PONTIFÍCIA UNIVERSIDADE CATÓLICA DE MINAS GERAIS
Programa de Pós-graduação em Odontologia

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AVALIAÇÃO DOS PROGRAMAS DE RASTREAMENTO COMO ESTRATÉGIA DE DETECÇÃO PRECOCE DO CÂNCER DE BOCA: uma revisão sistemática

Belo Horizonte
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Dissertação apresentada ao Programa de Pós-graduação em Odontologia da Pontifícia Universidade Católica de Minas Gerais, como requisito parcial para a obtenção do título de Mestre em Odontologia, Área de Concentração: Clínicas Odontológicas - Área Temática: Estomatologia.
Linha de Pesquisa: Sistema estomatognático: desenvolvimento, estrutura, funções e alterações.

Orientadora: Profa. Dra. Giovanna Ribeiro Souto
Coorientadora: Profa. Dra. Vânia Eloisa de Araújo Silva

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2021

FICHA CATALOGRÁFICA
Elaborada pela Biblioteca da Pontifícia Universidade Católica de Minas Gerais

Ribeiro, Marcela Ferreira Abrahão
R484a Avaliação dos programas de rastreamento como estratégia de detecção precoce do câncer de boca: uma revisão sistemática / Marcela Ferreira Abrahão Ribeiro. Belo Horizonte, 2021.
90 f. : il.

Orientadora: Giovanna Ribeiro Souto
Coorientadora: Vânia Eloisa de Araújo Silva
Dissertação (Mestrado) - Pontifícia Universidade Católica de Minas Gerais. Programa de Pós-Graduação em Odontologia

1. Programas de Rastreamento. 2. Detecção Precoce de Câncer. 3. Neoplasias Bucais. 4. Lesões Pré-Cancerosas. 5. Exame físico. 6. Percepção visual. 7. Revisão Sistemática. 8. Abordagem GRADE. I. Souto, Giovanna Ribeiro. II. Silva, Vânia Eloisa de Araújo. III. Pontifícia Universidade Católica de Minas Gerais. Programa de Pós-Graduação em Odontologia. IV. Título.

CDU: 616.31

Ficha catalográfica elaborada por Fabiana Marques de Souza e Silva - CRB 6/2086

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DATA DA APRESENTAÇÃO E DEFESA: 25 de maio de 2021

A dissertação, nesta identificada, foi aprovada pela Banca Examinadora

Profa. Dra. Giovanna Ribeiro Souto
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“Por mais duro que seja, o caminho é esse mesmo. Ninguém cresce sem se esforçar.”

(MARCELO MIRANDA)

AGRADECIMENTOS

Agradeço, primeiramente, a Deus, por ser meu guia nas escolhas e caminhos certos.

Aos meus pais, que sempre estiveram ao meu lado.

Aos familiares e amigos, pelo apoio e incentivo.

Ao Bruno, pelo amor, ajuda e paciência.

À Olivia e à Gabriela, pois nelas eu busco forças para vencer as dificuldades. É o amor materno que me traz o entusiasmo e a coragem para sonhar e realizar sonhos. Possa eu sempre ser motivo de orgulho de vocês!

À Professora Doutora Giovanna, pela proveitosa orientação científica, pelos desafios e estímulos.

À Professora Doutora Vânia, minha coorientadora, que me encorajou a fazer o mestrado e foi fundamental para a minha formação. Sem a contribuição e disponibilidade de vocês, a construção deste trabalho não seria possível.

Aos meus colegas, Maria Inês e Fábio, pelo companheirismo e pelos ensinamentos.

À Coordenação e aos funcionários do Programa de Pós-Graduação em Odontologia da Pontifícia Universidade Católica de Minas Gerais, minha gratidão ao suporte, principalmente, durante a minha gestação.

Aos professores do Curso de Mestrado Acadêmico, pelos conhecimentos compartilhados e aos colegas da turma, pela troca de experiências.

RESUMO

Revisão sistemática sobre a avaliação dos programas de rastreamento como estratégia de detecção precoce do câncer de boca. O objetivo deste estudo foi avaliar se o rastreamento através da inspeção visual é capaz de identificar lesões em estágios iniciais, aumentar a sobrevida e diminuir a incidência e a mortalidade do câncer de boca. Foram incluídos estudos utilizando a inspeção visual para rastreamento do câncer de boca e lesões potencialmente malignas em indivíduos aparentemente saudáveis acima de 18 anos sem diagnóstico prévio da doença. Os bancos de dados MEDLINE/PubMed, Cochrane Library, EMBASE e LILACS, incluindo busca manual e literatura cinzenta foram pesquisados até janeiro de 2021, sem restrições de idioma e data. O risco de viés e a qualidade metodológica foram avaliados de acordo com a ferramenta adequada para cada desenho do estudo. A análise dos resultados foi narrativa. Foram incluídos 17 estudos que incluiu estudos de coorte, acurácia e ensaio clínico randomizado. O tipo de rastreamento realizado foi oportunístico e organizado em uma variedade de ambientes. A idade mínima dos participantes variou entre 18 e 60 anos e em alguns programas apenas as pessoas com hábitos de risco para o câncer de boca foram incluídas. Os rastreadores eram profissionais da saúde, médicos e dentistas. Dois estudos relataram dados sobre taxa de incidência de casos graves e mortalidade, e mostraram redução quando os pacientes eram de risco para a doença e participavam do programa mais de uma vez. Uma limitação desta revisão foi a grande variabilidade observada nas estimativas do efeito do rastreamento entre os estudos, que dificultou realizar comparações. Se o programa de rastreamento for contínuo e capaz de garantir a inclusão de indivíduos de alto risco pode contribuir para uma melhora na sobrevida com uma mudança de estágio e provocar um impacto significativo na incidência e mortalidade da doença. Registro na OSF (Open Science Framebook) com o link osf.io/zg8nr.

