[All Fields])) OR ("hepatocellular carcinoma"[All Fields]))) AND (((("Early Detection of Cancer"[Mesh]) OR (("screening"[All Fields]) OR ("surveillance"[All Fields]))) AND (((("Ultrasonography"[Mesh])	13
	OR (((("ultrasound"[All Fields]) OR ("ultrasonography"[All Fields])) OR ("sonogram"[All Fields]))) OR (((("alpha-Fetoproteins"[Mesh]) OR (((("alpha fetoprotein"[All Fields]) OR ("alpha foetoprotein"[All Fields])) OR ("afp"[All Fields])))))	
	Meta-Analysis, Systematic Review	
8	((("Carcinoma, Hepatocellular"[Mesh]) OR (((("liver cancer"[All Fields]) OR ("liver carcinoma"[All Fields])) OR ("hepatic carcinoma"[All Fields])) OR ("hepatic cancer"[All Fields])) OR ("hepatocellular carcinoma"[All Fields]))) AND (((("Early Detection of Cancer"[Mesh]) OR (("screening"[All Fields]) OR ("surveillance"[All Fields]))) AND (((("Ultrasonography"[Mesh])	
	OR (((("ultrasound"[All Fields]) OR ("ultrasonography"[All Fields])) OR ("sonogram"[All Fields]))) OR (((("alpha-Fetoproteins"[Mesh]) OR (((("alpha fetoprotein"[All Fields]) OR ("alpha foetoprotein"[All Fields])) OR ("afp"[All Fields])))))	
	AND (((("practice guideline"[Publication Type]) OR ("clinical practice guideline"[All Fields])))	

Identified articles:

1. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol.* 2004 Jul;130(7):417-22. doi: 10.1007/s00432-004-0552-0. PMID: 15042359.
2. Zhang B, Yang B. Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. *J Med Screen.* 1999;6(2):108-10. doi: 10.1136/jms.6.2.108. PMID: 10444731.

GRADE SUMMARY OF EVIDENCE

Studies	Risk of bias	Certainty assessment				No of patients		Effect		Certainty	Importance
		Inconsistency	Indirectness	Imprecision	Other considerations	Screening using US + AFP	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Mortality (assessed with: RR)											
1 randomised trial	very serious ^a	not serious	serious ^b	not serious		32/9373 (0.3%)	54/9443 (0.6%)	RR 0.60 (0.39, 0.92)	2 fewer per 1,000 (from 3 fewer to 0 fewer)	-	CRITICAL
Proportion of Resectable Tumors											
1 randomised trial	very serious ^a	not serious	serious ^b	not serious		40/86 (46.5%)	5/67 (7.5%)	RR 8.06 (3.18, 20.41)	527 more per 1,000 (from 163 more to 1,000 more)	-	CRITICAL
Proportion of Stage 1 HCC Detected (assessed with: RR)											
1 randomised trial	very serious ^a	not serious	serious ^b	not serious		52/86 (60.5%)	0/67 (0.0%)	RR 82.07 (5.16, 1305.59)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	-	CRITICAL
1-year Survival (assessed with: %)											
1 randomised trial	very serious ^a	not serious	serious ^b	not serious		61.9	31.2	-	0 (0 to 0)	-	IMPORTANT
3-year Survival (assessed with: %)											
1 randomised trial	very serious ^a	not serious	serious ^b	not serious		52.7	7.2	-	0 (0 to 0)	-	IMPORTANT
5-year Survival (assessed with: %)											
1 randomised trial	very serious ^a	not serious	serious ^b	not serious		46.4	0	-	0 (0 to 0)	-	IMPORTANT

CI Confidence interval; RR Risk ratio

a. Unclear random sequence generation, Unclear concealment, Unclear Blinding, Incomplete outcome data, Selective outcome reporting

b. Study population includes patients who are at risk to develop hepatocellular carcinoma

Reference: Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417-22. doi: 10.1007/s00432-004-0552-0. PMID: 15042359.

Sensitivity	0.92 (95% CI: 0.81, 0.98)	Prevalences	0.02%	0.5%	4%
Specificity	0.93 (95% CI: 0.93, 0.93)				

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0.02%	pre-test probability of 0.5%	pre-test probability of 4%	
True positives (patients with HCC)	1 study (n=51)	cross-sectional (cohort type accuracy study)	not serious	serious ^a	not serious	not serious		18 (16, 20)	461 (406, 489)	3686 (3245, 3913)	
False negatives (patients incorrectly classified as not having HCC)								2 (0, 4)	39 (11, 94)	314 (87, 755)	
True negatives (patients without HCC)	1 study (n=20,243)	cross-sectional (cohort type accuracy study)	serious ^b	serious ^a	not serious	not serious		93001 (92651, 93341)	92555 (92207, 92893)	89299 (88963, 89626)	
False positives (patients incorrectly classified as having HCC)								6979 (6639, 7329)	6945 (6607, 7293)	6701 (6374, 7037)	

CoE certainty of evidence

a. Subjects had risk factor(s) for HCC

b. Individuals with (-) US and (-) AFP test results were no longer subjected to confirmatory testing

Reference: Zhang B, Yang B. Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. J Med Screen. 1999;6(2):108-10. doi: 10.1136/jms.6.2.108. PMID: 10444731.

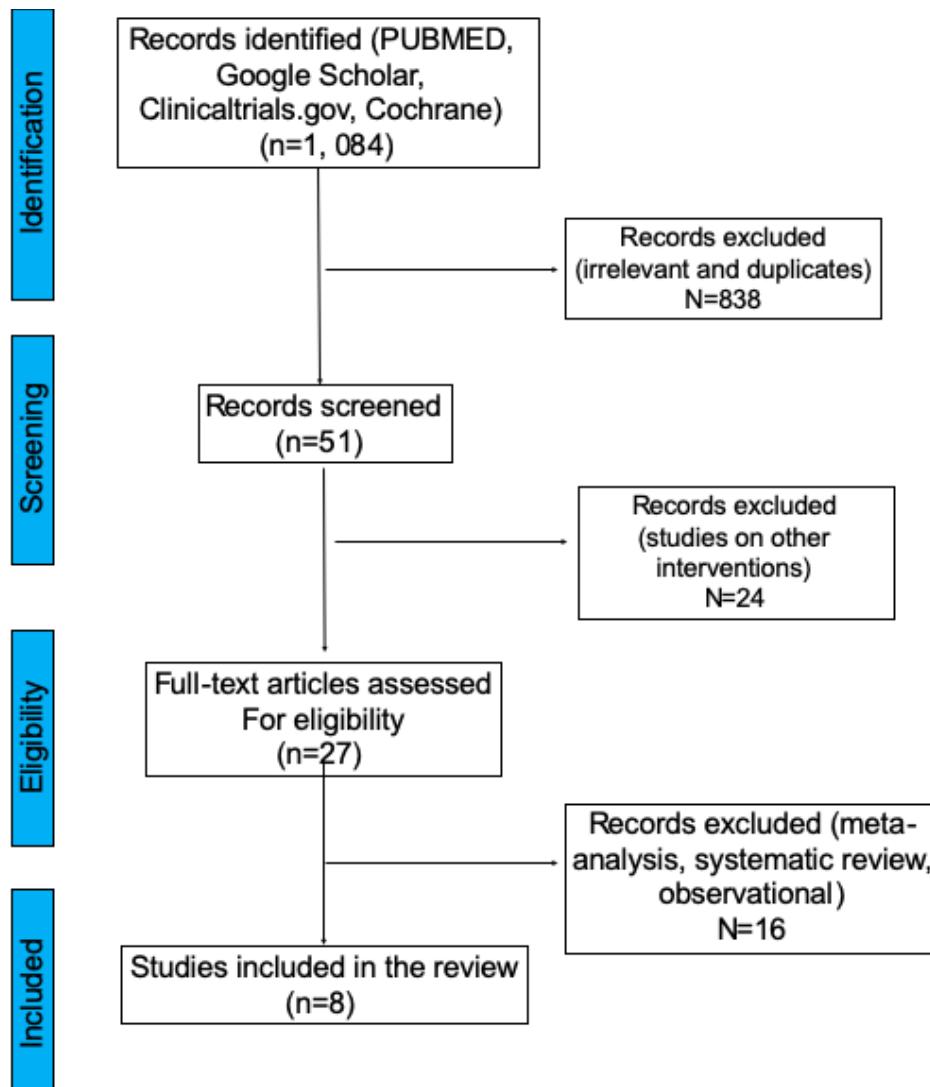
4. Screening for Cervical Cancer

SEARCH STRATEGY

Date of search: 11 October 2021

#	Search terms	Results
5	#1 AND #2 AND #3 AND #4	1,062
4	cancer screening test[MeSH Terms]	30,424
3	((randomized controlled trial [pt]) or (controlled clinical trial [pt]) or (randomized [tiab]) or (placebo [tiab]) or (drug therapy[sh]) or (randomly [tiab]) or (trial [tiab]) or (groups [tiab])) not (animals [mh] NOT humans [mh])	4,539,808
2	((cancer screening[MeSH Terms]) OR (pap smear[MeSH Terms])) OR (pananicolaou smear[MeSH Terms])) OR (pananicolaou test[MeSH Terms]) OR (thinprep)) OR (HPV test)) OR (liquid-based cytology)) OR (LBC)) OR (HPV DNA test)) OR (papillomavirus test)) OR (cotesting)) OR (cotest)) OR (conventional pap)	48,155
1	((cervical cancer, uterine[MeSH Terms]) OR (cervical intraepithelial neoplasia[MeSH Terms])) OR (cervical intraepithelial neoplasia[MeSH Terms])	80,124

PRISMA Search Strategy



CHARACTERISTICS OF INCLUDED STUDIES

Author	Country	No of participants	Intervention	Control	Outcome	Follow-up
Sankarayanan	India	131,746	VIA, primary HPV testing (HC2) or conventional cytology	Standard care	Incidence of cervical cancer, stage II and above cervical cancer, death, rates of CIN detection	8 years; 1 round
NTTC Phase I Ronco 2010	Italy	N=45,174 25–60 years old	hrHPV (HC2) + LBC → colposcopy if (+) fro 35-60; 24-35 repeat after 1 year hrHPV	Conventional cytology (ASCUS+) → managed according to guidelines	Incidence of CIN2+, CIN3+ and invasive cancer	Every 3 years (2 rounds, maximum 7 years) Round 2 used cytology only
SWEDESCREEN Elfstrom 2014 Nacler 2007	Sweden	N=12,527 32–38 years old	hrHPV PCR + conventional cytology → repeat cotesting at 12 months if hrHPV+/Cytology-	Conventional cytology	Incidence of CIN2+, CIN3+ and invasive cancer	1 round (4 years)
Artistic Kitchener 2009, 2014	UK	N=25,078 20–64 years old	hrHPV(HC2) + LBC (HSIL+ → colpo; LSIL → repeat 6 months; if borderline cytology repeat at 6 and 12 months)	LBC (HSIL+ → colpo; LSIL → repeat 6 months; if HR+ but cytology normal → repeat at 12 months → repeat after 12 months or colpo)	Incidence of CIN2+, CIN3+ and invasive cancer	2 rounds (3 year interval, same)
POBASCAM Rijken 2012 Dijkstra 2016	Netherlands	N=40,105 29–61 years old	hrHPV (PCR) + conventional cytology (hrHPV+ and normal cytology → repeat at 6 and 18 months; HSIL+ → colpo; less than HSIL → cotest at 6 months)	Conventional cytology (HSIL+ → colpo)	Incidence of CIN2+, CIN3+ and invasive cancer	2 rounds (every 5 years)
Mayrand	USA	10,154 30–69 years old	HPV DNA	Cytology testing	Sensitivity and specificity of each test	
Chan	China	N=15,955 30–60 years old	Digene HC2 + LBC contesting (if HR HPV → colposcopy and bx)	LBC (referred for colposcopy if > ASCUS, ASCUS plus HPV+, 2 consecutive ASCUS)	CIN2+ and CIN3+ detection	2 rounds (every 3 years)

GRADE SUMMARY OF EVIDENCE

Cytology and HPV testing vs standard of care

Studies	Certainty assessment					No of patients		Effect		Certainty	Importance
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening	no screening	Relative (95% CI)	Absolute (95% CI)		
Cytology (mortality)											
1 randomised trial	serious ^a	not serious	not serious	serious ^b	none	54/32058 (0.2%)	64/31488 (0.2%)	HR 0.89 (0.62, 1.27)	0 fewer per 1,000 (from 1 fewer to 1 more)	⊕⊕○○ Low	
Primary HPV (mortality)											
1 randomised trial	serious ^a	not serious	not serious	not serious	none	34/34126 (0.1%)	64/31488 (0.2%)	HR 0.52 (0.33, 0.83)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕⊕○ Moderate	
Cytology (incidence of stage II+ cervical cancer)											
1 randomised trial	serious ^a	not serious	not serious	serious ^b	none	58/31488 (0.2%)	82/31488 (0.3%)	HR 0.75 (0.51, 1.10)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕○○ Low	
Primary HPV (incidence of stage II+ cervical cancer)											
1 randomised trial	serious ^a	not serious	not serious	not serious	none	39/34126 (0.1%)	82/31488 (0.3%)	HR 0.47 (0.32, 0.69)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕⊕○ Moderate	
Cytology for detection of CIN 2+											
1 randomised trial	serious ^a	not serious	not serious	serious ^c	none	345/25549 (1.4%)	56/31488 (0.2%)	RR 8.60 (6.49, 11.40)	14 more per 1,000 (from 10 more to 18 more)	⊕⊕○○ Low	
Primary HPV for CIN 2+											
1 randomised trial	serious ^a	not serious	not serious	serious ^b	none	318/26874 (1.2%)	56/31488 (0.2%)	RR 6.65 (5.01, 8.83)	10 more per 1,000 (from 7 more to 14 more)	⊕⊕○○ Low	

CI confidence interval; HR hazard Ratio; RR risk ratio

a. Randomization and allocation concealment were not explicitly mentioned. Although patients and clinicians were not blinded, outcome assessors were.

b. Crossed line of no effect.

c. Wide CI.

Co-testing vs cytology alone

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	screening	no screening	Relative (95% CI)	Absolute (95% CI)		
HPV cotesting (cumulative CIN3+)											
4 randomised trials	serious ^a	serious ^f	serious ^b	serious ^c	publication bias strongly suspected ^d	757/75,281 (1.0%)	563/62,893 (0.9%)	RR 1.05 (0.89, 1.23)	0 fewer per 1,000 (from 1 fewer to 2 more)	⊕○○○	Very low
HPV Cotesting (cumulative Invasive Cancer)											
3 randomised trials	serious ^e	not serious	serious ^b	serious ^c	publication bias strongly suspected ^d	25/44,642 (0.1%)	29/32,500 (0.1%)	RR 0.70 (0.40, 1.23)	0 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕○○○	Very low
HPV cotesting (cumulative CIN2+)											
4 randomised trials	serious ^a	serious ^f	serious ^b	not serious	publication bias strongly suspected ^d	1,396/75,281 (1.9%)	872/62,893 (1.4%)	RR 1.23 (1.05, 1.44)	3 more per 1,000 (from 1 more to 6 more)	⊕○○○	Very low

CI confidence interval; RR risk ratio

a. Some studies had no unclear allocation concealment and blinding.

b. Studies compared HPV cotesting and cytology.

c. Confidence interval crosses line of no effect.

d. Funnel plot asymmetric.

e. Wide confidence interval

f. High heterogeneity.

AGREE-II ASSESSMENT

American Cancer Society 2020 Guidelines

AGREE-II CRITERIA	SCORE	COMMENTS
1. Overall objective/s of the guideline/s is/are specifically described.	7	
2. Health question/s covered by the guideline is/are specifically described	7	
3. Population (patients, public, etc.) to whom the guideline is meant to apply	7	
Total for this Domain (SCOPE & PURPOSE)	21	
4. Guideline development group includes individuals from all relevant perspectives	7	
5. Views and preferences of the target population (patients, public, etc.) have been considered	7	
6. Target users of the guideline are clearly defined.	7	
Total for this Domain (STAKEHOLDER INVOLVEMENT)	21	
7. Systematic methods were used to search for evidence.	6	
8. Criteria for selecting the evidence are clearly described.	3	
9. Strengths and limitations of the body of evidence are clearly described.	7	
10. Methods for formulating the recommendations are clearly described.	7	
11. Health benefits, side effects, and risks have been considered in formulating the recommendations	7	
12. There is an explicit link between the recommendations and the supporting evidence	7	
13. Guidelines has been externally reviewed by experts prior to its publication	7	
14. A procedure for updating the guideline is provided.	7	
Total for this Domain (RIGOUR OF DEVELOPMENT)	51	
15. Recommendations are specific and unambiguous.	7	
16. The different options for management of the condition or health issue are clearly described	7	
17. Key recommendations are easily identifiable.	7	
Total for this Domain (CLARITY OF PRESENTATION)	21	
18. Guideline describes facilitators and barriers to its application.	7	
19. Guideline provides advice and/or tools on how the recommendations should be applied	7	
20. Potential resource implications of applying the recommendations have been considered	4	Cost were included in the analysis but no cost effectiveness analysis was performed.
21. Guideline presents monitoring and/or auditing criteria.	2	No auditing criteria noted.
Total for this Domain (APPLICABILITY)	20	
22. Views of the funding body have not influenced the content of the guideline	7	
23. Competing interests of guideline development group members have been declared	7	
Total for this Domain (EDITORIAL INDEPENDENCE)	14	
OVERALL GUIDELINE ASSESSMENT		
1. Rate the overall quality of this guideline.	High	
2. I would recommend this guideline for use.	Yes.	