Palavras-chave: Câncer de boca. Inspeção visual. Programas de rastreamento. Detecção precoce.

ABSTRACT

Systematic review of the evaluation of screening programs as a strategy for early detection of oral cancer. The aim of the study was to assess whether screening through visual inspection can identify lesions in early stages, increase survival and decrease incidence and mortality from oral cancer. Studies using visual inspection method for screening of oral cancer and potentially malignant lesions in apparently healthy individuals over 18 years old with no previous diagnosis of the disease were included. The MEDLINE/PubMed, Cochrane Library, EMBASE and LILACS databases, including manual search and gray literature, were searched until January 2021. No language and data restrictions. The risk of bias and a methodological quality were obtained according to the appropriate tool for each design of the study. The analysis of the results was narrative. 17 studies of cohort, accuracy and randomized clinical trial of screening programs were included. The type of screening performed was opportunistic and organized in a variety of environments. The minimum age of the participants ranged between 18 and 60 years and in some programs only people with risky habits for oral cancer were included. The screeners were health professionals, physicians and dentists. Two studies reported data on the incidence rate of severe cases and mortality, and showed reduction when patients were at risk for the disease and participated in the program more than once. A limitation of this review was the great variability observed in the marks of the screening effect between studies, which made it difficult to make comparisons. Whether the screening program for continuous and capable of guaranteeing the inclusion of high-risk risk can contribute to an improvement in survival with a change in stage and cause a significant impact on the occurrence and mortality of the disease. Registration at OSF (Open Science Framebook) with the link osf.io/zg8nr.

Keywords: Mouth cancer. Visual inspection. Screening programs. Early detection.

LISTA DE ABREVIATURAS E SIGLAS

CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CCE	carcinomas de células escamosas
GRADE	Grading of Recommendations Assessment, Development and Evaluation
OATD	Open Access Theses and Dissertations
OMS	Orgnaização Mundial de Saúde
OSF	Open Science Framebook
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
VPN	valor preditivo negativo
VPP	valor preditivo positivo

SUMÁRIO

1 INTRODUÇÃO

O câncer de cabeça e pescoço é um problema de saúde global com alta mortalidade e morbidade (KUJAN; SLOAN, 2013). É o sétimo câncer mais comum em todo o mundo, o quinto mais comum em homens e o décimo segundo em mulheres. Quase 50% dos cânceres de cabeça e pescoço surgem na cavidade bucal (WILD; WEIDERPASS; STEWART, 2020). O número de casos novos de câncer de lábio e cavidade bucal no mundo em 2020 foi 377.713, e 177.757 mortes (SUNG *et al*., 2021).

As maiores taxas de incidência padronizada por idade (por 100.000 indivíduos) são observadas em Papua Nova Guiné (20,4), Paquistão (12,2), Bangladesh (9,5), Índia (9,1), Sri Lanka (7,6) e Hungria (7,5). O centro-sul da Ásia comporta um terço das taxas globais de câncer de boca. A Índia, em 2018, foi o país com as taxas mais altas, com 120.000 novos casos, sendo a principal causa a mastigação de betel (WILD; WEIDERPASS; STEWART, 2020). No Brasil, de acordo com os dados do Instituto Nacional do Câncer (INCA) o risco estimado, para cada ano, no triênio 2020-2022 é de 10,69 a cada 100 mil homens e 3,71 para cada 100 mil mulheres, o que corresponde a 11.180 e 4.010 novos casos de câncer da cavidade oral, respectivamente (BRASIL, 2019).

Os cânceres de boca surgem das estruturas anatômicas do trato aerodigestivo superior, principalmente a cavidade oral e as estruturas adjacentes. Já os cânceres de cabeça e pescoço incluem a faringe, as regiões tonsilares, a laringe e os seios paranasais. Mais de 90% desses cânceres têm origem no epitélio de revestimento da mucosa e são denominados carcinomas de células escamosas (CCE). O lábio inferior, a língua e o assoalho bucal são os principais sítios de localização do tumor primário na cavidade oral em mais de 75% dos pacientes com CCE (PERKS *et al*., 2019).

Há uma grande variação geográfica no grau de incidência e localização anatômica do CCE de cabeça e pescoço em todo o mundo. Essa variação é predominantemente atribuída às diferenças nos hábitos de consumo de tabaco e de álcool ou na exposição crônica à radiação solar (VIGNESWARAN; WILLIAMS, 2014).

Uma grande variedade de lesões potencialmente malignas está associada ao desenvolvimento do CCE. As mais comuns são a leucoplasia, a eritroplasia, o líquen plano oral e a fibrose submucosa oral. Estas lesões apresentam variável potencial de transformação maligna. De acordo com a Organização Mundial de Saúde (OMS), as lesões potencialmente malignas são classificadas quanto ao grau de displasia em: leve, moderada, acentuada e carcinoma *in situ* (MONTERO; PATEL, 2015).