2018 US Preventive Screening Task Force

AGREE II CRITERIA	SCORE	COMMENTS
1. Overall objective/s of the guideline/s is/are specifically described.	7	
2. Health question/s covered by the guideline is/are specifically described.	7	
3. Population (patients, public, etc.) to whom the guideline is meant to apply is/s are clearly defined.	7	
Total for this Domain (SCOPE & PURPOSE)	14	
4. Guideline development group includes individuals from all relevant professions.	7	
5. Views and preferences of the target population (patients, public, etc.) have been considered.	7	
6. Target users of the guideline are clearly defined.	7	
Total for this Domain (STAKEHOLDER INVOLVEMENT)	21	
7. Systematic methods were used to search for evidence.	7	
8. Criteria for selecting the evidence are clearly described.	7	
9. Strengths and limitations of the body of evidence are clearly described.	7	
10. Methods for formulating the recommendations are clearly described.	7	
11. Health benefits, side effects, and risks have been considered in formulating the recommendations.	7	
12. There is an explicit link between the recommendations and the supporting evidence.	7	
13. Guidelines has been externally reviewed by experts prior to its publication.	7	
14. A procedure for updating the guideline is provided.	7	
Total for this Domain (RIGOUR OF DEVELOPMENT)	56	
15. Recommendations are specific and unambiguous.	7	
16. The different options for management of the condition or health issue are clearly described.	7	
17. Key recommendations are easily identifiable.	7	
Total for this Domain (CLARITY OF PRESENTATION)	21	
18. Guideline describes facilitators and barriers to its application.	7	
19. Guideline provides advice and/or tools on how the recommendations can be applied.	7	
20. Potential resource implications of applying the recommendations have been considered.	4	Costs were not factored into the recommendations.
21. Guideline presents monitoring and/or auditing criteria.	2	No auditing criteria are provided.
Total for this Domain (APPLICABILITY)	20	
22. Views of the funding body have not influenced the content of the guideline.	7	
23. Competing interests of guideline development group members have been recorded.	7	
Total for this Domain (EDITORIAL INDEPENDENCE)	14	
OVERALL GUIDELINE ASSESSMENT		
1. Rate the overall quality of this guideline.	High	
2. I would recommend this guideline for use.	Yes	

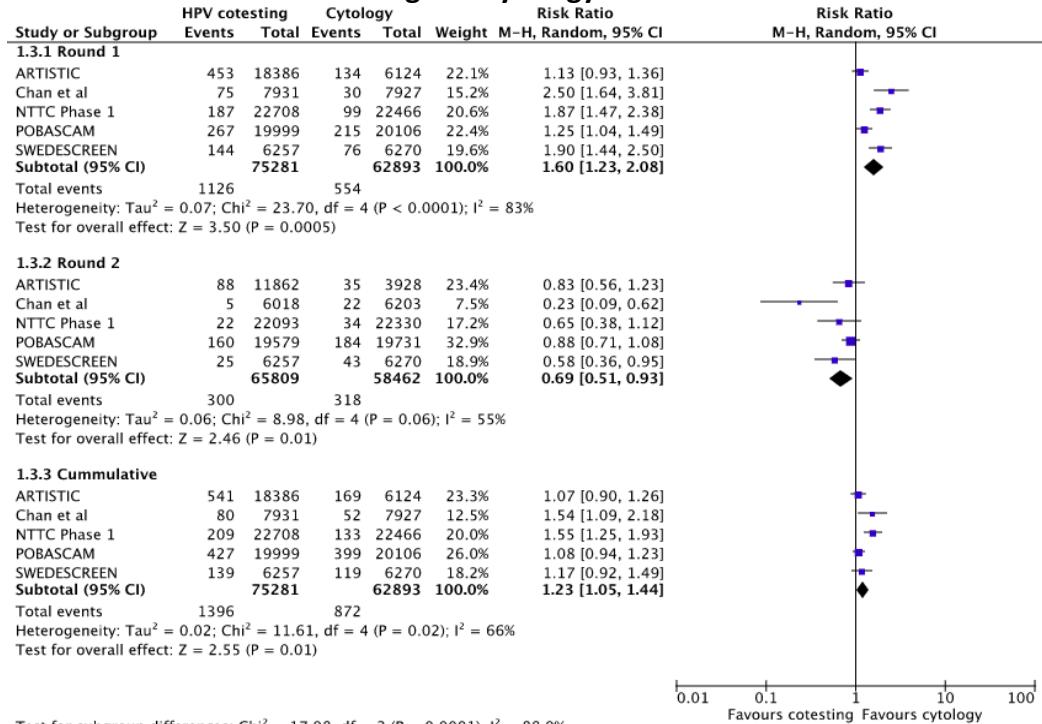
RISK OF BIAS OF INCLUDED STUDIES

Study ID	sequence generation	allocation concealment	blinding	incomplete outcome data	selective outcome reporting	Overall	Comments
Sankarayanan	Unknown	Unknown	L	H	L	Some concerns	Outcome is objective and blinding is not feasible. 78-79% follow-up rate.
NTTC	L	L	L	H	L	H	Outcome assessment is blinded (random review by a pathologist). 72-73% follow-up rate.
SWEDESCREEN	L	L	H	H	L	H	No mention of blinding among patient and clinicians. Lost to follow more than 20% on some interventions.
POBASCAM	L	U	U	L	L	S	No mention of blinding among patient and clinicians. 9-15% lost to follow-up rate.
ARTISTIC	L	U	H	H	L	L	No mention of blinding among patient and clinicians. 64.4% follow-up rate on round 2.
Mayrand	L	L	L	L	L	L	
Chan	L	L	U	H	L	H	No mention of blinding among patient and clinicians. 75% to 78% follow-up rate on round 2.

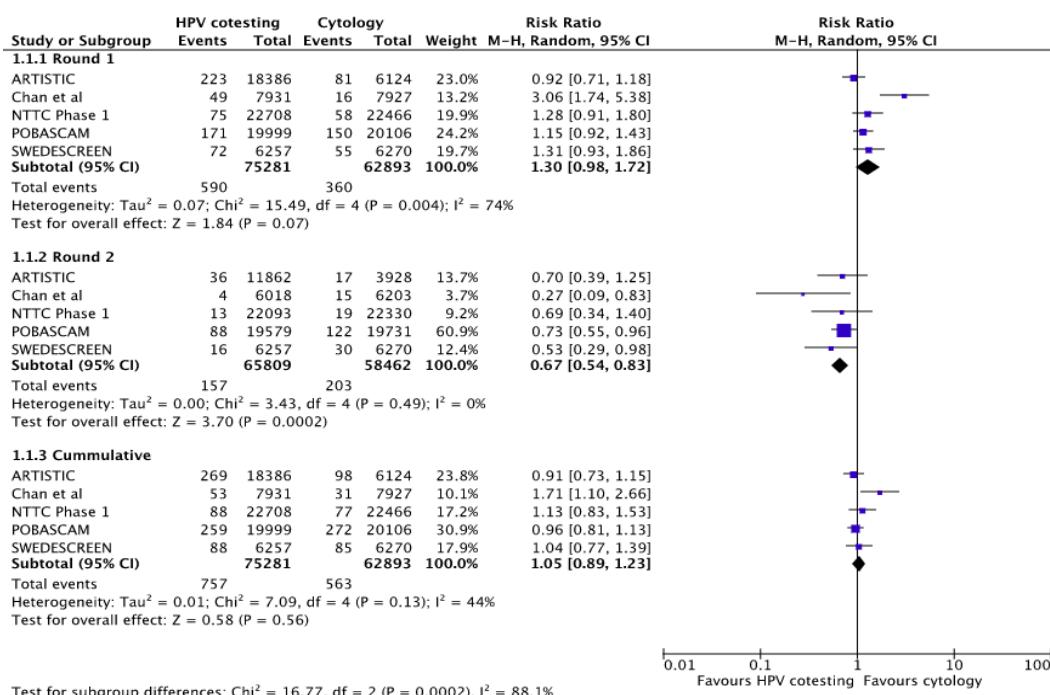
L low; H high

FOREST PLOTS

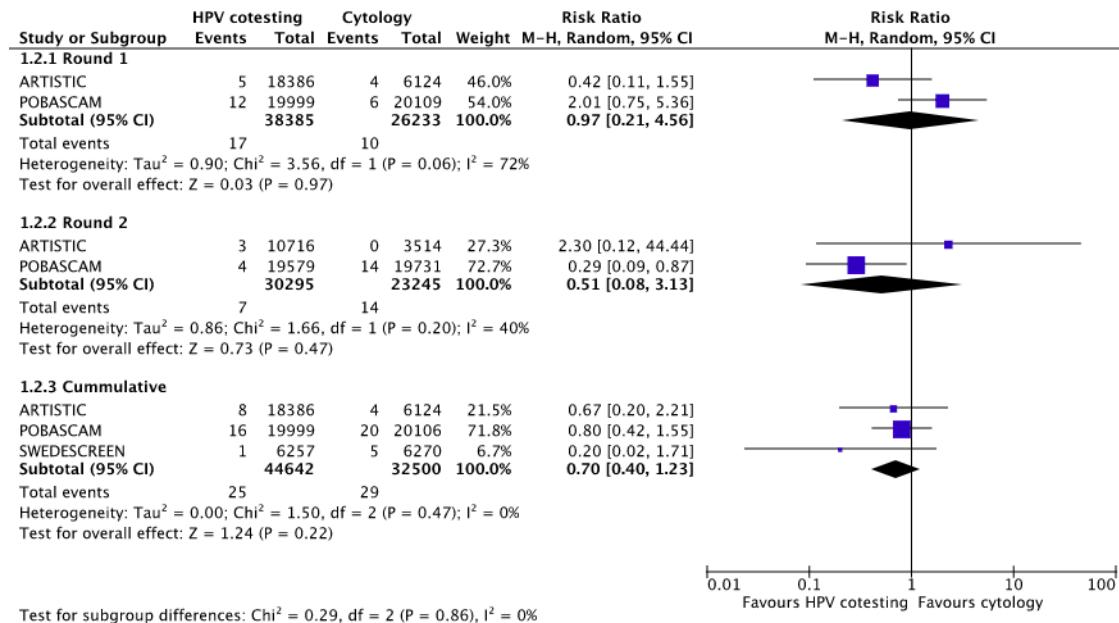
Incidence of CIN2+ between co-testing and cytology



Incidence of CIN3+ between co-testing and cytology



Incidence of invasive cancer between co-testing and cytology



5. Screening for Oral Cancer

SEARCH STRATEGY

Pre-appraised CPGs (NICE, USPSTF, CTFPHC) for oral cancer were outdated. Handsearching of these CPGs was also done. We performed another search of other CPGs of medical societies using the following keywords on MEDLINE through PubMed in medical subject heading (MeSH) terms or free text. In our search, we prioritized guidelines with questions on initial stages of oral cancer and on screening.

Name of Database: **PubMed**

Search Date	Search terms	Yield	Hit
2 August 2021 13:37:49	"guideline"[Publication Type] OR "practice guideline"[Publication Type] OR "recommendation"[Title] OR "recommendation*"[Title] OR "standard*"[Title] OR "guideline*"[Title]	238,513	-
2 August 2021 13:37:57	(((((guideline[Publication Type]) OR (practice guideline[Publication Type])) OR (recommendation[Title])) OR (recommendation*[Title])) OR (standard*[Title])) OR (guideline*[Title])) AND (((oral cancer[Title/Abstract]) OR (oral cancer[MeSH Terms])) OR (oral squamous cell cancer[MeSH Terms])) OR (oral squamous cell cancer[Title/Abstract]))	306	4 Latest: 2017
23 August 2021 7:54pm	((((((((mouth AND (y_5[Filter])) OR (LIP [mh:exp])) OR (GINGIVA [mh:exp])))) OR (TONGUE [mh:exp])) OR (OROPHARYNX [mh:exp])) OR (HYPOPHARYNX [mh:exp])) OR (PALATE [mh:exp])) OR (CHEEK [mh:exp])) OR (mouth OR lip* OR tongue* or ginger* OR oropharynx or palate or cheek*)) AND (((((MOUTH NEOPLASMS [mh:exp])) OR (PRECANCEROUS CONDITIONS [mh:exp])) OR (tumor* OR tumor* or cancer* or carcinoma*)) OR (malignant*)) OR (dysplasia*)) OR ("oral cancer*")) AND (((((((MASS SCREENING [mh:exp]) OR ("visual* screen*")))) OR (tolonium chloride [mh:noexp])) OR ("toluidine blue")) OR (TOLUIDINES [mh:exp])) OR ("toluidine dye")) OR ("brush biopsy" or "exfoliate cytology") OR ("fluorescent imaging")) OR (fluorescent dye* OR fluorescent antibody technique OR fluorescence)) OR (prevent*)) OR (screen*)) OR (early detect*)) AND ((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])))) OR (randomized [tiab])) OR (placebo [tiab])) OR (randomly [tiab])) OR (trial [tiab])) OR (groups [tiab])))	2,258 --- Filtered: Start date: 2021/3/17 End date: 2021/8/21 59	0 new trials 1 publication was based on Kerala Trial (Cheung 2021) which results were included in SR found in previous search and included in this review

Name of Database: **Cochrane Library**

Search Date	Search terms	Yield	Hit
10 August 2021 11:46 PM	[(oral cancer):ti,ab,kw OR MeSH descriptor: (Mouth Neoplasms) explode all trees] AND [screening OR MeSH descriptor: (Mass Screening) explode all trees] Filter used: 2013 to 2021 (since the last search for the Cochrane Review was 2013)	1100	2 SR (Walsh 2013-outdated; Brocklehurst 2013) 6 publications – 1 trial (Kerala) 1 ongoing trial (NCT04919460)

Excluded CPGs and reasons for exclusion

Study/Guideline	Reason for Exclusion
Nibu 2017 Japanese CPG	<ul style="list-style-type: none"> • symptomatic • no screening test, only diagnosis and management
Rethman 2010 ADA CPG	<ul style="list-style-type: none"> • outdated
Crossan 2019	<ul style="list-style-type: none"> • not available for full text
Zoorob 2001	<ul style="list-style-type: none"> • outdated
Rethman 2012 ADA CPG	<ul style="list-style-type: none"> • outdated

Included CPG/s for appraisal using AGREE II

- Lingen MW 2017: Score 130
 - Used SR: Walsh. 2013 – diagnostic accuracy of conventional oral examination; used observational studies
 - Did not include: Brocklehurst 2013 (Nov) SR with update this March 2021

Included SR/s for appraisal

- Brocklehurst 2013 with update explicitly stated in the review: March 17, 2021 (direct evidence) – (Supplementary File for Risk of Bias Assessment)

On-going Trial

Identifier	Intervention	Expected Completion Date
NCT04919460 Research on Optimization and Evaluation of Oral Cancer Screening Methods	RCT: clinical observation + pathological biopsy vs. clinical observation + in vivo staining (reagent: toluidine blue) + pathological biopsy Clinical observation: Inspecting and palpating the oral cavity and neck of the screened object In vivo staining: performed at the same time as the inspection and palpation of the oral cavity and neck. If abnormal lesions or abnormal living body staining is found, pathological biopsy is performed.	Dec 2023

References

1. Lingen M, Abt E, Agrawal N, Chaturvedi A, Cohen E, D'Souza G, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: A report of the American Dental Association. J Am Dent Assoc. 2017;148(10):712-27.
2. Brocklehurst P, Kujan O, O'Malley L, Ogden G, Shepherd S, Glenny A. Screening programmes for the early detection and prevention of oral cancer (Review). Cochrane Database of Systematic Reviews. 2013(11):CD004150.

GRADE Summary of Evidence

Evidence on screening for oral cancer (ENT screening exam and dental check-up) versus no screening from one cluster RCT in India

Certainty assessment							Summary of Findings				
Participants (Studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall CoE	Study event rates (%)		Relative (95% CI)	Anticipated absolute effects	
							With no screening	With screening		Risk with no screening	Risk difference with screening
Oral cancer mortality, all individuals (follow-up: 15 years)											
523 (1 RCT)	serious ^a	not serious	not serious	serious ^b	none	⊕⊕○○ Low	154/244 (63.1%)	138/279 (49.5%)	RR 0.88 (0.69, 1.12)	631 per 1,000	76 fewer per 1,000 (from 196 fewer to 76 more)
Oral cancer mortality, all individuals (follow-up: 9 years)											
363 (1 RCT)	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate	87/158 (55.1%)	77/205 (37.6%)	RR 0.68 (0.54, 0.86)	551 per 1,000	176 fewer per 1,000 (from 253 fewer to 77 fewer)
Oral cancer mortality among tobacco or alcohol users, or both (follow-up: 15 years)											
486 (1 RCT)	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate	147/232 (63.4%)	129/254 (50.8%)	RR 0.80 (0.69, 0.94)	634 per 1,000	127 fewer per 1,000 (from 196 fewer to 38 fewer)
Oral cancer mortality among tobacco or alcohol users, or both (follow-up: 9 years)											
346 (1 RCT)	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate	85/156 (54.5%)	70/190 (36.8%)	RR 0.68 (0.54, 0.86)	545 per 1,000	174 fewer per 1,000 (from 251 fewer to 76 fewer)
Oral cancer incidence (follow-up: 15 years)											
191873 (1 RCT)	serious ^a	not serious	not serious	serious ^b	none	⊕⊕○○ Low	244/95356 (0.3%)	279/96517 (0.3%)	RR 1.14 (0.91, 1.44)	3 per 1,000	0 fewer per 1,000 (from 0 fewer to 1 more)
Proportion of cancers at Stage III or worse* (follow-up: 15 years)											
486 (RCTs)	serious ^a	not serious	not serious	not serious ^b	none	⊕⊕⊕○ Moderate	154/232 (66.4%)	138/254 (54.3%)	RR 0.82 (0.71, 0.95)	664 per 1,000	119 fewer per 1,000 (from 193 fewer to 33 fewer)

RCT randomized controlled trial; CI confidence interval; CoE certainty of evidence; RR risk ratio

a. Exact procedures were not stated although it was mentioned that block randomization was used. No allocation concealment was done. Although there was no blinding of outcome assessors, the outcome (mortality) was unlikely to be influenced by subjective judgment. No clear explanation/reporting on withdrawals and drop-outs although the analysis was an intention-to-treat analysis.

b. The risk reported has a relatively wide confidence interval

6. Screening for Colorectal Cancer

SEARCH STRATEGY

Date of search: 27 July 2021

Name of database: PubMed

#	Search terms	Results
1	"Colorectal Neoplasms"[MeSH Terms]	212,537
2	"early detection of cancer"[MeSH Terms]	29,359
3	#1 OR #2	235,761
4	(("faecally"[All Fields] OR "fecally"[All Fields] OR "fecals"[All Fields] OR "feces"[MeSH Terms] OR "feces"[All Fields] OR "faecal"[All Fields] OR "faecal"[All Fields]) AND ("immunochemical"[All Fields] OR "immunochemicals"[All Fields])) AND "research design"[MeSH Terms]	35
5	"occult blood"[MeSH Terms]	5,773
6	("nephron clin pract"[Journal] OR "clin pract lond"[Journal] OR ("clinical"[All Fields] AND "practice"[All Fields]) OR "clinical practice"[All Fields]) AND "guidelines as topic"[MeSH Terms]	54,185
7	#4 OR #5	5,782
8	#3 AND #7	4,173
9	#8 AND #6	50

GRADE SUMMARY OF EVIDENCE

Studies	Certainty assessment					Other considerations	No of patients		Effect		Certainty	Importance
	Risk of bias	Inconsistency	Indirectness	Imprecision	FIT		No screening	Relative (95% CI)	Absolute (95% CI)			
CRC specific mortality (follow up: mean 6 years)												
1 observational study	not serious	not serious	not serious	not serious	none		523/3099215 (0.0%)	9860/24984492 (0.0%)	RR 0.90 (0.84, 0.95)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT
Serious Bleeding												
11 randomised trials	not serious	not serious	not serious	not serious	none	78793 participants		not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT	
						-	0.0%					
Perforations												
12 randomised trials	not serious	not serious	not serious	not serious	none	341922 participants		not estimable		⊕⊕⊕⊕ HIGH	IMPORTANT	
						-	0.0%					

CI confidence interval; RR risk ratio

Sensitivity	0.74 (95% CI: 0.64 to 0.83)
Specificity	0.94 (95% CI: 0.93 to 0.96)

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
True positives (patients with CRC)	9 studies 34352 patients	cohort & case-control type studies	not serious	not serious	not serious	not serious	none	0 (0 to 0)	⊕⊕⊕⊕ HIGH
False negatives (patients incorrectly classified as not having CRC)								0 (0 to 0)	
True negatives (patients without CRC)	9 studies 34352 patients	cohort & case-control type studies	not serious	not serious	not serious	not serious	none	940 (930 to 960)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having CRC)								60 (40 to 70)	

7. Screening for Breast Cancer

SEARCH STRATEGY

Date of search: **28 July 2021**

Name of database: **PUBMED, Google Scholar**

Benefits of breast cancer screening

#	Search terms	Results
1	(("breast neoplasms"[MeSH Terms]) OR ("breast cancer"[All Fields])) OR ("breast carcinoma"[All Fields])	403,484
2	(cancer screening[MeSH Terms]) OR (breast cancer screening)	160,484
3	#1 AND #2	125,955
4	(("mammography"[MeSH Terms]) OR ("mammogram"[All Fields])) OR ("screening mammogram"[All Fields])	32,647
5	((("ultrasonography, mammary"[MeSH Terms]) OR ("breast ultrasound"[All Fields])) OR ("breast ultrasonography"[All Fields])) OR ("sonomammogram"[All Fields])	6,455
6	("clinical breast examination"[All Fields]) OR ("breast examination"[All Fields])	1,694
7	#4 OR #5 OR #6	37,424
8	#3 AND #7	28,495
9	(("mortality"[MeSH Terms]) OR ("all cause mortality"[All Fields])) OR ("mortality reduction"[All Fields])	431,718
10	#8 AND #9	870
11	#8 AND #9 (2015-2021)	157

Date of search: **30 July 2021**

Name of database: **Pub Med, Google Scholar**

Harms of breast cancer screening

#	Search terms	Results
1	(("breast neoplasms"[MeSH Terms]) OR ("breast cancer"[All Fields])) OR ("breast carcinoma"[All Fields])	403,671
2	(cancer screening[MeSH Terms]) OR (breast cancer screening)	160,590
3	#1 AND #2	126,014
4	((("mammography"[MeSH Terms]) OR ("mammogram"[All Fields])) OR ("screening mammogram"[All Fields])	32,661
5	((("ultrasonography, mammary"[MeSH Terms]) OR ("breast ultrasound"[All Fields])) OR ("breast ultrasonography"[All Fields])) OR ("sonomammogram"[All Fields])	6,456
6	("clinical breast examination"[All Fields]) OR ("breast examination"[All Fields])	1,694
7	#4 OR #5 OR #6	37,438
8	#3 AND #7	28,509
9	(("medical overuse"[MeSH Terms]) OR (overdiagnosis)) OR ("overtreatment"[All Fields])	20,404
10	("false positive results"[All Fields]) OR ("false positive reactions"[MeSH Terms])	35,759
11	("false negative results"[All Fields]) OR ("false negative reactions"[MeSH Terms])	24,166
12	#10 OR #11	52,075
13	#9 AND #12	542
14	#8 AND #13	111
15	#8 AND #13 (2015-2021)	47

GRADE SUMMARY OF EVIDENCE

Mammogram +/- CBE – Breast Cancer Mortality (Short-Case Accrual) (All Ages; follow up: range 17.7 years to 29.0 years)

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mammogram +/- CBE	Usual Care	Relative (95% CI)	Absolute (95% CI)		
8 RCTs ^a #R: Unclear #A: Unclear	very serious ^b	not serious ^c	not serious ^d	not serious ^e	none ^f	1154/296914 (0.4%) ^g	0.2%*	RR 0.85 (0.78, 0.93)	30 fewer per 100,000 (from 14 fewer to 44 fewer)*	 LOW	
									71 fewer per 100,000 (from 33 fewer to 103 fewer)*		
									104 fewer per 100,000 (from 48 fewer to 152 fewer)*		

CI confidence interval; RCT randomized controlled trial; RR risk ratio; #R: Number randomized; #A: Number analyzed

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

- a. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- c. Heterogeneity may be low ($I^2=11\%$); (p -value=0.34)
- d. Studies seemed relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2016 included one round of screening in the control group as part of the short-case accrual calculation. Therefore, the study estimates may be underestimated (a larger benefit from the intervention may be possible).
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs excludes the null, and does not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials).
- g. Numerators and denominators were either unclear or not reported for all included studies.

References:

- | | | |
|------------------------------|----------------------------|--|
| 1. AGE (Duffy 2020) | 4. HIP (Shapiro 1988) | 7. Stockholm (Nystrom 2016) |
| 2. CNBSS 1 & 2 (Miller 2014) | 5. Malmo I (Nystrom 2016) | 8. Swedish Two County (Kopparberg & Ostergotland) (Tabar 2011) |
| 3. Gothenburg (Nystrom 2016) | 6. Malmo II (Nystrom 2016) | |

Mammogram +/- CBE – Breast Cancer Mortality (Short-Case Accrual) (All Ages; follow up: range 17.7 years to 29.0 years)

Outcomes	Anticipated absolute effects ⁺ (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments**
	Risk with Usual Care	Risk with Mammogram +/- CBE				
Main Analysis: Breast Cancer Mortality (All Ages) #Randomized: Unclear #Analyzed: Unclear follow up: range 17.7–29.0 years	Low 200 per 100,000*	170 per 100,000 (156 to 186)	RR 0.85 (0.78, 0.93)	615,023 (8 RCTs) ^{a,b}	⊕⊕○○ LOW ^{c,d,e,f,g}	NNS (Low): 3,333 (2,273 to 7,143)
	Moderate 470 per 100,000*	399 per 100,000 (367 to 437)				NNS (Moderate): 1,408 (971 to 3,030)
	High 690 per 100,000*	587 per 100,000 (538 to 642)				NNS (High): 962 (658 to 2,083)

CI *Confidence interval*; RR *Risk ratio*

+The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

** Short-Case Accrual: Only deaths from breast cancer cases diagnosed during the screening period are included in the analysis.

- a. Numerators and denominators were either unclear or not reported for all included studies.
- b. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- c. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- d. Heterogeneity may be low ($I^2=11\%$); ($p\text{-value}=0.34$)
- e. Studies seemed relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2016 included one round of screening in the control group as part of the short-case accrual calculation. Therefore, the study estimates may be underestimated (a larger benefit from the intervention may be possible).
- f. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs excludes the null, and does not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- g. Cannot assess publication bias (insufficient number of trials).

Mammogram +/- CBE – Breast Cancer Mortality (Short-Case Accrual) (Stratified by Age)

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mammogram +/- CBE	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Breast Cancer Mortality (40-49 years) (follow up: range 17.7 years to 25.7 years)											
8 RCTs ^a #R: Unclear #A: Unclear	very serious ^b	not serious ^c	not serious ^d	not serious ^e	none ^f	436/167,966 (0.3%) ^h	736/204,420 (0.4%)*	RR 0.88 (0.76, 1.01)	43 fewer per 100,000 (from 4 more to 86 fewer)	⊕⊕○○ LOW	
Breast Cancer Mortality (50-59 years) (follow up: range 18 years to 30 years)											
6 RCT ^a #R: Unclear #A: Unclear	very serious ^b	serious ^g	not serious ^d	serious ^e	none ^f	403/56,919 (0.7%) ^h	462/50,184 (0.9%)*	RR 0.84 (0.71, 1.00)	147 fewer per 100,000 (from 0 fewer to 267 fewer)*	⊕○○○ VERY LOW	
Breast Cancer Mortality (60-69 years) (follow up: range 13.1 years to 30 years)											
4 RCT ⁱ #R: Unclear #A: Unclear	very serious ^b	not serious ^j	not serious ^d	not serious ^k	none ^f	70/12,586 (0.6%) ^h	74/8,653 (0.9%)*	RR 0.70 (0.56, 0.88)	257 fewer per 100,000 (from 103 fewer to 376 fewer)**	⊕⊕○○ LOW	
Breast Cancer Mortality (70-74 years) (follow up: range 13.2 years to 13.6 years)											
2 RCT ^a #R: Unclear #A: Unclear	very serious ^b	not serious ^l	not serious ^d	serious ^m	none ^f	64/10,635 (0.6%) ^h	60/7,598 (0.8%)*	RR 0.89 (0.58, 1.38)	87 fewer per 100,000 (from 300 fewer to 332 more)**	⊕○○○ VERY LOW	

CI Confidence interval; RCT randomized controlled trial; RR Risk ratio

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

** The baseline risk (in the control group) may not be representative of all included studies because the numerators and/or denominators were either unclear or not reported for all studies. The number randomized for those publications where event rates were given were used to estimate baseline risk. The numbers randomized were initially not used to estimate baseline risk, since an independent investigation found that we could not be confident that the numbers randomized were used to calculate RR.

- a. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- c. Heterogeneity may be low ($I^2=28\%$; $p\text{-value}=0.20$)
- d. Studies seemed relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 and Nystrom 2016 included one round of screening in the control group as part of the short-case accrual calculation. Therefore, the study estimates may be underestimated (a larger benefit from the intervention may be possible).
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs exclude the null, and does not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials).
- g. Heterogeneity may be moderate ($I^2=24\%$); ($p\text{-value}=0.26$)
- h. Numerators and denominators were either unclear or not reported for all included studies. Values provided reflect those studies which provided complete data.
- i. One study considered quasi-randomized (Stockholm)
- j. Heterogeneity may be low ($I^2=0\%$); ($p\text{-value}=0.49$)
- k. (i) The total population is large (>2000); and (ii) the 95% CIs do not include the null but do cross appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted.
- l. Heterogeneity may be low ($I^2=0\%$); ($p\text{-value}=0.92$)
- m. (i) The total population is large (>2000); and (ii) the 95% CIs include the null and do cross appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted

References:

- AGE (Duffy 2020)
- CNBSS 1 (Miller 2014)
- CNBSS 2 (Miller 2014)
- Gothenburg (Nystrom 2016)
- HIP (Shapiro 1988)
- Malmo I (Nystrom 2002)
- Malmo I (Nystrom 2016)
- Malmo II (Nystrom 2016)
- Stockholm (Nystrom 2002)
- Stockholm (Nystrom 2016)
- Swedish Two County (Kopparberg & Ostergotland) (Tabar 2011)

Mammogram +/- CBE – Breast Cancer Mortality (Short-Case Accrual) (Stratified by Age)

Patient or population: Asymptomatic, healthy women Setting: Community			Intervention: Mammogram +/- CBE Comparison: Usual Care			
Outcomes	Anticipated absolute effects ⁺ (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments***
	Risk with Usual Care	Risk with Mammogram +/- CBE				
Subgroup: Breast Cancer Mortality (40–49 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 17.7–25.7 years	360 per 100,000 [*]	317 per 100,000 (274 to 364)	RR 0.88 (0.76, 1.01)	372,386 (8 RCTs) ^a	⊕⊕○○ LOW ^{b,c,d,e,f}	NNS: 2,326 (1,163 to -25,000); CIs include ∞
Subgroup: Breast Cancer Mortality (50–59 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 18–30 years	921 per 100,000 ^{**}	773 per 100,000 (654 to 921) ^g	RR 0.84 (0.71, 1.00)	107,103 (6 RCTs) ^{a,g}	⊕○○○ VERY LOW ^{b,d,e,f,h}	NNS (Low): 2,041 (1,111 to ∞) NNS (Moderate): 1,250 (690 to ∞) NNS (High): 1,041 (575 to ∞)
Subgroup: Breast Cancer Mortality (60–69 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 18–30 years	855 per 100,000 ^{**}	599 per 100,000 (479 to 753) ^g	RR 0.70 (0.56, 0.88)	21,239 (4 RCTs) ⁱ	⊕⊕○○ LOW ^{b,d,f,j,k}	NNS: 389 (266 to 971)
Subgroup: Breast Cancer Mortality (70–74 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 13.2–13.6 years	790 per 100,000 ^{**}	703 per 100,000 (458 to 1,090) ^g	RR 0.89 (0.58, 1.38)	18,233 (2 RCTs) ^a	⊕○○○ VERY LOW ^{b,d,f,j,m}	NNS: 1149 (301 to 333); CIs include ∞

CI Confidence interval; NNS number needed to screen; RR Risk ratio

⁺The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

** The baseline risk (in the control group) may not be representative of all included studies because the numerators and/or denominators were either unclear or not reported for all studies. The number randomized for those publications where event rates were given were used to estimate baseline risk. The numbers randomized were initially not used to estimate baseline risk, since an independent investigation found that we could not be confident that the numbers randomized were used to calculate RR.

*** Short-Case Accrual: Only deaths from breast cancer cases diagnosed during the screening period are included in the analysis.

Mammogram +/- CBE – Breast Cancer Mortality (Long-Case Accrual) (All Ages; follow up: range 12.5 years to 23 years)

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mammogram +/- CBE	Usual Care	Relative (95% CI)	Absolute (95% CI)		
6 RCTs ^a #R: Unclear #A: Unclear	very serious ^b	very serious ^c	not serious ^d	not serious ^e	none ^f	1,047/211,365 (0.5%)	0.2%*	RR 0.81 (0.70, 0.92)	44 fewer per 100,000 (from 18 fewer to 69 fewer)	⊕○○○ VERY LOW	
							0.6%*		104 fewer per 100,000 (from 44 fewer to 165 fewer)		
							1.1%*		209 fewer per 100,000 (from 88 fewer to 330 fewer)		

CI Confidence interval; RR Risk ratio

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

Note: Long-case accrual unavailable for the following studies: Malmo I, Malmo II and Stockholm

- a. One study considered quasi-randomized (Gothenburg)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas
- c. Heterogeneity may be substantial ($I^2=66\%$; $p\text{-value}=0.01$)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Gothenburg, AGE and Swedish Two-County - usual care arm received screening at end of study period.
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs exclude the null, but do cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials).

References:

1. AGE (Duffy 2020)
2. CNBSS 1 & 2 (Miller 2014) AGE (Duffy 2020)
3. CNBSS 1 & 2 (Miller 2014)
4. Gothenburg (Bjurstrom 2003)
5. HIP (Habbema 1986)
6. Kopparberg (Tabbar 1995)
7. Gothenburg (Bjurstrom 2003)
8. HIP (Habbema 1986)
9. Kopparberg (Tabbar 1995)
10. Ostergotland (Tabbar 1995)

Mammogram +/- CBE – Breast Cancer Mortality (Long-Case Accrual) (All Ages; follow up: range 12.5 years to 23 years)

Patient or population: Asymptomatic, healthy women

Setting: Community

Intervention: Mammogram +/- CBE

Comparison: Usual Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments*
	Risk with Usual Care	Risk with Mammogram +/- CBE				
Main Analysis: Breast Cancer Mortality (Long Case Accrual) (All Ages) #Randomized: Unclear #Analyzed: Unclear follow up: range 12.5– 21.9 years	Low		RR 0.81 (0.70 to 0.92)	422,730 (6 RCTs) ^a	⊕○○○ VERY LOW <small>b,c,d,e,f</small>	NNS (Low): 2,273 (1,149 to 5,556) NNS (Moderate): 962 (606 to 2,273) NNS (High): 478 (303 to 1,136)
	230 per 100,000	186 per 100,000 (161 to 212)				
	Moderate					
	550 per 100,000	446 per 100,000 (385 to 506)				
	High					
	1,100 per 100,000	891 per 100,000 (770 to 1,012)				

CI Confidence interval; NNS number needed to screen; RR Risk ratio

+The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

* Long-Case Accrual: All deaths from breast cancer cases diagnosed during the screening period and follow-up period are included in the analysis.

Mammogram +/- CBE – Breast Cancer Mortality (Long-Case Accrual) (Stratified by Age)

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mammogram +/- CBE	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Breast Cancer Mortality (Long Case) (40-49 years) (follow up: range 12.5 years to 23 years)											
6 RCTs ^a #R: Unclear #A: Unclear	very serious ^b	not serious ^c	not serious ^d	not serious ^e	none ^f	531/124,560 (0.4%) ^g	0.2%*	RR 0.89 (0.78, 1.01)	23 fewer per 100,000 (from 2 more to 46 fewer)*	⊕⊕○○ LOW	
									41 fewer per 100,000 (from 4 more to 81 fewer)*		
									110 fewer per 100,000 (from 10 more to 220 fewer)*		
Breast Cancer Mortality (Long Case) (50-59 years) (follow up: range 12.5 years to 21.9 years)											
5 RCTs ^a #R: Unclear #A: Unclear	very serious ^b	serious ^h	not serious ^d	not serious ⁱ	none ^f	447/66,163 (0.7%) ^g	536/65,351 (0.8%)*	RR 0.82 (0.68, 0.99)	148 fewer per 100,000 (from 8 fewer to 262 fewer)*	⊕○○○ VERY LOW	
Breast Cancer Mortality (Long Case) (60-69 years) (follow up: range 12.5 years to 14.0 years)											
3 RCTs #R: Unclear #A: Unclear	very serious ^b	not serious ^j	not serious ^d	not serious ^k	none ^f	113/27,062 (0.4%) ^g	136/19,919 (0.7%)*	RR 0.65 (0.50, 0.85)	239 fewer per 100,000 (from 102 fewer to 341 fewer)*	⊕⊕○○ LOW	
Breast Cancer Mortality (Long Case) (70-74 years) (follow up: range 12 years)											
2 RCTs #R: Unclear #A: Unclear	very serious ^b	not serious ^l	not serious ^d	serious ^m	none ^f	57/10,339 (0.6%)	50/7,307 (0.7%)*	RR 0.79 (0.51, 1.22)	144 fewer per 100,000 (from 151 more to 335 fewer)*	⊕○○○ VERY LOW	

CI Confidence interval; RR Risk ratio

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

- a. One study considered quasi-randomized (Gothenburg)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- c. Heterogeneity may be low ($I^2=17\%$); (p-value=0.35)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Gothenburg, AGE and Swedish Two-County - usual care arm received screening at end of study period.
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs include the null, but do not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials)
- g. Numerators and/or denominators were either unclear or not reported for all included studies.
- h. Heterogeneity may be moderate ($I^2=38\%$); (p-value=0.17)
 - i. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs do not cross the null, but do cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
 - j. Heterogeneity may be low ($I^2=0\%$); (p-value=0.57)
 - k. (i) The total population is large (>2000); and (ii) the 95% CI crosses the null and also crosses appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted.
 - l. Heterogeneity may be low ($I^2=0\%$); (p-value=0.88)
 - m. (i) The total population is large (>2000); and (ii) the 95% CI crosses the null, and also crosses appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted.

References:

1. AGE (Duffy 2020)
2. CNBSS 1 (Miller 2014)
3. CNBSS 2 (Miller 2014)
4. Gothenburg (Bjurstrom 2003)
5. HIP (Habbema 1986)
6. Swedish Two-County (Kopparberg) (Tabbar 1995)
7. Swedish Two-County (Ostergotland) (Tabbar 1995)

Note: Long-case accrual unavailable for the following studies: Malmo I, Malmo II and Stockholm

Mammogram +/- CBE compared to Usual Care for Breast Cancer Screening (Long-Case Accrual) (Stratified by Age)

Patient or population: Asymptomatic, healthy women

Setting: Community

Intervention: Mammogram +/- CBE

Comparison: Usual Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments**
	Risk with Usual Care	Risk with Mammogram +/- CBE				
Low						
Subgroup: Breast Cancer Mortality (Long Case) (40-49 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 12.5–21.9 years	210 per 100,000*	187 per 100,000 (164 to 212)	RR 0.89 (0.78, 1.01)	300,505 (6 RCTs) ^a	⊕⊕○○ LOW ^{b,c,d,e,f}	NNS (Low): 4,348 (2,174 to - 50,000), CIs include ∞
	Moderate	370 per 100,000* (289 to 374)				NNS (Moderate): 2,439 (1,235 to - 25,000), CIs include ∞
	High	1,000 per 100,000* (780 to 1,010)				NNS (High): 909 (455 to -10,000), CIs include ∞
Subgroup: Breast Cancer Mortality (Long Case) (50-59 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 12.5–21.9 years	820 per 100,000*	673 per 100,000 (558 to 812) ^g	RR 0.82 (0.68, 0.99)	131,514 (5 RCTs) ^a	⊕○○○ VERY LOW ^{b,d,f,h,i}	NNS: 676 (382 to -12,500), CIs include ∞
	Subgroup: Breast Cancer Mortality (Long Case) (60-69 years)	445 per 100,000 (342 to 582) ^g				RR 0.65 (0.50, 0.85)
	#Randomized: Unclear #Analyzed: Unclear follow up: range 12.5–14.0 years	684 per 100,000*				34,369 (3 RCTs) ⊕⊕○○ LOW ^{b,d,f,j,k} NNS: 418 (292 to 971)
Subgroup: Breast Cancer Mortality (Long Case) (70-74 years) #Randomized: Unclear #Analyzed: Unclear follow up: range 12.5 years	684 per 100,000*	541 per 100,000 (349 to 835)	RR 0.79 (0.51, 1.22)	17,646 (2 RCTs)	⊕○○○ VERY LOW ^{b,d,f,l,m}	NNS: 694 (299 to 662)

CI Confidence interval; NNS number needed to screen; RR Risk ratio

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

** Long-Case Accrual: All deaths from breast cancer cases diagnosed during the screening period and follow-up period are included in the analysis.