No controle do câncer de boca as estratégias de prevenção primária visam eliminar ou reduzir os fatores de risco para a doença. As estratégias de prevenção secundária têm o objetivo de detectar precocemente lesões potencialmente malignas ou câncer em estágios iniciais. E ambas as ações podem impactar na redução da incidência e da mortalidade pela doença (BRASIL, 2014). A prevenção terciária é a ação para limitar o dano e inclui a reabilitação. A prevenção quaternária tem o intuito de proteger os indivíduos de intervenções diagnósticas ou terapêuticas excessivas. Assim, ao aplicar um teste diagnóstico em uma população, é imprescindível conhecer suas propriedades e a capacidade de identificar corretamente os indivíduos doentes e os não doentes (BRASIL, 2010).

Aproximadamente 2/3 das lesões de câncer de boca são identificadas em um estágio avançado, o que requer terapia mais complexa, com aumento da morbidade dos pacientes e do custo do tratamento. A expectativa de que o manejo das lesões potencialmente malignas e CCE em estágio inicial levará ao aumento da sobrevida fazem aumentar os esforços para a detecção precoce (EPSTEIN, 2014).

1.1 Estratégias para detecção precoce

A detecção precoce significa identificar lesões pré-cancerosas ou o câncer quando ele está localizado no órgão de origem, antes de invadir tecidos próximos e órgão distantes. É parte de uma estratégia mais ampla, que inclui o diagnóstico, o tratamento da condição detectada e o acompanhamento. Essas atividades precisam ser integradas em níveis adequados de serviços de saúde (WORLD HEALTH ORGANIZATION, 2002) .

Existem dois tipos de estratégias de detecção precoce: diagnóstico precoce e rastreamento. O diagnóstico precoce são ações destinadas a identificar a doença em estágio inicial a partir de sinais e sintomas clínicos. Já o rastreamento consiste na identificação de lesões pré-cancerosas ou câncer a partir da realização de testes ou exames diagnósticos em populações ou pessoas assintomáticas (BRASIL, 2010).

Para realização do diagnóstico precoce é importante a conscientização do indivíduo sobre as manifestações sugestivas de câncer para buscar o atendimento e conseguir o acesso aos cuidados (WORLD HEALTH ORGANIZATION, 2017). O rastreamento identifica pessoas com maior probabilidade de apresentar a doença e depois é necessário um teste confirmatório em todos os indivíduos positivos para que se possa estabelecer um diagnóstico definitivo (BRASIL, 2010).

O mesmo exame, geralmente a inspeção visual, é utilizado tanto no rastreamento como no diagnóstico precoce, o que difere é o contexto. No rastreamento, toda uma população-alvo é avaliada e a maioria dos indivíduos testados não terá a doença. Enquanto na ação de diagnóstico precoce, o exame é realizado só em pessoas sintomáticas e a chance de detectar a doença é maior (WORLD HEALTH ORGANIZATION, 2017).

Para estabelecer um programa de diagnóstico precoce ou rastreamento deve haver evidências científicas da efetividade da estratégia, levando em consideração a importância da doença na saúde pública, características dos testes de detecção precoce, custo e potenciais danos versus benefícios (WORLD HEALTH ORGANIZATION, 2002, 2017).

1.2 Exame de inspeção visual

O exame clínico bucal é o principal método usado para detectar alterações anormais da mucosa oral. Ele é, geralmente, feito por um cirurgião dentista e consiste em um exame completo da cabeça e do pescoço: avaliação da mucosa bucal por meio de inspeção visual sob luz incandescente ou iluminação halógena, e palpação (EPSTEIN *et al.*, 2012*)*.

A cavidade bucal é facilmente acessível para exame de rotina, e o exame bucal convencional tem a vantagem de ser minimamente invasivo, ter alta validade (sensibilidade e especificidade, no caso de examinadores experientes), ser aplicável no ambiente de cuidados primários e ser rápido (SPEIGHT *et al.*, 2017).

Apesar da inspeção visual ser o método mais comum, existem outros testes que incluem o uso de um 'corante' azul, iluminação com uma luz especial e um autoexame pelo indivíduo (WALSH *et al.*, 2013).

1.3 Tipos de rastreamento

Existe uma distinção entre programas de rastreamento organizado e o oportunístico. O primeiro é sistematizado e realizado por instituições de saúde de abrangência populacional (usualmente Sistemas Nacionais de Saúde). Detém maior controle das ações e informações no tocante ao rastreamento. O oportunístico ocorre quando a pessoa procura o serviço de saúde por algum outro motivo e o profissional de saúde aproveita o momento para rastrear alguma doença ou fator de risco (BRASIL, 2010).

Os programas de triagem podem ser realizados por médicos, dentistas ou outros profissionais da saúde, e ser direcionado a grupos de alto risco ou à população como um todo.

O convite para participar de um programa de rastreamento é um tipo de estratégia organizada (SARTORI; FRAZÃO, 2012).

Tanto o rastreio por convite como o oportunístico apresenta limitações para atingir a parte mais representativa da população. Uma campanha nacional de conscientização e conhecimento para a prevenção do câncer de boca, poderia causar sensibilização na população e aumentar a taxa de rastreamento por convite (MONTEIRO *et al.*, 2015).