- a. One study considered quasi-randomized (Gothenburg)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- c. Heterogeneity may be low ($I^2=17\%$); (p-value=0.35)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Gothenburg, AGE and Swedish Two-County - usual care arm received screening at end of study period.
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs include the null, but do not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials)
- g. Numerators and/or denominators were either unclear or not reported for all included studies.
- h. Heterogeneity may be moderate ($I^2=38\%$); (p-value=0.17)
- i. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs do not cross the null, but do cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- j. Heterogeneity may be low ($I^2=0\%$); (p-value=0.57)
- k. (i) The total population is large (>2000); and (ii) the 95% CI crosses the null and also crosses appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted.
- l. Heterogeneity may be low ($I^2=0\%$); (p-value=0.88)
- m. (i) The total population is large (>2000); and (ii) the 95% CI crosses the null, and also crosses appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted

Mammogram +/- CBE – All-Cause Mortality (All Ages; follow up: range 7.9 years to 25.0 years)

Studies	Risk of bias	Certainty assessment				No of patients		Effect		Certainty	Importance
		Inconsistency	Indirectness	Imprecision	Other considerations	Mammogram +/- CBE	Usual Care	Relative (95% CI)	Absolute (95% CI)		
8 RCTs ^a #R: Unclear #A: Unclear	very serious ^b	not serious ^c	not serious ^d	not serious ^e	none ^f	Unavailable*	4.0%	RR 0.99 (0.98, 1.01)	40 fewer per 100,000 (from 40 more to 80 fewer)**	⊕⊕○○ LOW	
							6.9%		69 fewer per 100,000 (from 69 more to 138 fewer)**		
							10.4%		104 fewer per 100,000 (from 104 more to 208 fewer)**		

CI Confidence interval; RR Risk ratio; #R Number randomized; #A Number analyzed

* Complete data was not available. Numerators and/or denominators were either unclear or not reported for all included studies.

** The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

- a. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- c. Heterogeneity may be low ($I^2=0\%$; $p\text{-value}=0.49$)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 included one round of screening in the control group.
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs include the null, but do not cross appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials)

References:

1. AGE (Duffy 2020)
2. CNBSS 1 & 2 (Miller 2014)
3. Gothenburg (Nystrom 2002)
4. HIP (Aron & Prorak 1986)
5. Malmo I (Nystrom 2002)
6. Malmo II (Nystrom 2002)
7. Stockholm (Nystrom 2002)
8. Swedish Two County – Ostergotland (Nystrom 2002)

Mammogram +/- Clinical Breast Examination (CBE) – All-Cause Mortality (All Ages)

Patient or population: Asymptomatic, healthy women

Setting: Community

Intervention: Mammogram +/- CBE

Comparison: Usual Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual Care	Risk with Mammogram +/- CBE				
Low						
All-Cause Mortality (All Ages)	4,000 per 100,000*	3,960 per 100,000 (3,920 to 4,040)				NNS (Low): 2,500 (1,250 to -2,500); CIs include ∞
Moderate						
#Randomized: Unclear #Analyzed: Unclear follow up: range 7.9–25 years	6,900 per 100,000*	6,831 per 100,000 (6,762 to 6,969)	RR 0.99 (0.98, 1.01)	(8 RCTs) ^a	⊕⊕○○ LOW ^{b,c,d,e,f}	NNS (Moderate): 1,449 (725 to -1.449); CIs include ∞
High						
	10,400 per 100,000*	10,296 per 100,000 (10,192 to 10,504)				NNS (High): 962 (481 to -962); CIs include ∞

CI Confidence interval; RR Risk ratio

+The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

- a. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- b. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas.
- c. Heterogeneity may be low ($I^2=0\%$; p -value=0.49)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 included one round of screening in the control group.
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs include the null, but do not cross appreciable benefit (RR 0.75). Given the large sample size, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials)

Mammogram +/- CBE – All-Cause Mortality (Stratified by Age)

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mammogram +/- CBE	Usual Care	Relative (95% CI)	Absolute (95% CI)		
All-Cause Mortality (40-49 years) (follow up: range 7.9 years to 23 years)											
7 RCTs ^a #R: 311,066 #A: Unclear	very serious ^b	not serious ^c	not serious ^d	not serious ^e	none ^f	Unavailable*	0.2%*	RR 1.01 (0.98, 1.05)	2 fewer per 100,000 (from 4 more to 10 fewer)**	⊕⊕○○ LOW	
									21 fewer per 100,000 (from 42 more to 105 fewer)**		
									40 fewer per 100,000 (from 80 more to 200 fewer)**		
All-Cause Mortality (50-59 years) (follow up: range 7.9 years to 13 years)											
3 RCTs #R: 79,749 #A: 79,695	very serious ^b	not serious ^g	not serious ^d	not serious ^e	none ^f	1,836/43,196 (4.3%)	3.5% 4.8%	RR 1.02 (0.96, 1.09)	70 more per 100,000 (from 140 fewer to 315 more)	⊕⊕○○ LOW	
									96 more per 100,000 (from 192 fewer to 432 more)		
All-Cause Mortality (60-69 years) (follow up: 7.9 years)											
2 RCTs #R: 39,681 #A: 39,681	very serious ^b	not serious ^h	not serious ^d	not serious ^e	none ^f	2,899/23,412 (12.4%)	2,080/16,269 (12.8%)	RR 0.97 (0.91, 1.03)	384 fewer per 100,000 (from 384 more to 1,151 fewer)	⊕⊕○○ LOW	
All-Cause Mortality (70-74 years) (follow up: 7.9 years)											
2 RCTs #R: 17,646 #A: 17,646	very serious ^b	very serious ⁱ	not serious ^d	not serious ^e	none ^f	2869/10,339 (27.7%)	26.1% 29.5%	RR 0.98 (0.87, 1.11)	523 fewer per 100,000 (from 2,877 more to 3,400 fewer)	⊕○○○ VERY LOW	
									590 fewer per 100,000 (from 3,243 more to 3,832 fewer)		

CI Confidence interval; RR Risk ratio; #R Number randomized; #A Number analyzed

* Complete data was not available. Numerators and/or denominators were either unclear or not reported for all included studies.

** The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

- a. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- b. Randomization and allocation concealment were either not reported or there were serious outcomes in these areas.
- c. Heterogeneity may be low ($I^2=0\%$; (p-value=0.61)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 included one round of screening in the control group.
- e. (i) The number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs include the null, but do not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials).
- g. Heterogeneity may be low ($I^2=0\%$; (p-value=0.56)
- h. Heterogeneity may be low ($I^2=0\%$; (p-value=0.64)
- i. Heterogeneity may be substantial ($I^2=72\%$; (p-value=0.06)

References:

2. AGE (Duffy 2020)
3. CNBSS 1 (Miller 2002)
4. CNBSS 2 (Miller 2000)
5. Gothenburg (Bjurstrom 1997)

6. Malmo II (Nystrom 2002)

7. Stockholm (Frisell 1997)

8. Swedish Two-County (Kopparberg) (Tabbar 1989) 9. Swedish Two-County (Ostergotland) (Tabbar 1989)

Mammogram +/- CBE – All-Cause Mortality (Stratified by Age)

Patient or population: Asymptomatic, healthy women

Setting: Community

Intervention: Mammogram +/- CBE

Comparison: Usual Care

Outcomes	Anticipated absolute effects ⁺ (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments**			
	Risk with Usual Care	Risk with Mammogram +/-							
Low									
All-Cause Mortality (40-49 years) #Randomized: 311,066 #Analyzed: Unclear follow up: range 7.9–25 years	200 per 100,000*	202 per 100,000 (196 to 210)	RR 1.01 (0.98, 1.05)	(7 RCTs) ^a	⊕⊕○○ LOW ^{b,c,d,e,f}	NNS (Low): 50,000 (10,000 to -25,000); CIs include ∞			
Moderate									
	2,100 per 100,000*	2,121 per 100,000 (2,058 to 2,205)				NNS (Moderate): 4,672 (952 to -2,381); CIs include ∞			
High									
	4,000 per 100,000*	4,040 per 100,000 (3,920 to 4,200)				NNS (High): 2,500 (500 to -1,250); CIs include ∞			
Low									
All-Cause Mortality (50-59 years) #Randomized: 79,749 #Analyzed: 79,695 follow up: range 7.9–13 years	3,500 per 100,000	3,570 per 100,000 (3,360 to 3,815)	RR 1.02 (0.96, 1.09)	79,695 (3 RCTs)	⊕⊕○○ LOW ^{b,d,e,f,g}	NNS (Low): -1,429 (714 to -317); CIs include ∞			
High									
	4,800 per 100,000	4,896 per 100,000 (4,608 to 5,232)				NNS (High): 1,042 (521 to -231); CIs include ∞			
All-Cause Mortality (60-69 years) #Randomized: 39,681 #Analyzed: 39,681 follow up: 7.9 years	12,785 per 100,000	12,401 per 100,000 (11,634 to 13,169)	RR 0.97 (0.91, 1.03)	39681 (2 RCTs)	⊕⊕○○ LOW ^{b,d,e,f,h}	NNS (Low): 260 (87 to -260); CIs include ∞			
Low									
All-Cause Mortality (70-74 years) #Randomized: 17,646 #Analyzed: 17,646 follow up: 7.9 years	26,100 per 100,000	25,578 per 100,000 (22,707 to 28,971)	RR 0.98 (0.87, 1.11)	10339 (2 RCTs)	⊕○○○ VERY LOW ^{b,d,e,f,i}	NNS (Low): 191 (29 to -35); CIs include ∞			
High									
	29,500 per 100,000	28,910 per 100,000 (25,665 to 32,745)				NNS (High): 169 (26 to -31); CIs include ∞			

CI Confidence interval; NNS number needed to screen; RR Risk ratio

+The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

* The baseline risk (in the control group) may not have been representative of all included studies because the numerators and/or denominators were either unclear or not reported. Values provided reflect those studies which provided complete data.

** Long-Case Accrual: All deaths from breast cancer cases diagnosed during the screening period and follow-up period are included in the analysis.

- a. Two studies are considered quasi-randomized (Gothenburg & Stockholm)
- b. Randomization and allocation concealment were either not reported or there were serious outcomes in these areas.
- c. Heterogeneity may be low ($I^2=0\%$); (p-value=0.61)
- d. Studies are relevant to the PICO being addressed. Breast density was not addressed. For some studies, the control group received screening after the screening period. Studies reported in Nystrom 2002 included one round of screening in the control group.
- e. (i) the number of events and total population are large (>300 threshold for events); and (ii) the 95% CIs include the null, but do not cross appreciable benefit (RR 0.75). Given the large sample sizes, an optimal sample size calculation was not warranted.
- f. Cannot assess publication bias (insufficient number of trials).
- g. Heterogeneity may be low ($I^2=0\%$); (p-value=0.56)
- h. Heterogeneity may be low ($I^2=0\%$); (p-value=0.64)

1. i. Heterogeneity may be substantial ($I^2=72\%$); (p -value=0.06)

CBE vs Usual Care

Certainty assessment						No of patients		Effect		Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical Breast Examination (CBE)	Usual Care	Relative (95% CI)	Absolute (95% CI)		
Breast Cancer Mortality (All Ages) (follow-up: 13 years)											
1 RCT ^a	serious ^b	not serious	not serious	serious ^c	none	213/75,360 (0.3%)	251/76,178 (0.3%)	RR 0.85 (0.71, 1.01)	49 fewer per 100,000 (from 96 fewer to 3 more)	⊕⊕○○ LOW	
Breast Cancer Mortality (<50 years) (follow-up: 13 years)											
1 RCT ^a	serious ^b	not serious	not serious	serious ^c	none	149/54,212 (0.3%)	158/54,188 (0.3%)	RR 0.93 (0.79, 1.09)	20 fewer per 100,000 (from 61 fewer to 26 more)	⊕⊕○○ LOW	
Breast Cancer Mortality (≥50 years) (follow-up: 13 years)											
1 RCT ^a	serious ^b	not serious	not serious	not serious ^d	none	64/20,965 (0.3%)	93/21,909 (0.4%)	RR 0.71 (0.54, 0.94)	123 fewer per 100,000 (from 195 fewer to 25 fewer)	⊕⊕⊕○ MODERATE	
All-Cause Mortality (All Ages) (follow-up: 13 years)											
1 RCT ^a	serious ^b	not serious	not serious	serious ^c	none	11,261/75,360 (14.9%)	11,853/76,178 (15.6%)	RR 0.95 (0.81, 1.10)	778 fewer per 100,000 (from 2,956 fewer to 1,556 more)	⊕⊕○○ LOW	
All-Cause Mortality (<50 years) (follow-up: 13 years)											
1 RCT ^a	serious ^b	not serious	not serious	serious ^c	none	4,450/54,212 (8.2%)	4,708/54,188 (8.7%)	RR 0.93 (0.83, 1.05)	599 fewer per 100,000 (from 1,486 fewer to 391 more)	⊕⊕○○ LOW	
All-Cause Mortality (≥50 years) (follow-up: 13 years)											
1 RCT ^a	serious ^b	not serious	not serious	serious ^d	none	6,811/20,965 (32.5%)	7,145/21,909 (32.6%)	RR 0.98 (0.90, 1.07)	522 fewer per 100,000 (from 3,196 fewer to 2,381 more)	⊕⊕○○ LOW	

CI Confidence interval; RCT randomized controlled trial; RR Risk ratio

- a. Cluster randomization was done.
- i. Randomization and allocation concealment unclear.
- j. The 95% Confidence interval includes the null.
- k. Total number of events is <230 (predefined number of events for mortality analysis to be recommended) but the sample size is large

Reference: Mumbai (Mittra 2021)

CBE vs Usual Care

Patient or population: Asymptomatic healthy women

Setting: Community

Intervention: Clinical Breast Examination (CBE)

Comparison: Usual Care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual Care	Risk with CBE				
Breast Cancer Mortality (All Ages)	329 per 100,000	280 per 100,000 (234 to 333)	RR 0.85 (0.71, 1.01)	151538 (1 RCT) ^a	⊕⊕○○ LOW ^{b,c}	
Breast Cancer Mortality (<50 years)	292 per 100,000	271 per 100,000 (230 to 318)	RR 0.93 (0.79, 1.09)	108400 (1 RCT) ^a	⊕⊕○○ LOW ^{b,c}	
Breast Cancer Mortality (≥50 years)	424 per 100,000	301 per 100,000 (229 to 399)	RR 0.71 (0.54, 0.94)	42874 (1 RCT) ^a	⊕⊕⊕○ MODERATE ^b	
All Cause Mortality (All Ages)	15,560 per 100,000	14782 per 100,000 (12,603 to 17,116)	RR 0.95 (0.81, 1.10)	151538 (1 RCT) ^a	⊕⊕○○ LOW ^{b,c}	
All Cause Mortality (<50 years)	8,688 per 100,000	8089 per 100,000 (7,203 to 9,079)	RR 0.93 (0.83, 1.05)	108400 (1 RCT) ^a	⊕⊕○○ LOW ^{b,c}	
All Cause Mortality (≥50 years)	32,612 per 100,000	32090 per 100,000 (29,416 to 34,993)	RR 0.98 (0.90, 1.07)	42874 (1 RCT) ^a	⊕⊕○○ LOW ^{b,c}	

CI Confidence interval; RR Risk ratio

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

- a. Cluster randomization was done
- I. Randomization and allocation concealment unclear.
- m. Confidence interval is wide.

Mammogram +/- CBE – Overdiagnosis

Certainty assessment						Impact	Certainty	Importance
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Invasive + In Situ (follow up: range 20 years to 29 years)								
3 RCTs	very serious ^a	very serious ^b	not serious ^c	serious ^d	none ^e	Results were reported differently between studies. One study reported no overdiagnosis [RR 1.00 (0.92 – 1.08)]. Another study reported 55% and 16% of overdiagnosis for 40-49, and 50-59, respectively. The remaining study reported that there was a 10% incidence in the control group.	⊕○○○ VERY LOW	
Invasive only (follow up: range 20 years to 29 years)								
3 RCTs	very serious ^a	very serious ^b	not serious ^c	serious ^d	none ^e	Results were reported differently between studies. One study reported no overdiagnosis [RR 0.99 (0.92 – 1.07)]. Another reported 48% and 5% overdiagnosis for 40-49, and 50-59, respectively. The remaining study reported 7% overdiagnosis.	⊕○○○ VERY LOW	
In Situ only (follow up: range 20 years to 29 years)								
2 RCTs	very serious ^f	very serious ^b	not serious ^c	serious ^d	none ^e	Results were reported differently between studies. One study noted that there was overdiagnosis in the screening arm (although not statistically significant) [RR 1.17 (0.88 – 1.55)]. The remaining study reported 3% overdiagnosis. ^g	⊕○○○ VERY LOW	

CI Confidence interval

a. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas. Baseline imbalances apparent in two studies.

b. Reporting of estimates varied between studies. One cannot be confident that the same methodological approach was used.

c. Studies are relevant to the PICO being addressed.

d. Narrative analysis. Effect sizes were not provided consistently across studies.

e. Cannot assess publication bias (insufficient number of trials).

f. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas. Baseline imbalances apparent in one study.

g. Overdiagnosis characteristics were extracted as reported in the overviews.

References:

1. Malmo I (Zackrisson 2006)
2. Baines 2016 (CNBSS 1 & 2)
3. Swedish Two County (Kopparberg) (Yen 2012)

Mammogram +/- CBE – Overdiagnosis

Patient or population: Asymptomatic, healthy women

Setting: Community

Intervention: Mammogram +/- CBE

Comparison: Usual Care

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Invasive + In Situ follow up: range 20 years to 29 years	Results were reported differently between studies. One study reported no overdiagnosis [RR 1.00 (0.92 – 1.08)]. Another study reported 55% and 16% of overdiagnosis for 40-49, and 50-59, respectively. The remaining study reported that there was a 10% incidence in the control group.	(3 RCTs)	⊕○○○ VERY LOW a,b,c,d,e
Invasive only follow up: range 20 years to 29 years	Results were reported differently between studies. One study reported no overdiagnosis [RR 0.99 (0.92 – 1.07)]. Another reported 48% and 5% overdiagnosis for 40-49, and 50-59, respectively. The remaining study reported 7% overdiagnosis.	(3 RCTs)	⊕○○○ VERY LOW a,b,c,d,e
In Situ only follow up: range 20 years to 29 years	Results were reported differently between studies. One study noted that there was overdiagnosis in the screening arm (although not statistically significant) [RR 1.17 (0.88 – 1.55)]. The remaining study reported 3% overdiagnosis. ^f	(2 RCTs)	⊕○○○ VERY LOW b,c,d,e,g

CI Confidence interval

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

- a. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas. Baseline imbalances apparent in two studies.
- b. Reporting of estimates varied between studies. One cannot be confident that the same methodological approach was used.
- c. Studies are relevant to the PICO being addressed.
- d. Narrative analysis. Effect sizes were not provided consistently across studies.
- e. Cannot assess publication bias (insufficient number of trials).
- f. Overdiagnosis characteristics were extracted as reported in the overviews.
- g. Randomization and allocation concealment were either not reported or there were serious deficiencies in these areas. Baseline imbalances apparent in one study.

8. Screening for Prostate Cancer

SEARCH STRATEGY

13	#12 or #11	"death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields] OR "mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]
12	death	"death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields]
11	mortality	"mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]
screening		"diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields] OR "screen"[All Fields] OR "screenings"[All Fields] OR "screened"[All Fields] OR "screens"[All Fields]
10		
8	#5 or #6 or #7	"prostate cancer"[All Fields] OR "prostate carcinoma"[All Fields] OR "prostate adenocarcinoma"[All Fields]
7	"prostate adenocarcinoma"	"prostate adenocarcinoma"[All Fields]
6	"prostate carcinoma"	"prostate carcinoma"[All Fields]
5	"prostate cancer"	"prostate cancer"[All Fields]
4	#1 and #2	"prostate specific antigen"[All Fields] AND "PSA"[All Fields]
3	#1 or #2	"prostate specific antigen"[All Fields] OR "PSA"[All Fields]
2	PSA	"PSA"[All Fields]
1	"prostate specific antigen"	"prostate specific antigen"[All Fields]

GRADE SUMMARY OF EVIDENCE

PSA + DRE compared to no screening for Prostate Cancer

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
All cause Mortality assessed with: Incidence Rate Ratio Nº of participants: 6847656 (3 RCTs)	RR 0.99 (0.97 to 1.02)	1.6%	1.5% (1.5 to 1.6)	0.0% fewer (0 fewer to 0 fewer)		Low ^a
Prostate Cancer Mortality assessed with: Incidence Rate Ratio Nº of participants: 6847656 (3 RCTs)	RR 0.92 (0.80 to 1.07)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)		Low ^{a,b}
Prostate Cancer Mortality With Prostatectomy assessed with: Deaths Nº of participants: 2524 (3 RCTs)	RR 0.77 (0.58 to 1.03)	9.4%	7.3% (5.5 to 9.7)	2.2% fewer (4 fewer to 0.3 more)		High ^{a,b}
Prostate Cancer Mortality with Radiation Therapy assessed with: Deaths Nº of participants: 1090 (1 RCT)	RR 0.51 (0.15 to 1.69)	1.5%	0.7% (0.2 to 2.5)	0.7% fewer (1.2 fewer to 1 more)		High ^{a,b}
Prostate Cancer Incidence assessed with: Incidence Rate Ratio Nº of participants: 6349943 (3 RCTs)	RR 0.90 (0.79 to 1.03)	0.5%	0.5% (0.4 to 0.5)	0.1% fewer (0.1 fewer to 0 fewer)		Low ^{a,b}
Prostate Cancer Localized Stages (Stage I and II) assessed with: Incidence Rate Ratio Nº of participants: 647751 (3 RCTs)	RR 1.39 (1.09 to 1.79)	3.5%	4.8% (3.8 to 6.2)	1.4% more (0.3 more to 2.7 more)		Low ^{a,b}
Prostate Cancer Advanced Stage (Stage III and IV) assessed with: Incidence Rate Ratio Nº of participants: 647841 (3 RCTs)	RR 0.85 (0.72 to 1.00)	1.2%	1.0% (0.9 to 1.2)	0.2% fewer (0.3 fewer to 0 fewer)		Low ^{a,b}

CI confidence interval; RR risk ratio

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. inadequate concealment of allocation during randomisation resulting in potential for selection bias; inadequate or lack of blinding of participants and personnel, resulting in potential for performance bias; some contamination;

b. There are different intervals and frequency of screening tests done for each RCT. The CAP trial recruited patients during a more recent PSA testing era between 2001 and 2009 compared with between 1993 and 2003 in the ERSPC trial and 1993 and 2001 in the PLCO trial.

PLCO Trial (Cutoff of >4 ng/ml)

	Disease Present	Disease Absent	
Test Positive	489	2228	2717
Test Negative	66	2017	2083
Total	555	4245	4800
Sensitivity	0.881		
Specificity	0.475		

PLCO Trial (Cutoff of >4 ng/ml or abnormal DRE)

	Disease Present	Disease Absent	
Test Positive	556	4246	4802
Test Negative	66	2017	2083
Total	555	4245	4800
Sensitivity	0.894		
Specificity	0.322		

Finnish Subset Test Performance First Round (Cutoff of >4 ng/ml or 3-4ng/ml + abnormal DRE)

	Disease Present	Disease Absent	
Test Positive	508	1358	1866
Test Negative	42	18783	18825
Total	550	20141	20691
Sensitivity	0.924		
Specificity	0.933		

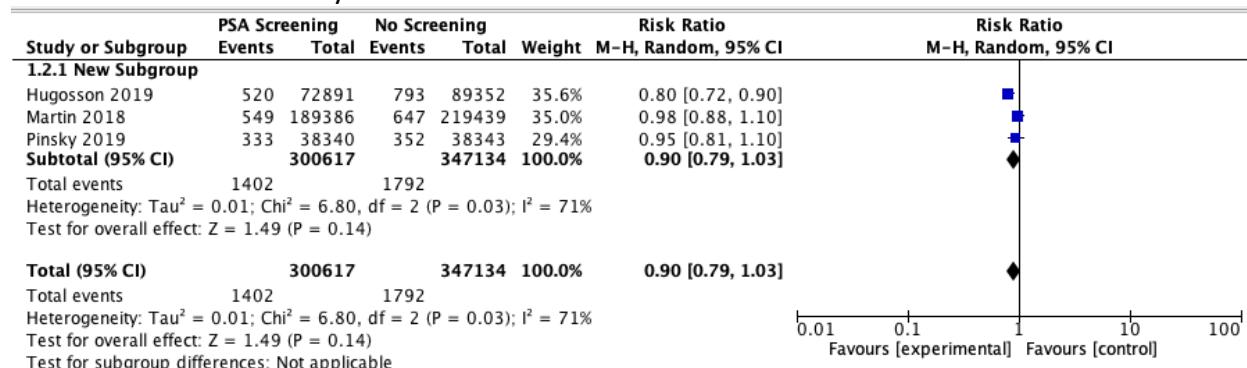
Finnish Subset Test Performance Second Round (Cutoff of >4 ng/ml or 3-4ng/ml + abnormal DRE)

	Disease Present	Disease Absent	
Test Positive	583	1573	2156
Test Negative	45	16264	16309
Total	628	17837	18465
Sensitivity	0.928		
Specificity	0.912		

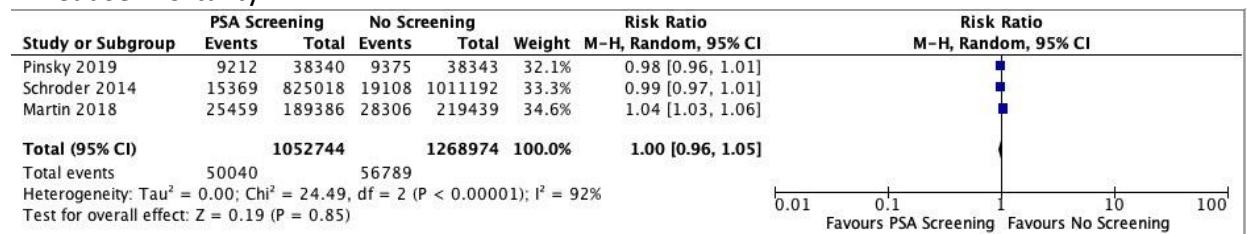
FOREST PLOTS

PSA +/- DRE vs No Screening

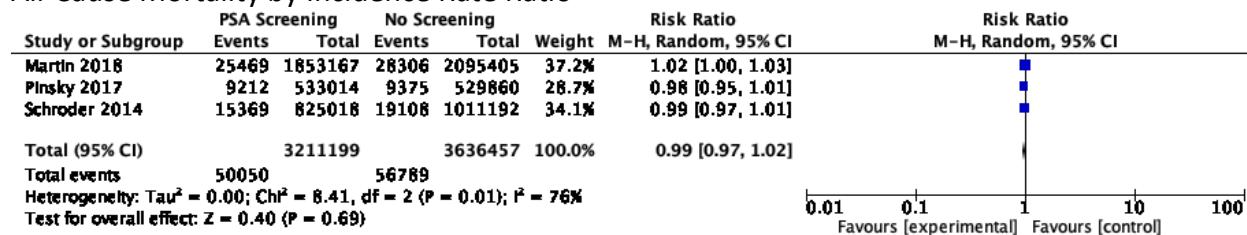
Prostate Cancer Mortality



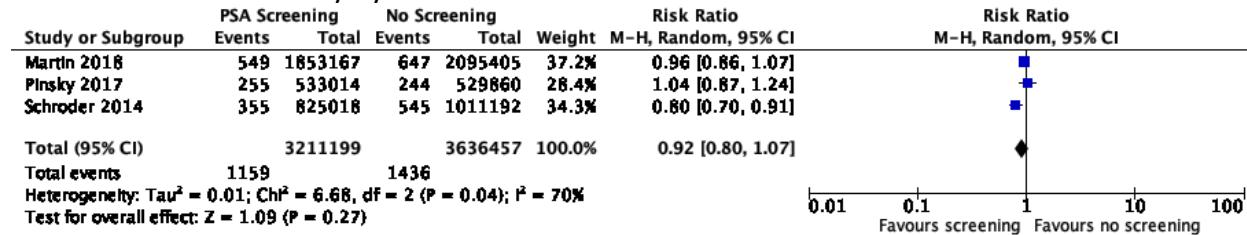
All-Cause Mortality



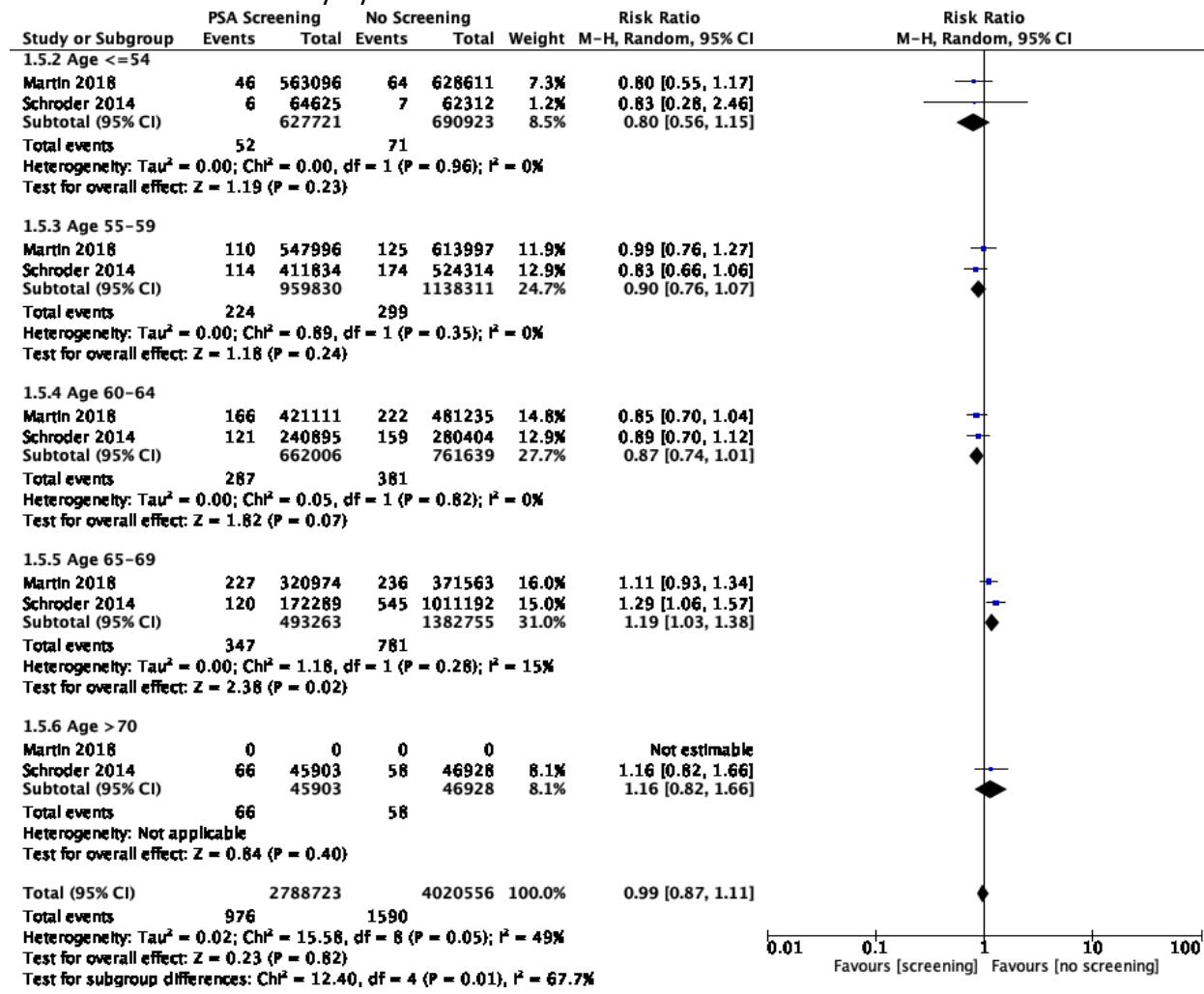
All-Cause Mortality by Incidence Rate Ratio



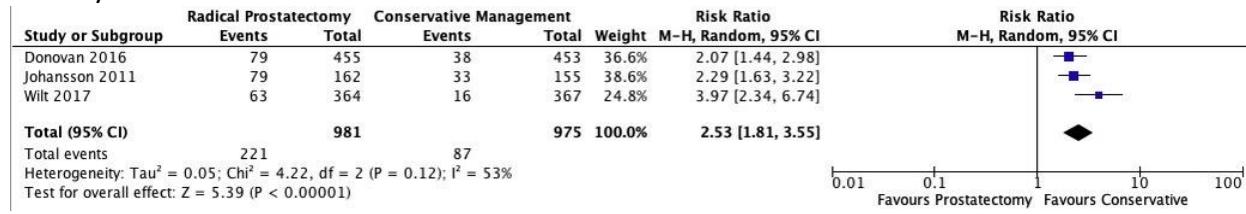
Prostate Cancer Mortality by Incidence Rate Ratio



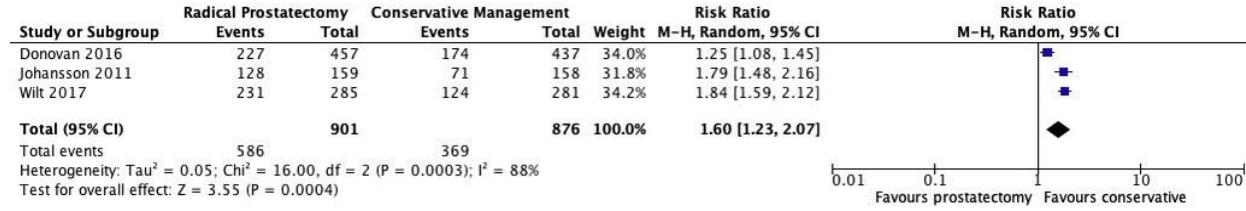
Prostate Cancer Mortality by Incidence Rate Ratio



Urinary Incontinence

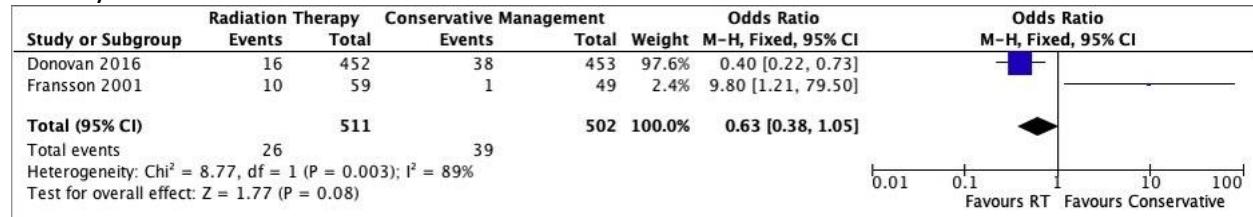


Erectile Dysfunction

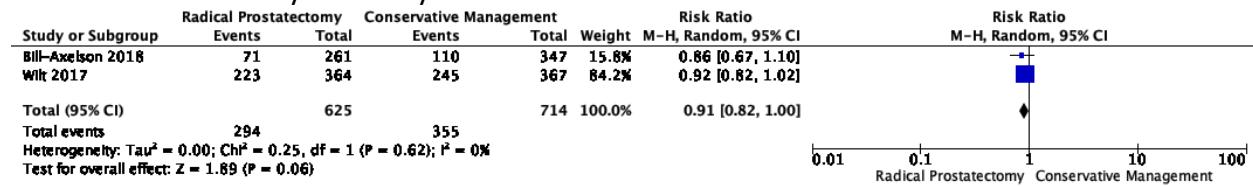


Radiation Therapy

Urinary Incontinence



Radical Prostatectomy Mortality



9. Screening for Lung Cancer

SEARCH STRATEGY

Total (duplicates not yet removed): 4,623 titles

Electronic Databases	Yield	Purpose	Search strategy
MEDLINE	3,778	RCTs Observational studies Systematic reviews (450) Economic evaluation	("screen*"[Title/Abstract] OR ("Mass Screening"[MeSH Terms] AND "Mass Screening"[MeSH Terms])) AND (("tomography, x ray computed"[MeSH Terms] OR "computed tomography"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "LDCT"[Title/Abstract]) AND ("lung cancer"[Title/Abstract] OR "lung carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract]))
CENTRAL	603	Cochrane reviews (93) Cochrane protocols (6) Trials (504)	(lung cancer OR "Lung Neoplasms"[MeSH: explode all trees] OR lung carcinoma) AND (("Tomography Scanners, X-Ray Computed"[MESH: explode all trees] OR low-dose CT OR low dose CT OR CT scan OR computed tomography) AND (screening OR "Mass Screening"[MESH: explode all trees]) with Cochrane Library publication date from May 2014 to Aug 2021, in Cochrane Reviews, Cochrane Protocols and Trials
NHS EED and HTA (via crd.york.ac.uk)	29	Systematic reviews Economic evaluation HTA	(lung cancer OR lung carcinoma OR lung neoplasm):TI AND (screening):TI AND (low-dose CT OR low dose CT CT OR CT scan OR computed tomography):TI IN DARE, NHSEED, HTA WHERE LPD FROM 01/01/1972 TO 01/08/2021
HERDIN (herdin.ph)	213	Local studies (ongoing – 21; Completed – 213; Trials – 31)	Lung cancer

Detailed Search: MEDLINE (Date of Search: 01 August 2021; Updated Search: 15 November 2021)