Um programa de rastreamento será efetivo se a maioria da população susceptível for rastreada, caso contrário, não haverá redução nos indicadores de morbimortalidade (BRASIL, 2010). A revisão sistemática mais recente da Colaboração Cochrane (BROCKLEHURST *et al*., 2013) que avaliou a efetividade do rastreamento do câncer de boca identificou apenas um ensaio clínico randomizado com alto risco de viés (SANKARANARAYANAN *et al*., 2013). A justificativa para uma nova revisão sistemática é estabelecer se as descobertas a partir da análise de outros indicadores e outros tipos de estudos são consistentes e podem servir como evidências sobre o rastreio do câncer de boca.

2 OBJETIVOS

2.1 Objetivo geral

Avaliar se os programas de rastreamento utilizando a inspeção visual são capazes de identificar lesões em estágios iniciais, diminuir a incidência, aumentar a sobrevida e reduzir a mortalidade do câncer de boca.

2.2 Objetivos específicos

a) sintetizar os resultados dos programas de rastreamento do câncer de boca que utilizaram a inspeção visual como método de triagem;
b) avaliar a capacidade dos programas de rastreamento em detectar lesões em estágios iniciais e reduzir os diagnósticos em estágios avançados;
c) avaliar a capacidade dos programas de rastreamento em aumentar a sobrevida e diminuir a incidência e mortalidade dos pacientes com CCE.

3 MATERIAL E MÉTODOS

3.1 Critérios de elegibilidade

Foram incluídos estudos primários que avaliaram programas de rastreamento e diagnóstico precoce do câncer de boca em indivíduos aparentemente saudáveis acima de 18 anos sem diagnóstico prévio da doença, através de inspeção visual da cavidade bucal. Foram excluídos estudos que abordaram modalidades de triagem diferentes, estudos de prevalência, caso controle, de opiniões, também as revisões sistemáticas, cartas, comentários, resumos de congresso, protocolos, diretrizes e recomendações.

3.2 Fontes de informação e estratégia de busca

Em 17/09/2020 MFAR pesquisou quatro bases de dados eletrônicas: MEDLINE/PubMed, Cochrane Library, EMBASE e LILACS/Bireme. O acesso à literatura cinzenta realizado entre os dias 25 e 27/01/2021 foi feito por busca manual nas edições de 2020 e janeiro 2021 de uma revista de relevância na área (Oral Oncology), na lista de "Referências Bibliográficas" dos estudos incluídos nessa revisão e em revisões sistemáticas semelhantes (Screening for Oral Cancer: A Targeted Evidence Update for the U.S. Preventive Services Task Force; Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults (Review)); e pelas bases de dados que indexam este tipo de literatura: catálogo de teses e dissertações da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) e no Open Access Theses and Dissertations (OATD).

A definição dos termos de busca foi feita considerando o problema e a intervenção da pesquisa. Utilizou-se os descritores MeSH, Emtree, DECs, os sinônimos e palavras relacionadas, que foram combinados empregando os operadores booleanos. A estratégia de busca foi adaptada para cada base de dados (ANEXO A). Não houve restrição de idioma ou ano de publicação.

3.3 Seleção dos estudos

Um gerenciador de referências *Software EndNote*® foi utilizado para agrupar todas as referências bibilográficas exportadas das bases de dados e remover as duplicatas, e outro software RAYYAN (https://rayyan.qcri.org/) foi utilizado na seleção dos estudos.

Dois revisores (MFAR, ACL) independentes avaliaram os títulos e resumos dos 50 primeiros estudos e discutiram as inconstâncias para obter um consenso. E depois avaliaram todos os títulos e resumos dos artigos selecionados. No caso das discordâncias, um terceiro revisor (GRS) foi consultado e tomou a decisão final. Depois esses mesmos dois revisores leram todos os artigos selecionados na íntegra e as discordâncias também resolvidas por um terceiro revisor.

3.4 Coleta de dados e síntese dos resultados

Os dados foram extraídos de textos, figuras, tabelas e/ou gráficos dos estudos incluídos, por dois revisores independentes. A padronização das variáveis decidida por consenso em reunião. A coleta de dados foi realizada numa planilha de extração de dados do excel, especialmente desenvolvida para esta revisão. Foram coletados dados de características gerais dos estudos e resultados dos desfechos avaliados.

As variáveis de características gerais dos estudos incluíram: informações sobre autor, ano e país de publicação, desenho e duração do estudo, características da amostra (tamanho amostral, população alvo, porcentagem de participação masculina) e descrição dos programas de rastreamento (tipo, critérios para classificar uma lesão como sendo positiva, examinadores e padrão de referência para o diagnóstico); foram coletados também os desfechos de interesse encontrados em cada estudo. Os desfechos primários foram incidência, mortalidade, sobrevida e estágio do câncer no momento do diagnóstico, e os secundários: positividade da triagem, adesão ao encaminhamento, acurácia, taxa de detecção.

Os resultados dos desfechos foram: porcentagem de redução da incidência do diagnóstico em estágio avançado, porcentagem de redução da mortalidade, porcentagem de aumento da sobrevida em três, cinco e dez anos, porcentagem de aumento do diagnóstico inicial e redução do diagnóstico avançado, porcentagem de casos positivos na triagem e taxa de detecção de lesões potencialmente malignas e câncer de boca, adesão ao encaminhamento para confirmação do diagnóstico, medidas de acurácia e porcentagem de lesões diagnosticadas pelos estudos

Qualquer medida de acurácia (sensibilidade, especificidade, valor preditivo positivo (VPP) e valor preditivo negativo (VPN)) e tempo de sobrevida (3, 5 e 10 anos) foi elegível para definir os resultados.

A síntese de dados quantitativos (meta-análise) não foi realizada devido à heterogeneidade dos estudos. Portanto, os resultados foram avaliados qualitativamente.

3.6 Risco de viés e qualidade metodológica dos estudos incluídos

Dois revisores avaliaram independentemente a qualidade dos estudos incluídos. Quando ocorreram divergências, elas foram resolvidas por discussão ou por consulta a um terceiro autor da revisão. Três ferramentas distintas foram utilizadas: Ferramenta de Risco de Viés da Cochrane (RoB 2), QUADAS 2 (Quality Assessment of Diagnostic Accuracy Studies) e a escala de Newcastle-Ottawa, dependo do delineamento de cada estudo.

A RoB 2 (ANEXO B) foi a ferramenta utilizada para avaliar o risco de viés do ensaio clínico randomizado. Ela é estruturada em um conjunto fixo de domínios, com foco em diferentes aspectos do desenho, condução e relatórios do estudo. Dentro de cada domínio, uma série de perguntas ('perguntas de sinalização') visa obter informações sobre as características do estudo que são relevantes para o risco de viés. Uma proposta de julgamento sobre o risco de viés decorrente de cada domínio é gerada e pode ser classificada como de risco 'Baixo' ou 'Alto' de parcialidade, ou pode expressar 'Algumas preocupações'

A ferramenta QUADAS - 2 (ANEXO C) foi utilizada para avaliar os estudos de diagnóstico e consiste em quatro domínios principais: seleção de pacientes, teste de índice, padrão de referência e fluxo e tempo. Para ajudar no julgamento do risco de viés perguntas de sinalização são incluídas. A ferramenta foi adaptada para essa revisão (WHITING *et al*., 2011) e uma pergunta de sinalização foi omitida por não se aplicar 'Foi evitado um projeto de controle de caso?' (este desenho de estudo foi excluído dessa revisão).

A escala de Newcastle-Ottawa (ANEXO D) foi utilizada para os estudos de coorte e possui um 'sistema de estrelas' em que um estudo é julgado em três perspectivas amplas: a seleção dos grupos de estudo; a comparabilidade dos grupos; e a verificação da exposição ou do desfecho de interesse. Um estudo pode receber 0 a 9 pontos e foi classificado como de alta qualidade (8–9 pontos), média qualidade (6–7 pontos) e baixa qualidade (<6) (HUANG; OUYANG; REDDING, 2019).

3.7 Avaliação da certeza do corpo de evidências (GRADE)

As considerações do Grading of Recommendations Assessment, Development and Evaluation (GRADE) (limitações metodológicas, inconsistência do efeito, evidência indireta, imprecisão e viés de publicação) foram usadas para avaliar a certeza do corpo de evidências para cada desfecho (GUYATT *et al*., 2011) (ANEXO E). A certeza da evidência foi avaliada como alta, moderada, baixa ou muito baixa. Considerou-se os seguintes critérios para aumentar a certeza da evidência, se apropriado nos estudos observacionais: grande efeito, gradiente dose-resposta e efeito de confusão plausível. Todas as decisões foram justificadas para diminuir ou aumentar a certeza dos estudos usando notas de rodapé.

4 ARTIGO CIENTÍFICO

Evaluation of screening programs as a strategy for early detection of oral cancer: a systematic review

Os resultados e a discussão desta revisão sistemática estão descritos no artigo, que será submetido à revista **Oral Oncology (Qualis A1).**

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Evaluation of screening programs as a strategy for early detection of oral cancer: a systematic review

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ABSTRACT

Systematic review on the evaluation of screening programs as a strategy for early detection of oral cancer. The aim of this study was to assess whether screening through visual inspection is able to identify injuries in early stages, increase the survival and decrease the incidence and mortality of oral cancer. Included are studies using visual inspection to screen for oral cancer and lesions potentially malignant in apparently healthy individuals over 18 years without previous diagnosis of the disease. The MEDLINE/PubMed, Cochrane databases Library, EMBASE and LILACS, including manual search and gray literature were searched through January 2021, with no language and date restrictions. The risk of bias and the methodological quality were evaluated according to the appropriate tool for each study design. The analysis of the results was narrative. Seventeen studies were added that included cohort, accuracy and randomized clinical trial studies. The screening type performed was opportunistic and organized in a variety of environments. The minimum age of participants ranged between 18 and 60 years and in some programs only people with risk habits for oral cancer were included. The screeners were professionals of health, physicians and dentists. Two studies reported data on the incidence rate of severe cases and mortality, and showed a reduction when patients were at risk for the disease and participated in the program more than once. A limitation of this review was the great variability observed in the estimates of the screening effect among the studies, which made comparisons difficult. If the screening program is continuous and able to ensure the inclusion of high-risk individuals, it can contribute to improvement in survival with a change of stage and having a significant impact in the incidence and mortality due to the disease. Registration in the OSF (Open Science Framebook) with the osf.io/zg8nr link.

Keywords: Mouth cancer. Visual inspection. Screening Programs. Early detection.