#	Query	Filters	Search Details	Results
18	Updated search from 2021/08/01		((("screen*"[Title/Abstract] OR ("Mass Screening"[MeSH Terms] AND "Mass Screening"[MeSH Terms])) AND (("tomography, x ray computed"[MeSH Terms] OR "computed tomography"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "LDCT"[Title/Abstract]) AND ("lung cancer"[Title/Abstract] OR "lung carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract]))) AND ((meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter])) AND (2021/8/1:2021/11/15[pdat]))	+ 6
17	#15 and #12	Systematic review, Randomized controlled trials from 2014/5/12 - 2021/8/1	((("screen*"[Title/Abstract] OR ("Mass Screening"[MeSH Terms] AND "Mass Screening"[MeSH Terms])) AND (("tomography, x ray computed"[MeSH Terms] OR "computed tomography"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "LDCT"[Title/Abstract]) AND ("lung cancer"[Title/Abstract] OR "lung carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract]))) AND ((meta analysis[Publication Type] OR "review"[Publication Type] OR "systematic review"[Filter]) AND 2014/05/12:2021/08/01[Date - Publication])) AND (randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	47
16	#15 and #12		((("screen*"[Title/Abstract] OR ("Mass Screening"[MeSH Terms] AND "Mass Screening"[MeSH Terms])) AND (("tomography, x ray computed"[MeSH Terms] OR "computed tomography"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "LDCT"[Title/Abstract]) AND ("lung cancer"[Title/Abstract] OR "lung carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract]))) AND ((meta analysis[Publication Type] OR "review"[Publication Type] OR "systematic review"[Filter]) AND 2014/05/12:2021/08/01[Date - Publication])) AND (randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	3,778

		carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract]))	
15	#13 or #14	"screen*[Title/Abstract] OR ("Mass Screening"[MeSH Terms] AND "Mass Screening"[MeSH Terms])	868,86 4
14	("Mass Screening"[Mesh]) AND ("Mass Screening"[Mesh])	"Mass Screening"[MeSH Terms] AND "Mass Screening"[MeSH Terms]	134,69 4
13	screen*[Title/Abstract]	"screen*[Title/Abstract]	827,04 6
12	#11 and #5	("tomography, x ray computed"[MeSH Terms] OR "computed tomography"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "LDCT"[Title/Abstract]) AND ("lung cancer"[Title/Abstract] OR "lung carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract])	29,888
11	#6 or #7 or #8 or #9 or #10	"tomography, x ray computed"[MeSH Terms] OR "computed tomography"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "low dose ct scan"[Title/Abstract] OR "LDCT"[Title/Abstract]	590,88 9
10	LDCT[Title/Abstract]	"LDCT"[Title/Abstract]	1,068
9	"low dose CT scan"[Title/Abstract]	"low dose CT scan"[Title/Abstract]	170
8	"low-dose CT scan"[Title/Abstract]	"low-dose CT scan"[Title/Abstract]	170
7	computed tomography[Title/Abstract]	"computed tomography"[Title/Abstract]	277,94 6
6	"Tomography, X-Ray Computed"[Mesh]	"tomography, x ray computed"[MeSH Terms]	457,41 1
5	#1 or #2 or #3 or #4	"lung cancer"[Title/Abstract] OR "lung carcinoma"[Title/Abstract] OR "Lung Neoplasms"[MeSH Terms] OR "lung neoplasm"[Title/Abstract]	306,45 0
4	lung neoplasm[Title/Abstract]	"lung neoplasm"[Title/Abstract]	534
3	"Lung Neoplasms"[Mesh]	"Lung Neoplasms"[MeSH Terms]	246,37 2
2	"lung carcinoma"[Title/Abstract]	"lung carcinoma"[Title/Abstract]	19,436
1	"lung cancer"[Title/Abstract]	"lung cancer"[Title/Abstract]	171,77 6

Detailed Search: Cochrane CENTRAL (Date of Search: 01 Aug 2021 06:12:54)

#1	lung cancer	27666
#2	MeSH descriptor: [Lung Neoplasms] explode all trees	8079
#3	lung carcinoma	9105
#4	#1 or #2 or #3 2	8667
#5	MeSH descriptor: [Tomography Scanners, X-Ray Computed] explode all trees	41
#6	low-dose CT	5929
#7	low dose CT	13827
#8	CT scan	8177
#9	computed tomography	17886
#10	#5 or #6 or #7 or #8 or #9	35562
#11	screening	64195
#12	MeSH descriptor: [Mass Screening] explode all trees	3906
#13	#11 or #12	64559
#14	#4 and #10 and #13	718
#15	#14 with Publication Year from 2014 to 2021, in Trials	401
#16	#14 with Cochrane Library publication date Between May 2014 and Aug 2021, in Cochrane Reviews, Cochrane Protocols, Trials	603

CHARACTERISTICS OF INCLUDED STUDIES

Included systematic reviews

#	Study	Population	Diagnostic Intervention	Comparison	Outcomes	Study designs	Date of Last Search	Number of studies included
1	Passiglia 2021	High-risk population - smoking history > 15 pack years - former smokers who quit w/in 15 years	CTLS (computed tomography lung screening)	CXR or NS	1. Lung cancer-related mortality 2. All-cause mortality 3. Resectability rate 4. Diagnosis of early stage tumors (stage I-II) 5. Diagnosis of late-stage tumors (stage IV) 6. Overdiagnosis	RCTs	Feb 13 2020	9
2	Jonas 2021	Adults at increased risk (populations and settings relevant to primary care in the US)	LDCT	Any type of screening	1. Incidence of lung cancer 2. Distribution of lung cancer types and stages 3. All-cause mortality 4. Lung cancer-related mortality 5. Quality of life 6. Accuracy of LDCT 7. Harms associated with LDCT 8. Harms associated with workup or nodule surveillance 9. Harms associated with surgical resection or SBRT	RCTs, nonrandomized CTs, prospective cohort (for harms)	Nov 20 2020	Benefit: 9 Accuracy: 13 Harm:
3	Hunger 2021	Current and former smokers	LDCT	CXR or NS	1. Lung cancer-related mortality 2. All-cause mortality 3. Lung cancer incidence (stage and histology) 4. Radiation exposure 5. Invasive diagnostic procedures 6. False positive screening results 7. Overdiagnosis 8. Health-related quality of life 9. Psychosocial consequences	RCTs, systematic reviews of RCTs	Apr-20	10 RCT, 23 SRs 24 - mortality 7 - QOL 8 - harms 4 - radiation exposure

Included RCTs

(Obtained from Jonas et al., 2021 and Passiglia et al., 2021 and Hunger et al., 2021).

#	RCT	Recruitment years	Sample size	Mean age (ages eligible), years	% Male	Baseline smoking status, %	Eligibility criteria for pack-years; years since quitting	Screening rounds, No.	Screening intervals, years	Comparison intervention	Nodule evaluation (positivity criteria)	Total median follow-up, years
1	DANTE (Italy)	2001-2006	2472	65 (60-74)	100	Current: 57 Former: 43 Mean no. of pack-years: 47	≥20; <10 y	5	0, 1, 2, 3, 4	Usual care n = 1408	> 10 mm diameter	8.4
2	DEPISCAN (France)	2002-2004	765	NR (50-75)	71	Current: 64 Former: 36 Mean no. of pack years: 45	>15, <15 y	3	0, 1, 2	Annual CXR n = 380	> 5 mm diameter	NR
3	DLCST (Denmark)	2004-2006	4104	58 (50-70)	56	Current: 76 Former: 24 Mean no. of pack-years: 36	≥20; quit after age 50 and <10 y ago	5	0, 1, 2, 3, 4	Usual care n = 2052	> 5 mm diameter All growing nodules	9.8
4	ITALUNG (Italy)	2004-2006	3206	61 (55-69)	65	Current: 65 Former: 35 Mean no. of pack-years: 39	≥20 in the last 10 y or quit within the last 10 y	4	0, 1, 2, 3	Usual care n = 1593	> 5 mm diameter All growing nodules	9.3
5	LSS (USA)	2000-2001	3318	NR (55-74)	59	Current: 58 Former: 42 Mean no. of pack-years: 54	≥30; <10 y	2	0, 1	Annual CXR n = 1658	> 5 mm diameter	5.2
6	LUSI (Germany)	2007-2011	4052	NR (50-69)	65	Current: 62 Former: 35 Mean no. of pack-years: NR	≥25 y or 15 cigarettes or ≥30 y of 10 cigarettes; ≤10 y	5	0, 1, 2, 3, 4	Usual care n = 2023	> 5 mm diameter	8.8
7	MILD (Italy)	2005-2018	4099	NR (49-75)	66	Current: 77 Former: 23 Mean no. of pack-years: NR	>20 y; <10 y	3 to 4	0, 1, 2 OR 0, 6m, 1, 1.5y	Usual care n = 1723	> 60 mm ³	10
8	NELSON (Netherlands, Belgium)	2003-2006	15792	58 (50-74)	84	Current: 55 Former: 45 Mean no. of pack-years: 38	>15 cigarettes/day for >25 y or >10 cigarettes/day for >30 y; ≤10 y	4	0, 1, 3, 5.5	Usual care n = 6612	> 50 mm ³	10
9	NLST (USA)	2002-2004	53542	61 (55-74)	59	Current: 48 Former: 52 Mean no. of pack-years: 56	≥30; ≤15 y	3	0, 1, 2	Annual CXR n = 26732	< 4mm diameter	12.3

Diagnostic accuracy

(Obtained from Jonas et al., 2021 eTables 17-18).

eTable 17. Accuracy of LDCT for Lung Cancer Screening in RCTs (KQ 3)

Trial Name Author, Year	Number Analyzed	Nodule Classification Framework*	Threshold for Positive†	Screening Protocol	Sn	Sp	PPV	NPV
DANTE Infante, 2015 ¹⁶	2450	I-ELCAP	>5 mm average diameter	5 annual screens	79.5%	75.5%	18.6%	98.1%
DLCST Pedersen, 2009 ³⁰	4104	DLCST	>15 mm maximum diameter or 5-15 mm with >25% volume increase on 3-month repeat	5 annual screens (4 reported)	NR	NR	9.5%	NR
ITALUNG Lopes Pegna, 2013 ¹⁷	1406	I-ELCAP	≥5 mm average diameter solid nodule, ≥10 mm GGN average diameter, any part-solid nodule	4 annual screens‡	95.0%	26.4%	3.6%	99.4%
LSS Croswell, 2010 ³¹	1610	NLST	≥3 mm maximum diameter T0, ≥4 mm maximum diameter for T1	2 annual screens	NR	NR	7.0%	NR
LUSI Becker, 2015 ¹⁸	2028	I-ELCAP	≥5 mm average diameter	5 annual screens (4 completed)	93.5%	62%	7.2%	99.7%
MILD Sverzellati, 2016 ²⁰	1152	Modified NELSON	Volume >250 mm ³ or 60-250 mm ³ with >25% volume increase on 3-month repeat	5 annual screens	68.5%	99.2%	40.6%	99.7%
MILD Sverzellati, 2016 ²⁰	1151	Modified NELSON	Volume >250 mm ³ or 60-250 mm ³ with >25% volume increase on 3-month repeat	3 biennial screens	73.5%	99.2%	42.4%	99.8%
NELSON De Koning, 2020 ^{21,302}	6583§	NELSON	Volume >500 mm ³ or 50-500 mm ³ with VDT<400 d on 3-month repeat	4 rounds; baseline and after 1 y, 3 y, 5.5 y	59.0%	95.8%§	43.5%§	97.7%§
NLST Pinsky, 2013 ¹⁹	26 022	NLST	≥4 mm longest diameter	3 annual screens	93.1%	76.5%	3.3%	99.9%
UKLS Field, 2016 ²⁹⁹	1994	Modified NELSON [¶]	Volume >500 mm ³ or 50-500 mm ³ with VDT<400 d on 3-month repeat	1 screen	NR	NR	36.8%	NR
Mean, range	NA	NA	NA	NA	80.3%, 59.0%- 95.0%	76.4%, 26.4%- 99.2%	21.3%, 3.3%- 43.5%	99.2%, 97.7%- 99.9%

* We categorized whether the approach to nodule classification was most similar to the approach used in NLST, NELSON, DLCST, or I-ELCAP.

† These are the abbreviated criteria for a positive screen. Studies also considered specific features of nodules, for example.

‡ Study ongoing at the time of this publication.

§ This evaluation excluded some NELSON participants because it was limited to males in the screening group (data were not presented for the 1317 females in the screening group). The accuracy calculations in this row used NELSON's approach to classifying results, with indeterminate results that required a 3-month followup LDCT being categorized as negatives as long as the 3-month followup LDCT was negative (whereas other studies categorized the same type of thing, when any additional LDCT was required for evaluation, as a false positive).

¶ Nodules with volumes <50 mm³ were split into two categories. Those <15 mm³ received no further followup. Those 15-49 mm³ received followup LDCT scan in 1 year.

eTable 18. Accuracy of LDCT for Lung Cancer Screening in Nonrandomized Studies (KQ 3)

Author, Year	Trial/Database	Country	Number Analyzed	Threshold for Positive*	Screening Protocol	Sn	Sp	PPV	NPV
Crucitti, 2015 ²⁹	"Un respiro per la vita"	Italy	1500	>4 mm, avg max and min	1 scan	NR	34.0%	4.6%	NR
Henschke, 2004 ²⁴	I-ELCAP	U.S.	2698	≥5 mm, avg max and min	2 annual scans	97.0%	90.0%	Baseline: 20.9% Annual: 11.0%	Baseline: 99.2% Annual: 100%
Henschke, 2013 ³²	I-ELCAP	Multi-national	21,136	≥5 mm, avg max and min ≥6 mm, avg max and min	Annual scans; data from Baseline scans	NR [†] NR [†]	NR [†] NR [†]	3.5% [†] 5.5% [†]	NR [†] NR [†]
Toyoda, 2008 ²⁷	Osaka	Japan	18 070	"Need for further clinical exam"	2 annual scans	88.9%	92.6%	NR	NR
Tsushima, 2008 ²⁶	Azumi & Shinshu	Japan	2486	>3 mm	Annual scans	100.0%	96.9%	9.9%	100.0%
Tammemagi, 2017 ²⁸	PanCan	Canada	2537	≥1 mm	T0: Baseline T1: 1 year T4: 4 years	92.7%	NR	NR	NR
Swensen, 2005 ²⁵	Mayo	U.S.	1520	NCN >4 mm, avg max and min	5 annual scans	95.5%	37.9%	5.8%	99.3%
Menezes, 2010 ²²	Toronto	Canada	3552	≥5 mm, avg max and min	6 annual screenings	87.7%	99.3%	NR	NR
Veronesi, 2008 ³³	COSMOS	Italy	5201	≥5 mm	1 scan	91.0%	99.7%	NR	NR
Mean, range	NA	NA	NA	NA	NA	93.3%, 87.7% to 100%	78.6%, 34.0% to 99.7%	8.7%, 3.5% to 20.9%	99.6%, 99.2% to 100%

* These are the abbreviated criteria for a positive screen. Studies also considered specific features of nodules, for example.

[†] Study reported data to allow calculation of PPV (reporting total positives and true positives) but did not report data to allow calculation of Sn, Sp, or NPV. However, an investigator from the study team submitted public comments on the draft report stating the following: Sn 97.5%, Sp 84.4%, and NPV 100% for the 5-mm threshold for a positive test and Sn 97.5%, Sp 90.3%, and NPV 100% for the 6-mm threshold for a positive test. The study also reported data for higher thresholds (7 mm, 8 mm, and 9 mm) that would allow calculation of PPV.

Abbreviations: avg=average; COSMOS=Continuing Observation of Smoking Subjects; I-ELCAP=International Early Lung Cancer Action Program; KQ=key question; LDCT=low-dose computed tomography; max=maximum; min=minimum; NA=not applicable; NCN=National Cancer Network; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; Sn=sensitivity; Sp=specificity; T=time; U.S.=United States.

Radiation exposure

(Obtained from Jonas et al., 2021 eTable 19).

eTable 19. LDCT Parameters, by Study Type

	kV	mAs	Slice Width (mm)	Overlap*	Multi/Single Detector	Estimated Dose/Study (mSv)
Trials						
COSMOS ^{40,55,288}	140	30	2.5	NR	MDCT	1.0 (men), 1.4 (women)
DANTE ³⁰³	140	40	5	Yes	Both	NR
DLCST ^{30,326}	120	40	3 and 1, 1.5 and 1	Yes	MDCT	NR
ITALUNG ^{39,304}	120-140	20-43	3	NR	Both	NR
LSS ⁴⁷	120-140	60	5	NR	NR	NR
LUSI ²⁹⁴	NR	NR	1	NR	MDCT	1.6-2
MILD ⁴⁹	120	30	0.75	NR	Both	0.7
NELSON ³²³	80-140	40-80	0.7	Yes	MDCT	NR
NLST ⁴⁶	120-140	40-80	1-2.5	Yes	MDCT	1.5
Cohort Studies						
Crucitti et al, 2015 ²⁹	120	35	1	No	MDCT	2.36
Mayo Lung Project ²⁵	120	40	3.75	NR	MDCT	0.65
PLuSS ⁸³	140	40-60	2.5	No	NR	NR
Toronto ⁴⁴	120	40-60	1-1.25	Yes	MDCT	NR
Tsushima et al, 2008 ²⁶	120	25	5	NR	MDCT	NR

* Overlap is an approach to image reconstruction. Helical (spiral) CT allows overlapping image reconstruction at arbitrary positions without additional radiation exposure to patients, theoretically increasing ability to detect smaller nodules (compared with consecutive reconstruction).

Abbreviations: COSMOS=Continuing Observation of Smoking Subjects; CT=computed tomography; DANTE=Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST=Danish Lung Cancer Screening Trial; ITALUNG=Italian Lung Cancer Screening Trial; LDCT=low-dose computed tomography; LSS=Lung Screening Study; LUSI=The German Lung Cancer Screening Intervention Trial; MDCT=multidetector computed tomography; MILD=Multi-centric Italian Lung Detection; NELSON=Nederlands-Leuven Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; NR=not reported; PLuSS=Pittsburgh Lung Screening Study.

False-positive results

(Obtained from Jonas et al., 2021 eTable 20).

eTable 20. Number and Percentage of False-Positive Results After Screening With LDCT

Study Author, Year Clinical Trials	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
DLCST Pedersen, 2009 ³⁰ Saghir 2012 ³⁰⁸	Denmark	NA	Baseline	≥5 mm	T0: 162 T1: 34 T2: 39 T3: 32 T4: 35	T0: 7.9% T1: 1.7% T2: 2.0% T3: 1.6% T4: 1.9%
LSS Gohagan, 2004 ⁴⁷ Gohagan, 2005 ³⁰⁰	U.S.	NA	0, 1	Baseline: >3 mm Year 1: ≥4 mm	T0: 295 T1: 352	T0: 18.6% T1: 25.2%
LUSI Becker, 2015 ¹⁸	Germany	NA	0, 1, 2, 3, 4	≥5 mm Incidence nodules: VDT <600 of known nodule	T0: 428 T1: 77 T2: 65 T3: 95 T4: 82	T0: 21.1% T1: 4.1% T2: 3.5% T3: 5.2% T4: 5.2%
MILD Sverzellati, 2016 ²⁰	Italy	NA	LDCT1 (annual screening): 0, T1, T2, T3, T4, T5, T6 LDCT2 (biennial screening): 0, T1, T2, T3 (T0.1, T1.1, and T2.1 indicate those converted to annual screening)	>60 mm ³ Incidence nodules: volume increase >25%	LDCT1: T0: 160 T1: 31 T2: 48 T3: 25 T4: 18 T5: 5 T6: 11 LDCT2: T0: 152 T0.1: 3 T1: 46 T1.1: 8 T2: 26 T2.1: 9 T3: 33 Total: 271	LDCT1: T0: 13.9% T1: 2.8% T2: 4.4% T3: 2.4% T4: 1.8% T5: 0.6% T6: 2.6% LDCT2: T0: 13.2% T0.1: 2.0% T1: 4.2% T1.1: 4.6% T2: 2.6% T2.1: 5.4% T3: 4.4% Total: 6.1%

eTable 20. Number and percentage of False-Positive Results After Screening With LDCT (continued)

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
NELSON van Klaveren, 2009 ³¹⁰ de Koning 2020 ²¹	Netherlands and Belgium	NA	0, 1, 3, 5.5	Volume >50 mm ³ (>9.8 mm in diameter) Incidence nodules: VDT <400 days	T0: 1500 [†] T1: 516 [†] T2 (males only): 521 T3 (males only): 175	T0: 19.8% [‡] T1: 7.1% [‡] T2 (males only): 9.0% T3 (males only): 3.9%
NLST Aberle, 2011 ⁴⁶ Pinsky, 2014 ³⁶	U.S.	NA	0, 1, 2	≥4 mm ≥65 subgroup: T0: 4796 T1: 4678 T2: 2603 ≥65 subgroup: T0: 2125 T1: 2058 T2: 1232	T0: 6921 T1: 6733 T2: 3843 <65 subgroup: T0: 4796 T1: 4678 T2: 2603 ≥65 subgroup: T0: 2125 T1: 2058 T2: 1232	T0: 26.3% T1: 27.2% T2: 15.9% <65 subgroup: T0: 24.8% T1: 25.7% T2: 14.6% ≥65 subgroup: T0: 30.3% T1: 31.5% T2: 19.5%
UKLS, Field, 2016 ⁷⁴	U.K.	NA	Baseline	>50mm ³	494	26.90%
Cohort Studies						
NA Henschke, 2013 ³²	International	I-ELCAP	Baseline	Based on size cut-off as indicated	5 mm 3277 6 mm 2040 7 mm 1385 8 mm 965 9 mm 727	5 mm 15.5% 6 mm 9.7% 7 mm 6.6% 8 mm 4.6% 9 mm 3.4%
NLST LDCT cohort Yip, 2014 ³⁸	U.S.	NA	Baseline	Based on size cutoff as indicated; assessed how false-positive screens would have been reduced if the NLST had used higher thresholds	5 mm: 3848 6 mm: 2470 7 mm: 1621 8 mm: 1144 9 mm: 858	5 mm: 14.4% 6 mm: 9.2% 7 mm: 6.1% 8 mm: 4.3% 9 mm: 3.2%

eTable 20. Number and percentage of False-Positive Results After Screening With LDCT (continued)