INTRODUCTION

Lip and oral cavity cancer is the seventeenth most common cancer in everyone [1]. More than 90% originate from the mucosal lining epithelium and are called squamous cell carcinomas (SCC). The lower lip, the tongue and the mouth floor are the main sites of primary tumor location in more than 75% of patients with SCC [2]. The main risk factor is the associated smoking habit or to alcohol consumption and intervention in these risk factors is an important way to prevent the onset of injuries [3].

Approximately 2/3 of injuries are identified at an advanced stage, which requires more complex therapy, with increased patient morbidity and the cost of treatment. The expectation is that the management of potentially malignant lesions and HCC at an early stage could lead to an improvement in the patient's prognosis, which increases efforts for early detection [4]. Strategies for early detection are the early diagnosis and screening. Early diagnosis are actions aimed at identifying early-stage disease from clinical signs and symptoms, while tracking consists of identifying injuries based on testing or diagnostic tests in asymptomatic population or people [5]. Scientific evidence of the effectiveness of these early detection strategies of injuries are still scarce in the literature. Studies evaluating these programs could contribute to the improvement of these strategies. Thus, the purpose of this systematic review is to gather scientific evidence of the capacity of screening programs to detect early-stage SCC lesions, increase survival and reduce patient mortality.

MATERIAL AND METHODS

Eligibility Criteria

Primary studies that evaluated screening programs and early diagnosis of oral cancer in apparently healthy individuals above 18 years old without previous diagnosis of the disease, through visual inspection of the cavity oral. Studies that addressed different screening modalities were excluded, prevalence studies, case-control, opinions, systematic reviews, letters, comments, congress abstracts, protocols, guidelines and recommendations.

Information sources and search strategy

On 09/17/2020 MFAR searched four electronic databases: MEDLINE via PubMed, Cochrane, EMBASE and LILACS/Bireme.

A manual search of gray literature was conducted between 25 and 27/01/2021. The search spanned the following sources: a relevant journal in the field (Oral Oncology), the bibliographic references of the studies included in this review and in similar systematic reviews (Screening for Oral Cancer: A Targeted Evidence Update for the US Preventive Services Task Force; Clinical assessment to screen for detection of oral cavity cancer and potentially malignant disorders in healthy adults (Review)), and databases that index this type of literature (Coordination for the Improvement of Higher Education Personnel (CAPES) and Open Access Theses and Dissertations (OATD)). The definition of the search terms was established considering the problem and the research intervention. We used the descriptors MeSH, Emtree, DECs, the synonyms and related words, which were combined using Boolean operators. The search strategy was adapted for each database.

Selection process

An *EndNote ® Software* reference manager was used to group all bibliographic references exported from the databases and remove duplicates, and another RAYYAN software (https://rayyan.qcri.org/) was used in the selection of studies. Two reviewers (MFAR, ACL) independently assessed the titles and abstracts of the 50 first studies and discussed the inconsistencies to reach a consensus and then evaluated all titles and abstracts of selected articles. In the case of disagreements, a third reviewer (GRS) was consulted and made the final decision. After these same two reviewers read all the articles chosen in full and the disagreements also resolved by a third reviewer.

Data collection process, data items and syntheses methods

Data were extracted from texts, figures, tables and/or graphics of the studies included, by two independent reviewers. The standardization of variables decided by consensus at a meeting and two tables were built: one with the general characteristics and another with the results of the outcomes of interest to the review. Data collection was performed in an excel data

extraction spreadsheet, specially developed for this review. Data were collected on general characteristics of the studies and results of the evaluated outcomes.

The variables of general characteristics of the studies included: information about author, year and country of publication, study design and duration, sample characteristics (sample size, target population, percentage of male participation) and description of screening programs (type, criteria to classify an injury as being positive, types of examiners and reference standard for diagnosis). The outcomes of interest found in each study were also collected. The primary outcomes were incidence, mortality, survival and stage of cancer at the time of diagnosis, and secondary outcomes were positive screening, adherence to referral, accuracy, and detection rate.

The outcome results were: percentage of reduction in the incidence of advanced stage diagnosis, percentage of mortality reduction, percentage of increased survival at three, five and ten years, percentage of increase in initial diagnosis and reduction of advanced diagnosis, percentage of positive cases in the screening and detection rate of potentially malignant lesions and oral cancer, adherence to the referral for confirmation of diagnosis, accuracy measures and percentage of injuries diagnosed by the studies.

Any measure of accuracy (sensitivity, specificity, predictive value positive (PPV) and negative predictive value (NPV)) and survival time (3, 5 and 10 years) was eligible to define the results.

The synthesis of quantitative data (meta-analysis) was not performed due to heterogeneity of studies; therefore, the results were qualitatively evaluated.

Study risk of bias assessment and methodological quality

Two reviewers independently assessed the quality of included studies. When disagreements occurred, they were resolved by discussion or by consulting a third review author. Three separate tools were used: Cochrane Risk of Bias (RoB 2), QUADAS 2 (Quality Assessment of Diagnostic Accuracy Studies), and the Newcastle-Ottawa scale, depending on the design of each study.

RoB 2 was the tool used to assess the risk of bias in the clinical trial randomized. It is structured into a fixed set of domains, focusing on different design, conduct, and reporting aspects of the study. Within each domain, a series of questions ('flag questions') aims to obtain information about the study characteristics that are relevant to the risk of bias. A proposal for

judgment on the risk of bias arising from each domain is generated and can be classified as risk 'Low' or 'High' of bias, or may express 'Some concerns'

The QUADAS - 2 tool was used to assess the diagnostic and consists of four main domains: patient selection, index test, pattern of reference and flow of time. To aid in judgment of risk of bias, signage are included. The tool was adapted for this review [6] and one question flag was omitted because it did not apply 'Was a case control project avoided?'(This study design was excluded from this review).

The Newcastle-Ottawa scale was used for cohort studies and has 'star system' in which a study is judged from three broad perspectives: selection of the study groups; the comparability of groups; and verification of exposure or outcome of interest. A study can receive 0 to 9 points and has been classified as a high quality (8-9 points), medium quality (6-7 points) and low quality (<6) as suggested by Huang *et al.* [7].

Certainty assessment

Considerations for Grading of Recommendations Assessment, Development and Evaluation (GRADE) (risk of bias, inconsistency, indirect evidence, imprecision and publication bias) were used to assess the certainty of the body of evidence for each outcome [8]. The certainty of the evidence was rated as high, moderate, low or very low. The following criteria were considered to increase the certainty of the evidence, if appropriate in observational studies: large effect, dose-response gradient and effect of plausible confusion. All decisions were justified to decrease or increase the certainty of studies using footnotes.

RESULTS

Study selection

The PRISMA flow diagram is shown in Figure 1. The initial search resulted in 2186 articles: 2,082 articles from the electronic search and 104 from the manual search. After the exclusion of duplicates, 1,943 publications from the databases were evaluated by the title and abstract. Of these, 86 articles were selected for full reading, three were excluded for not presenting the full text (attempt to switch or contact with unsuccessful authors) and 13 were considered eligible. Of the 104 publications in the search manual, 4 contemplated the inclusion

criteria. A total of 17 articles were included in this review: 11 observational cohort studies, five accuracy studies, and one randomized clinical trial.

Study characteristics

Table 1 presents the general characteristics of the included studies.

The duration of assessment of patients included in the programs ranged from six months to 20 years of follow-up. The studies included from 309 patients up to 10,167,999 of individuals participating in screening programs, and included individuals aged from 18 to 60 years. Studies that evaluated the general population [9-20], population of individuals with risk factors for mouth cancer (betel smokers and chewers) [21-23] and specific groups of people (Downer *et al.* [24] with company employees and Chang *et al*. [25] with patients from a tertiary referral center).

Screening programs recruited patients in an organized or opportunistic manner. Eight studies were included with recruitment organized by invitation [12,14, 16-19, 22,24], three studies organized with home visits [15,20,21], two studies that included patients opportunistically [13,25] and four studies that included both (organized and opportunistic) [9-11, 23]. The examiners were health professionals (without medical training or dental), dentists and physicians. Confirmation of diagnoses was made by specialists through biopsy and histopathological examination of suspicious lesions.

Risk of bias and methodological quality in studies

The randomized clinical trial [20] presented a high risk in the general classification of bias. Although blinding is not possible, the fact that participants and professionals knowing about the intervention could influence other outcomes. Losses and withdrawals of patients were not clearly described and the lack of data increased the risk of bias. Table 2 with the RoB 2 domains presents the reviewers' judgment and relevant comments.

Data on the QUADAS 2 domains for the accuracy studies are presented in Table 3. Patient selection was classified as having high risk of bias in all studies, none of the samples were random or consecutive and it was not clear if you avoided any inappropriate deletion. And the fact that not all patients of the same program have received the same confirmatory diagnostic test or have been included in the analysis classified the flow of patients as high risk as well. US studies by Warnakulasuriya *et al.* [9] and Mehta *et al.* [21] negative patients in screening did

not take another test to confirm the screening result. But regarding applicability to all domains (patients, index test and reference standard) in all studies had low concerns.

The data for judgment of the eight items of the Newcastle-Ottawa scale of each cohort studies is presented in Table 4. The quality of studies was rated as low in 5 studies [12-14, 17,19], average in 5 studies [11,16,18,23,25] and high in only one study [22], the only one in which the unexposed cohort was removed from its community and the analysis between screened and unscreened groups was performed comparing several factors such as: age, sex, habits and number of participations in the screening.

Results of individual studies

The percentage of suspicious injuries that were detected during the screening was termed screening positivity. Some studies have evaluated the positivity in two moments during the program. During the first evaluation of the screening, screening positivity rates ranged from 0.24% to 18% across the studies.

In seven [12-14, 16,19,20,22] studies, there was more than one evaluation of screening and screening positivity rates varied, in subsequent moments, from 0.55% to 14.8%. Considering the positivity rates of the first assessment, the lowest rate found (0.24%) was observed in the only study whose examiners were specialists in oral mucosal lesions (stomatologists) [13]. Additionally, the studies with the two highest detection rates (18 and 14%) [14,18] were the two studies that used criteria for inclusion of positive patients for less specific lesions such as: any acquired, reactive or infectious neoplastic process of soft tissue and persistent lesion for more than 14 days.

Nine studies [9,12,13,16, 20-23, 25] evaluated patient adherence to referral for histopathological confirmation of diagnoses. On average, only 62.5% of patients attend consultations for the biopsy.