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
NLST LDCT cohort, if using Lung-RADS Pinsky, 2018 ⁴²	U.S.	NA	Baseline, cumulative (includes up to 2 annual screens)	Lung-RADS	NR	Risk decile (based on Tammemagi risk prediction model, 6-year lung cancer risk): Baseline 1: 8.3% 2: 9.8% 3: 11.0% 4: 10.1% 5: 11.6% 6: 11.9% 7: 13.1% 8: 13.8% 9: 14.7% 10: 17.6% Cumulative 1: 12.9% 2: 15.3% 3: 16.2% 4: 15.7% 5: 18.3% 6: 19.2% 7: 21.3% 8: 20.7% 9: 22.3% 10: 25.9%

eTable 20. Number and percentage of False-Positive Results After Screening With LDCT (continued)

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
VHA demonstration Kinsinger, 2017 ⁸⁰	U.S.	NA	Baseline	Not reported clearly in the paper but cited Fleischner guidelines from 2013 state any nodule ≥ 5 mm; also recommended followup of small nodules if they were new or growing or had suspicious features.	All sites: 1226 Site 1: 333 Site 2: 66 Site 3: 178 Site 4: 238 Site 5: 153 Site 6: 61 Site 7: 109 Site 8: 88	All sites: 58% of veterans screened; 28.9% of those eligible for screening Percentages below are of those eligible for screening: Site 1: 38.3% Site 2: 14.0% Site 3: 45.8% Site 4: 30.6% Site 5: 53.1% Site 6: 22.4% Site 7: 12.6% Site 8: 28.0%
NA Menezes, 2010 ²²	Canada	I-ELCAP	0, 1, 2, 3, 4, 5	≥ 5 mm	Baseline: 556 Y1: 249 Y2: 64 Y3: 9 Y4: 5 Y5: 2	Baseline: 16.6% Y1: 9.3% Y2: 9.6% Y3: 5.2% Y4: 13.9% Y5: 28.6%
NA Henschke, 2006 ⁴³	Japan	I-ELCAP	0, 1	≥ 5 mm Incidence nodules: any new nodule	Baseline: 3781 Annual: 1386	Baseline: 12% Annual: 5.0%
NA Henschke, 2004 ²⁴	U.S.	I-ELCAP	0, 1	≥ 5 mm Incidence nodules: any new nodule	I-ELCAP 1: Baseline: 130 Annual: 137 I-ELCAP 2: Baseline: 238 Annual: 117	I-ELCAP 1: Baseline: 9.6% Annual: 12.2% I-ELCAP 2: Baseline: 9.9% Annual: 5.2%
NA Swensen, 2005 ²⁵	U.S.	NA	0, 1, 2, 3, 4	>4 mm (initially followup for any nodule was at least 6 months but later moved out to 12 months)	Baseline: All nodules: 749 >4 mm: 404 Incidence: All nodules: 773 >4 mm: 378	Baseline: All nodules: 49.3% >4 mm: 26.6% Incidence: All nodules: could not calculate >4 mm: could not calculate

eTable 20. Number and percentage of False-Positive Results After Screening With LDCT (continued)

Study Author, Year	Country	I-ELCAP or Lung-RADS	Screening Years	Definition of Positive Nodule by Study Authors*	False-Positive Results*	False-Positive Percentage*
NA Tsushima, 2008 ²⁶	Japan	NA	Baseline	<3 mm solid	175	7.0%
PLuSS Wilson, 2008 ⁸³	U.S.	NA	0,1	0.5-0.9 cm average diameter with spiculated border or >1.0 cm average diameter.	741	20.30%
NA Crucitti, 2015 ²⁹	Italy	NA	0, 1	Noncalcified nodule of any size resulted in another CT after 1 year; NCN ≥5 mm indicated further evaluation	Baseline: 500	Baseline: 33.3%

* Definition of positive for these calculations was the threshold leading to further evaluation (further CT scans, biopsy, etc.), including CT scans at intervals shorter than the next routine screening CT scan. False-positive results calculated using the number of tests leading to further evaluation (further CT scans, biopsy, etc.) and false-positive percentage calculated by dividing the number of false-positive results by the number of people screened with LDCT scan.

† Data reported here based on the systematic review's definition of positive tests. If indeterminant results are reclassified based on 3-month followup LDCT scans, then the number of false-positive results for the first two screening rounds would be 196 and 128, respectively. The protocol for reading nodules included the freedom of radiologists to manually up- or downgrade results. This led to a net decrease of 119 false-positive results in the baseline round.²⁸⁴

‡ Data reported here based on the systematic review's definition of positive tests. If indeterminant results are reclassified based on 3-month followup LDCT scans, then the false-positive percentage (percentage of all persons screened) would be 1.7% and 1.0%, respectively.

Abbreviations: CT=computed tomography; DLCST=Danish Lung Cancer Screening Trial; I-ELCAP=International Early Lung Cancer Action Program; LDCT=low-dose computed tomography; LSS=Lung Screening Study; LUSI=German Lung Cancer Screening Intervention Trial; MILD=Multi-centric Italian Lung Detection; NA=not applicable; NCN=National Cancer Network; NELSON=Nederlands-Leuven Longkanker Screenings Onderzoek; NLST=National Lung Screening Trial; NLST-CT=National Lung Screening Trial-Computed Tomography; PLuSS=Pittsburgh Lung Screening Study; T=time; U.K.=United Kingdom; UKLS= UK Lung cancer Screening; U.S.=United States; VHA=Veterans Health Administration; VDT=volume doubling time.

GRADE SUMMARY OF EVIDENCE

Diagnostic Accuracy*

*Some data obtained from Jonas et al. 2021 systematic review

Question: Should low dose CT scan be used to diagnose lung cancer in apparently healthy asymptomatic adults?

Sensitivity	0.59 to 0.95		Prevalences	0.016%	0.05%	0.1%
Specificity	0.26 to 0.99					

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0.016%	pre-test probability of 0.05%	pre-test probability of 0.1%	
True positives (patients with lung cancer)	13 studies 76856 patients	cross-sectional (cohort type accuracy study)	serious ^a	not serious	serious ^b	serious ^c	none	94 to 152	295 to 475	590 to 950	 Very low
False negatives (patients incorrectly classified as not having lung cancer)								8 to 66	25 to 205	50 to 410	
True negatives (patients without lung cancer)	13 studies 76856 patients	cross-sectional (cohort type accuracy study)	serious ^a	not serious	serious ^b	serious ^c	none	263958 to 991841	263868 to 991504	263736 to 991008	 Very low
False positives (patients incorrectly classified as having lung cancer)								7999 to 735882	7996 to 735632	7992 to 735264	

Explanations

a. Most studies had fair methodological quality

b. Heterogeneous participants included, fair to moderate reliability among radiologists, number of screening rounds, screening intervals, follow-up durations

c. Range of sensitivity and specificity estimates varied widely

Author(s): HHGBayona

Question: Low dose CT scan compared to no screening for lung cancer screening

Setting: Community; Public health

Bibliography:

N ^a of studies	Study design	Certainty assessment					N ^a of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	low dose CT scan	no screening	Relative (95% CI)	Absolute (95% CI)		
Lung cancer-related mortality (follow-up: range 3 years to 12 years)												
8	randomised trials	not serious	not serious	not serious	serious ^b	none	1525/44299 (3.4%)	1678/43577 (3.9%)	RR 0.87 (0.78 to 0.98)	5 fewer per 1,000 (from 8 fewer to 1 fewer)	⊕⊕⊕○	Moderate
All-cause mortality (follow-up: range 3 years to 12.3 years)												
8	randomised trials	not serious	not serious	not serious	serious ^b	none	6940/44299 (15.7%)	6997/43577 (16.1%)	RR 0.99 (0.94 to 1.05)	2 fewer per 1,000 (from 10 fewer to 8 more)	⊕⊕⊕○	Moderate
Diagnosis of early-stage tumors (follow-up: range 3 years to 12.3 years)												
9	randomised trials	serious ^c	not serious	not serious	not serious	none	1205/44635 (2.7%)	758/43862 (1.7%)	RR 2.42 (1.71 to 3.44)	25 more per 1,000 (from 12 more to 42 more)	⊕⊕⊕○	Moderate
Diagnosis of late-stage tumors (follow-up: range 3 years to 12.3 years)												
9	randomised trials	serious	not serious	not serious	not serious	none	666/44684 (1.5%)	873/43957 (2.0%)	RR 0.75 (0.68 to 0.83)	5 fewer per 1,000 (from 6 fewer to 3 fewer)	⊕⊕⊕○	Moderate
Overdiagnosis (follow-up: range 3 years to 12.3 years)												
6	randomised trials	serious	serious ^d	not serious	not serious	none	LDCT 30% (6 to 55%)				⊕⊕○○	Low
False-positive rates												
27	observational studies	serious	serious	not serious	serious	none	Baseline screening: 7.9 to 49.3% Screening rounds: 0.6-28.6%				⊕○○○	Very low
Complications following false-positive results												
9	observational studies	serious	serious	not serious	not serious	none	Needle biopsies: 0.09 to 0.56% Surgical procedures: 0.5 to 1.3% Surgical resections: 0.1 to 0.5% Deaths: 0 to 0.007% Any complication - 0.1% Major - 0.03% Intermediate - 0.05% Minor - 0.01%				⊕○○○	Very low
Psychological harms												
7	observational studies	serious	not serious	not serious	not serious	none	LDCT not associated with worse HRQOL, anxiety, distress. Higher anxiety for true-positives. Distress worse for indeterminate screening test results.				⊕○○○	Very low

CI: confidence interval; RR: risk ratio

Explanations

a. RR for LDCT vs. CXR crossed unity line; results of most trials except for NELSON and NLST trials were very imprecise and did not show statistically significant differences between groups

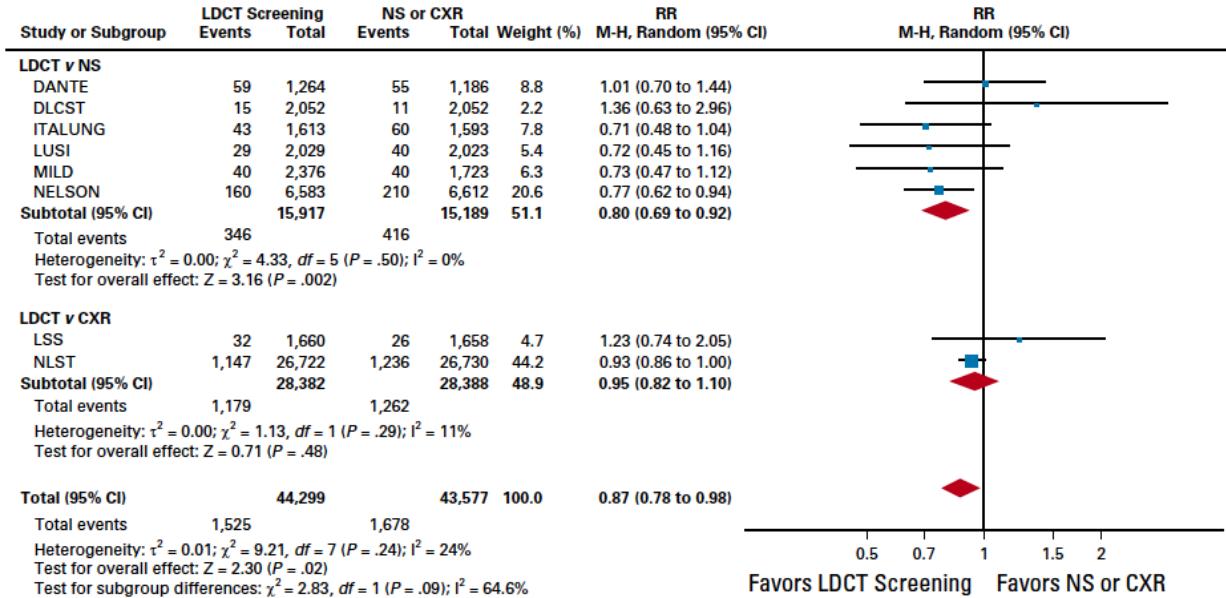
b. Other information size not reported

c. High risk for performance and detection bias

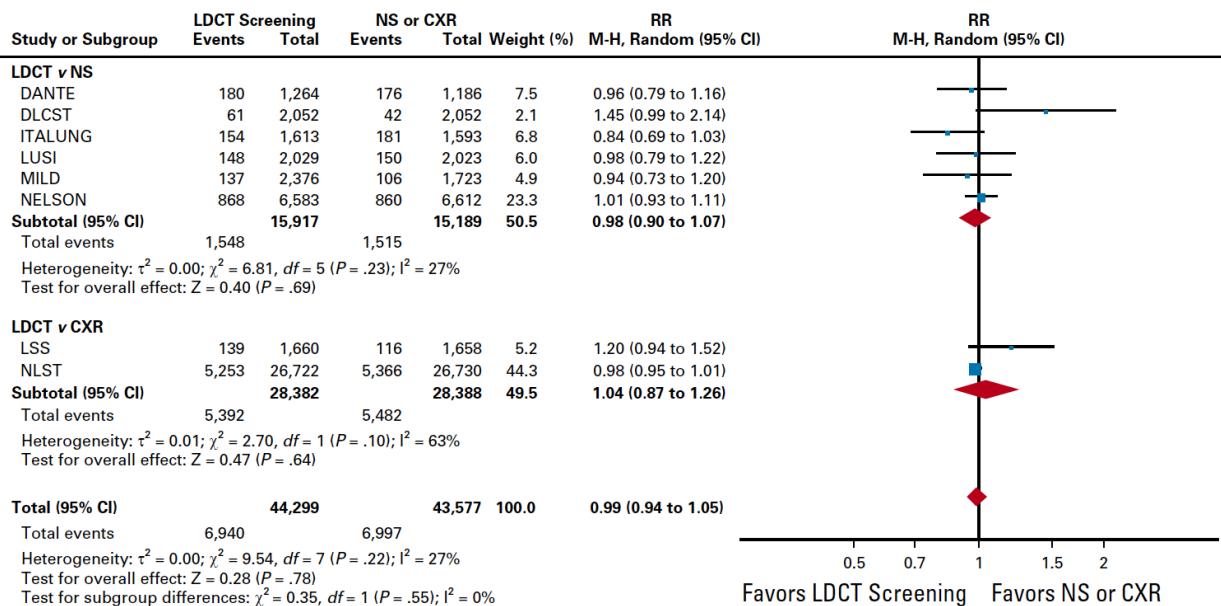
d. Inconsistency across studies and heterogeneity in measurement method

FOREST PLOTS

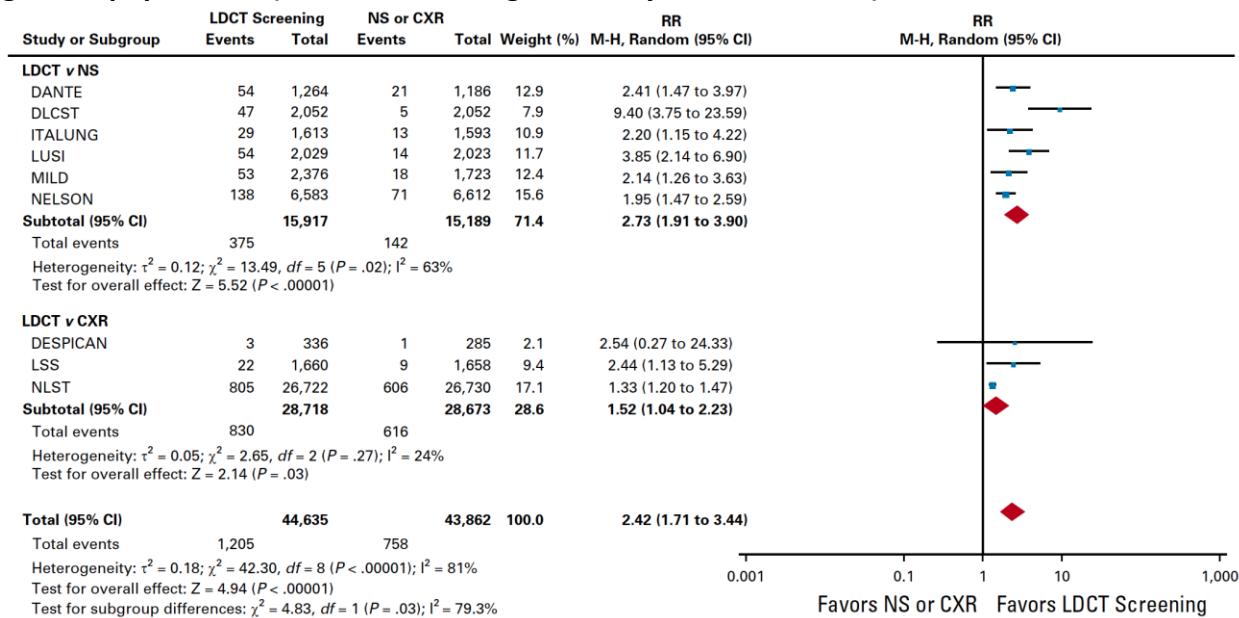
LDCT and NS or CXR screening for reducing lung cancer-related mortality among the general population. (Taken from Passiglia 2021 systematic review)



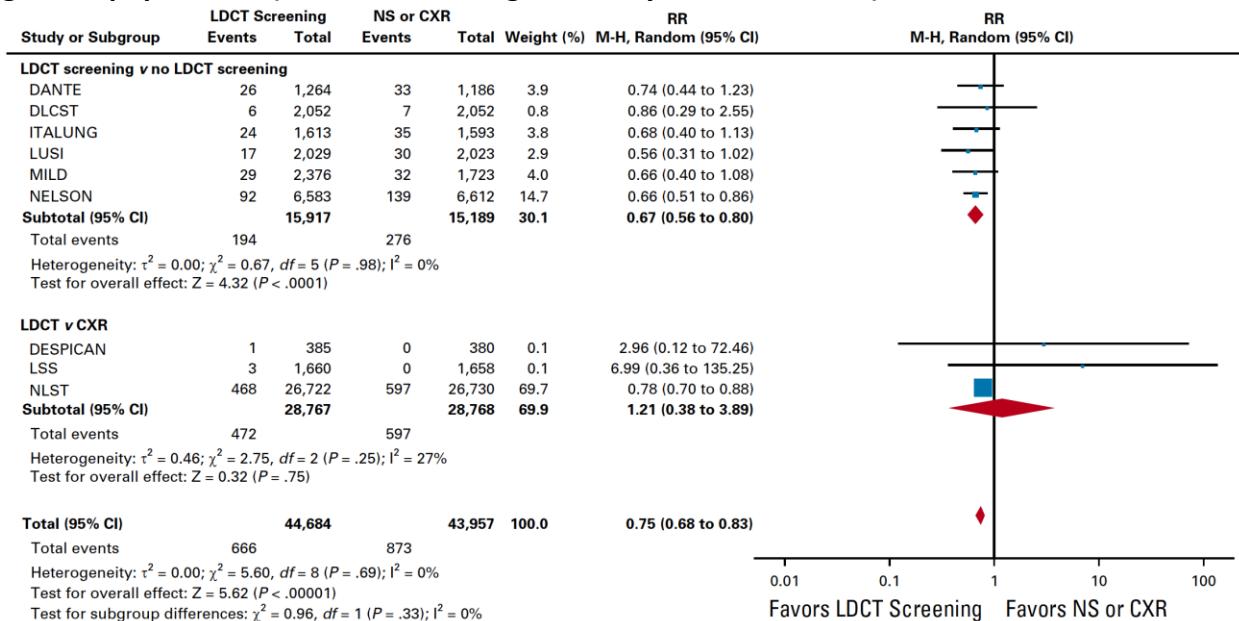
LDCT and NS or CXR screening for reducing all-cause mortality among the general population. All-cause (Taken from Passiglia 2021 systematic review)



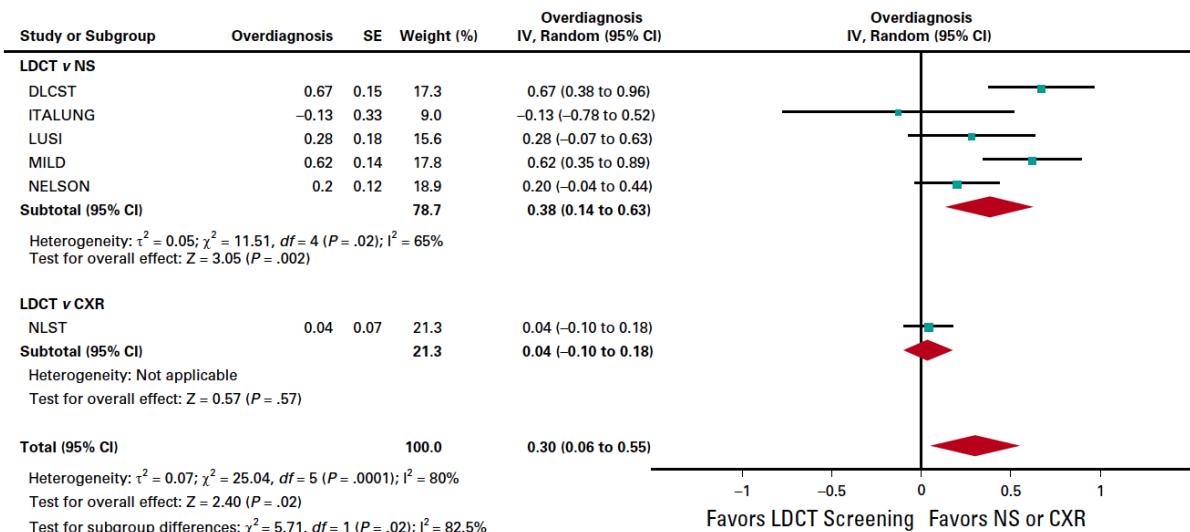
LDCT and NS or CXR screening for increasing detection of early-stage tumors among the general population. (Taken from Passiglia 2021 systematic review)



LDCT and NS or CXR screening for increasing detection of late-stage tumors among the general population. (Taken from Passiglia 2021 systematic review)



Overdiagnosis rate between LDCT vs. NS/CXR screening for the general population. (Taken from Passiglia 2021 systematic review)



10. Screening for Gastric Cancer

SEARCH STRATEGY

Date of search: 10 October 2021

Name of database: Pubmed

#	Query	Results
1	Search: ("gastric cancer"[All Fields] OR (gastric cancer[MeSH Terms]) Filters: in the last 10 years ("gastric cancer"[All Fields] OR "stomach neoplasms"[MeSH Terms]) AND (y_10[Filter]) Translations gastric cancer[MeSH Terms]: "stomach neoplasms"[MeSH Terms]	49,835
2	("upper gi series"[All Fields] OR "upper gastrointestinal series"[All Fields]) AND (y_10[Filter])	255
3	Search: ("systematic review"[All Fields] OR ("clinical practice guidelines"[All Fields]) Filters: in the last 10 years ("systematic review"[All Fields] OR "clinical practice guidelines"[All Fields]) AND (y_10[Filter])	208,671
4	Search: ("gastric cancer"[All Fields] OR "stomach neoplasms"[MeSH Terms]) AND "2011/11/15 00:00":"3000/01/01 05:00"[Date - Publication] AND ((("systematic review"[All Fields] OR "clinical practice guidelines"[All Fields]) AND "2011/11/15 00:00":"3000/01/01 05:00"[Date - Publication]))	1,201
5	("upper gi series"[All Fields] OR "upper gastrointestinal series"[All Fields]) AND "2011/11/15 00:00":"3000/01/01 05:00"[Date - Publication] AND ((("gastric cancer"[All Fields] OR "stomach neoplasms"[MeSH Terms]) AND "2011/11/15 00:00":"3000/01/01 05:00"[Date - Publication]))	36
6	#1 AND #2 AND #3	2

CHARACTERISTICS OF INCLUDED STUDIES

Benefits and Harms of Upper Endoscopy screening

AUTHOR/Year	Country	Study	Population	Intervention/Exposure	Control	Outcome/s
Zhang 2018	China	SRMA	10 studies (4 nested case-control, 6 cohort) N=342,013 ages 35 and above; East Asians	Endoscopic screening	6 Never screened; 1 radiographic screening; 3 expected deaths	Reduction in GC related mortality; Gastric cancer incidence; subgroups based on screening, age, sex, country
Jun 2017	Korea	Nested case control	N=54,418 pairs aged 40 and above of newly diagnosed gastric cancer and cancer-free cohort, followup from 3–8 years	Ever screened with upper endoscopy	Never screened	OR of those screened; GC incidence and MR; GC-specific MR; all cause deaths
Hamashima 2016	Japan	Population based cohort	N=14,274 40–79 y/o healthy indiv free to choose their screening program	Upper endoscopy by duly accredited physicians validated by experienced endoscopists	Radiography	RR of Gastric Cancer incidence, GC related death, All cause MR, All cause MR xc GC;
Hosokawa 2008	Japan	Retrospective cohort	N=11,763 asymptomatic undiagnosed patients 40–75 yrs old	Endoscopic screening	Not screened with X-ray or endoscopy	Rate of death from GC using endoscopic screening based on cancer registry, age specific MR
Chen 2016	China	Case control	N=2,189 Aged 40–69 yrs in 124 villages	Gastric cancer (match 2)	No gastric cancer (match 5)	OR of screened vs not screened; GC related MR
Matsumoto 2013	Japan	Case control	N = 143 Patients who died of GC aged ≥ 40 yrs	Endoscopic screening	Not Screened	OR of GC deaths in participants and non-participants of endoscopic screening
Lee 2010	Korea	cohort	N = 1 503 646 patients; data from cancer registry fr 2002 to 2004	Endoscopy	Upper GI xray	Accuracy of screening; direct cost of tests and biopsy
Leung 2018	Taiwan	Case control	N=20,066 newly diagnosed GC patients	Prior endoscopy at <2 years, 2-5 yrs	Prior endoscopy > 5 years	Hazards ratio of all cause mortality; HR of gastric cancer-specific mortality
Tashiro 2006	Japan	cohort	N =106 246 participants from mass screening program from 2002 - 2004 ages 40 and above	Endoscopy	photofluorography (MSP) and xray (ISX)	detection rate; cost analysis (close examination fee plus screening fee)
Reicken 2002	China	Prospective cohort	N=4,394 Healthy adults 35–64 y/o with gastroscopy with biopsy in 1989, 1994 and 1999	Gastroscopy with biopsy done 3x; in 1994, 3 groups given interventions: 1. Amoxicillin and omeprazole; 2. Vitamin C supplement; 3. Garlic extract supplement	None	Detection of Gastric cancer and severity, date of diagnosis, date and cause of death
Sato 2020	Japan	Retrospective cohort	N=13,120 Healthy adults ≥ 20 y/o on comprehensive health check-up	GI endoscopy	GI xray	Detection rate of upper GI malignancy, PPV, adverse events related to procedure

AUTHOR/Year	Country	Study	Population	Intervention/Exposure	Control	Outcome/s
Choi 2012	Korea	Cohort	N=924,822 (endoscopy) + 1,765,909 (UGIS) Healthy insurance beneficiaries of low to middle income bracket	Endoscopic screening	Upper GI Series	GC diagnosis via linkage with cancer registry. GC detection rate, incidence and interval cancers; Sn, Sp
Hamashima 2013	Japan	Retrospective cohort	N=50,988 40–79 y/o healthy indv free to choose their screening program	Upper endoscopy by duly accredited physicians validated by experienced endoscopists	Radiography	Sn, Sp, age specific GC; (done for both incidence and prevalence screening) confirmed by Cancer registry
Kang 2019	Korea	Retrospective chart review	N=149,792 Medical records of endoscopic procedures	GI endoscopy		Incidence of iatrogenic perforations and perforation-related mortality;

Benefit and Harm for Upper GI series

AUTHOR/Year	Country	Study	Population	Intervention/Exposure	Control	Outcome/s
Hamashima 2013	Japan	Retrospective cohort	N = 50,988 40 - 79 y/o healthy indv free to choose their screening program	Upper endoscopy by duly accredited physicians validated by experienced endoscopists	Radiography	Sn, Sp, age specific GC; (done for both incidence and prevalence screening) confirmed by Cancer registry
Tsubono 2000	Japan	SR	10 studies (3 cohorts, 7 case control); ages >20 yrs	Gastric Photofluorography with image intensifier	Never screened	Accuracy of photofluorography; 5- and 10-year survival rate; mortality rate
Choi 2012	Korea	Cohort	N = 924,822 (endoscopy) + 1,765,909 (UGIS) Healthy insurance beneficiaries of low to middle income bracket	Endoscopic screening	Upper GI Series	GC diagnosis via linkage with cancer registry. GC detection rate, incidence and interval cancers; Sn, Sp
Choi 2014	Korea	Review	9 studies (5 case control, 4 cohort)	UGIS or endoscopy Screened	Never screened	GC- related mortality; all-cause mortality; cost-effectiveness;
Sato 2020	Japan	Retrospective cohort	N = 13 120 Healthy adults ≥ 20 y/o on comprehensive health check-up	GI endoscopy	GI xray	Detection rate of upper GI malignancy, PPV, adverse events related to procedure
Hamashima 2013	Japan	Population based cohort	N = 14,274 40 - 79 y/o healthy indv free to choose their screening program	Upper endoscopy by duly accredited physicians validated by experienced endoscopists	Radiography	RR of Gastric Cancer incidence, GC related death, All cause MR, All cause MR xc GC;

Cost-effectiveness Studies

Author/Year	Country	Study Design	POPULATION	Health Status	Study Arms	OUTCOME
Shah 2020	USA	Markov model CEA	Age: 50 Asian American, incl Filipino,	H. Pylori, atrophic gastritis; dysplasia, local, regional and metastatic GC	<ol style="list-style-type: none"> 1. Time upper endoscopy (EGD) with biopsy q 3 yrs 2. EGD w/ BX at time of colonoscopy with biennial EGD even if histologically normal 3. No endoscopic screening 	<p>Cum Cost : one time (\$3642); biennial (\$25,589) Incremental effectiveness : -0.17 ICER : \$88,190/QALY</p> <p>FilAm males and females have the highest ICERs but still cost effective at predetermined willingness-to-pay threshold</p>
Saumoy 2018	USA	Markov Model, CEA	Age: 50, both M and F Base case: 50 y/o undergoing screening colonoscopy	Pre-neoplasia : Gastritis Neoplasia : local, regional or metastatic, Death	<ol style="list-style-type: none"> 1. No screening 2. EGD with biopsy and surveillance for IM 3. EGD with biopsy q 2 yrs 4. Followup of 30 years 	<p>WTP Threshold : \$100K/QALY Screening with EGD with continued surveillance if indicated NHW : \$122,428 NHB: Asian : \$71,451 Bieenial screening strategy</p> <p>Model was sensitive to IM prevalence, transition of Ca from local to regional, cost of endoscopy, and cost of resection</p>
Canakis 2020	USA	Systematic review	17 studies (8 screening, 4 surveillance, 5 screening and surveillance)	Endoscopy		<p>Endoscopic screening in countries with high GC incidence was cost-effective across all studies. Targeted screening of high risk populations in low-intermediate incidence countries was also cost effective.</p> <p>Most had high appraisal scores with 4 achieving perfect score on Drummond scale</p>

GRADE SUMMARY OF EVIDENCE

Author(s): GS Eubanas, P Patdu, Al Burog

Question: Endoscopy compared to No Endoscopy for screening of healthy population for gastric cancer?

Setting: Healthy adult population

Bibliography:

Nº of studies	Study design	Certainty assessment					Endoscopy	No Endoscopy	Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute (95% CI)		

Gastric Cancer Mortality after Endoscopic Screening (follow-up: range 2 years to 12 years)

10	observational studies	serious ^a	serious ^b	not serious	not serious	none			RR 0.60 (0.49 to 0.73)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕○○ Low	
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GC-related MR after Endoscopic Screening for Never Vs Ever Screened (follow-up: range 2 years to 12 years; assessed with: Mortality rate)

6	observational studies	serious ^a	not serious	not serious	not serious	none			RR 0.582 (0.484 to 0.700)	1 fewer per 1,000 (from 1 fewer to 0 fewer)	⊕⊕⊕○ Moderate	
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Gastric Cancer incidence after Screening (follow-up: range 7 years to 21 years)

2	observational studies	serious ^a	not serious	not serious	serious ^c	none			RR 1.14 (0.93 to 1.40)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	⊕○○○ Very low	
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CI: confidence interval; **RR:** risk ratio

Explanations

a. Self-selection bias and opportunistic screening is common and could not be avoided in these studies as they are mostly population-based. Authors noted that health-conscious people were more likely to undergo endoscopic screening. Presence of lead time bias may also overestimate the effect of endoscopic screening on mortality reduction.

b. There was substantial heterogeneity in the ten studies. One study, Riecken 2002 substantially influenced this heterogeneity and removing it significantly reduced heterogeneity (from $I^2 = 66.7\%$, $p = 0.001$ to 34.8% , $p = 0.14$)

c. There is no significant significance with a wide CI with tendency towards harm rather than benefit. There was no heterogeneity.

Sensitivity and specificity of Upper endoscopy and Upper GI series

Upper endoscopy

Should Upper endoscopy be used to screen for Gastric Cancer in asymptomatic individuals?

Patient or population: asymptomatic individuals

Setting: Community

New test: [comparator test] |Cut-off value:

Reference test: Histopath |Threshold:

Pooled sensitivity:0.70 (95% CI: 0.68 to 0.71)|Pooled specificity:0.96 (95% CI: 0.96 to 0.96)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence2.2% Typically seen in Philippines	Prevalence12.5% Typically seen in Korea	Prevalence5.6% Typically seen in world		
True positives	15 (15 to 16)	87 (85 to 89)	39 (38 to 40)	942843 (2)	⊕⊕○○ Low^a
False negatives	7 (6 to 7)	38 (36 to 40)	17 (16 to 18)		
True negatives	939 (937 to 941)	840 (838 to 842)	906 (904 to 908)	942843 (2)	⊕⊕○○ Low^{a,b}
False positives	39 (37 to 41)	35 (33 to 37)	38 (36 to 40)		

CI: confidence interval

Explanations

a. Characteristics of participants in two screenings were substantially different, ie. age and sex. The researchers were unable to distinguish between symptomatic and asymptomatic participants in the larger study and those with symptoms may more likely to have abnormal results. Also, some participants who continued to be screened chose to change to endoscopy from upper gastroscopy, potentially overestimating the effectiveness of endoscopy. There was insufficient follow-up and sensitivity may have been overestimated.

b.

Upper GI series

Question: Should Radiography be used to screen for gastric cancer in asymptomatic individuals?

Sensitivity	0.61 (95% CI: 0.60 to 0.62)
Specificity	0.90 (95% CI: 0.90 to 0.91)

Prevalences 2.2% 5.6% 12.5%

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 2.2%	pre-test probability of 5.6%	pre-test probability of 12.5%	
True positives (patients with gastric cancer)	13 studies 7482 patients	cohort & case-control type studies	serious ^a	not serious	serious ^b	not serious	strong association	13 (13 to 14)	34 (34 to 35)	76 (75 to 78)	 Moderate
False negatives (patients incorrectly classified as not having gastric cancer)								9 (8 to 9)	22 (21 to 22)	49 (47 to 50)	
True negatives (patients without gastric cancer)	13 studies 3790514 patients	cohort & case-control type studies	serious ^a	not serious	serious ^b	not serious	strong association	880 (882 to 885)	850 (851 to 854)	788 (789 to 792)	 Moderate
False positives (patients incorrectly classified as having gastric cancer)								98 (93 to 96)	94 (90 to 93)	87 (83 to 86)	

Explanations

a. Screening and screen-detected cases are subject to lead time bias, length bias (detect slow-growing but miss fast-growing lesions), and self-selection bias that may over- or underestimate the true benefit of screening.

b. Range of sensitivity is wide across studies despite the large population recruited. Specificity range is narrower.

PERIODIC HEALTH EXAMINATION TASK FORCE ON NEOPLASTIC DISEASES 2021

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CONFLICT OF INTEREST DECLARATION

Panelist (Affiliation)	COI based on Oversight Committee	Remarks
Cairo, Clarito Jr. U. (DOH)	Non-voting panelist	None declared
Cruz, Misael C. (Philippine Radiation Oncology Society; Philippine College of Radiologists)	Manageable B	Medical Director – Central Luzon Integrated Oncology Center
Germar, Maria Julieta V. (Philippine Obstetrical and Gynecological Society)	Manageable A	<u>Non-financial interests</u> <ul style="list-style-type: none"> • Chair; Team Leader/Author – Philippine Society of Cervical Pathology and Coloscopy CPG on Cervical Cancer Screening; Society of Gynecologic Oncologists of the Philippines Clinical Practice Guidelines on Gyn Malignancies • Head – Philippine Obstetrical and Gynecological Society Ad Hoc Committee on Clinical Consensus • Technical Adviser – Cervical Cancer Z Package • Secretary – Society of Gynecologic Oncologists of the Philippines, Philippine Society of Cervical Pathology and Colposcopy
Gomez, Katrina G. (Philippine Society of Public Health Physicians, Inc.)	Acceptable	None declared

Panelist (Affiliation)	COI based on Oversight Committee	Remarks
Miranda, Marcia Feria (Patient representative)	Acceptable	None declared
Nicodemus, Nemencio Jr. A. (Philippine College of Physicians)	Manageable A	Professor UPCM, Regent PCP, President Philippine Thyroid Assn., President PASOO, books on DM, CPGs, Clinical trials
Paje, Ma. Cecilia (Philippine Oncology Nurses Association)	Manageable A	<u>Non-financial interests</u> • Treasurer – Philippine Oncology Nurses Association
So, Jeffrey S. (Philippine Society of Pathologists, Inc.)	Manageable A	<u>Non-financial interests</u> • Board member – Philippine Society of Pathologists, Inc.
Strelbel, Heinrik Martin Jude (Philippine Society of Medical Oncology)	Manageable A	author of original paper – onco clinical trial, research and grants for onco trial, board member HPV
Teh, Catherine S.C. (Philippine College of Surgeons Cancer Commission)	Manageable B	<u>Non-financial interests</u> • President – Philippine Association of HPB Surgeons • Director – Philippine College of Surgeons Cancer Commission <u>Additional information</u> • Received payment / honoraria for speaking publicly on the subject of the CPG
Tuazon, Josefina A. (Health Technology Assessment Council – Department of Health)	Manageable A	<u>Non-financial interests</u> • Board member - Madre de Amor Hospice Foundation