The sensitivity and specificity of visual examination was assessed by eight studies [10,11,15,16,18,21,24,25]. It was observed that the sensitivity ranged from 59% to 98.9% and the specificity from 64% to 99%. The highest number of false positives, which sensitivity was 59% occurred when the screeners were health professionals [21]. However, a study that showed a very high sensitivity rate (94.3%) the examiners were also health professionals [15].

The lesions detected during screening by visual examination were confirmed through histopathological examination or re-examination by a specialist and the rates of detection of potentially malignant lesions and oral cancer were obtained. Detection rates of potentially

malignant lesions ranged from 0.14% to 39.5% of the exams performed. While oral cancer detection rates ranged from 0% to 9.1%.

Five studies [13,17,20,22,23] evaluated the proportion of diagnoses in initial stage or advanced stage. A study showed a 25.4% increase in the number of early stage diagnoses, while there was a 2.4% decrease in the number of diagnoses at an advanced stage, comparing the first with the second phase of the tracking [13]. Another study that evaluated only advanced diagnosis observed a 10.8% decrease in diagnoses in the second phase of the tracking [17]. In three studies [20,22,23], patients were screened for more than one screened group were compared with those not screened by the programs. There was an increase of 12.4% [20] 6.9% [22] and 6.2% [23] in diagnoses in early stage and a 10% decrease [23] in stage diagnosis rates advanced, when the tracked group was compared to the unscreened one.

Only three studies [17,20,23] evaluated the survival of patients in programs tracking. The study that evaluated survival at three years after diagnosis observed a 7.9% increase in survival in the group of screened patients [23]. The studies that evaluated survival at five years after diagnosis found a 8.2% [17] and 12.1% [20] increase in survival in the group of screened patients. Only one study evaluated survival at ten years after diagnosis and found an increase of 17.7% in survival [20].

Only two studies [20,22] evaluated the effects of screening programs in the mortality rates of patients diagnosed with mouth cancer. Sankaranarayanan *et al*. [20] observed a 38% reduction when patients were evaluated three times throughout the screening programs and 79% when they were evaluated four times. When only patients from the risk group were considered, mortality decreased 47% when they were evaluated three times and 81% when they were evaluated four times. In the study by Chuang *et al*. [22] the reduction in mortality was 26%.

A table with the outcome results was constructed (Table 5).

Results of syntheses

The outcomes identified in the largest number of studies were: positivity of screening and detection rate of potentially malignant lesions and oral cancer. The total number of subjects screened by visual inspection in the 16 included studies was 14,988,963. Only one study did not provide the initial number of people screened (they analyzed the mouth cancer registry database and identified the people who had participated in the screenings). The number of people with suspected injuries was 201,520, which corresponds to 0.01% of the population examined. And the number of injuries detected with malignancies was 9,920. As the event fees

were very small and the very large heterogeneity of the studies (> 90%) it was not possible to meta-analysis.

Certainty of Evidence - GRADE

All evaluated outcomes were classified as very low or low quality of evidence by the GRADE approach (Table 6). Heterogeneity of two outcomes (screen positivity and detection rate) lowered the inconsistency in most studies, making it difficult to carry out the meta-analysis or even making it impossible to carry out. For the risk of bias in GRADE, the reviewers based their results on the parameters of the Cochrane Collaboration tool for risk of bias assessment for intervention studies and on Newcastle Ottawa Scale for observational studies. The causes for lowering the risk of bias were lack of clarity in the randomization process and small number of clusters, selection of patients in different ways, low adherence of participants in some studies, and other factors. The downgrade in imprecision was observed in the analysis due to a small number of events and studies. Indirect evidence was serious and very serious in the studies. The profile of the populations was different between the studies, and some population at risk for the disease was not the target population of the programs. It may not be the only cause of the effect in some outcomes.

DISCUSSION

Screening for oral cancer is a non-invasive, simple procedure that uses only inspection of the oral mucosa, for about five minutes, with lighting, gauze, and gloves. While detection of most solid malignancies is in their asymptomatic stages, in other patient locations almost always require more invasive and costly techniques. For early detection of breast cancer there is evidence scientific studies showing that mammography is the screening strategy that presents greater impact on mortality reduction and better balance between risks and benefits [26]. So far there is no evidence to support the use of visual examination as a screening method for oral cancer. The WHO recommendation for mouth cancer is the use of measures to ensure that prevention is an integral part of national cancer control programs [27].

The analysis of the visual examination was performed using screening positivity rates and accuracy of exams. It was observed that there is a wide variation in positivity rates of the exams that may be related to the level of training of the examiners, which ranged from mouth injury specialists to untrained health professionals medical or dental. Another factor that

affected the detection rate in the visual examination was eligibility criteria for positive cases. Studies that found high rates included other non-malignant or potentially malignant lesions as positive cases in screening. It is observed that approximately 5–15% of the general population has abnormalities in the oral mucosa and most of these lesions are benign [28]. So, it is suggested that it is necessary to evaluate many patients for detection of suspicious injuries, due to the low incidence of these injuries, in addition to the calibration of examiners. Recent data suggest that some precancerous lesions may be in a mucosa that appears clinically normal by visual inspection only [28].

The accuracy of case detection is largely related to the calibration of screeners and the criteria used to determine which injuries are counted as positive [16]. The way to measure this accuracy is by calculating the accuracy of the exams. However, low adherence to the diagnostic test can generate rates that do not correspond to reality. In the present study, on average only 62.5% of patients attend the consultation to confirm the diagnosis. As is the case with the program reported by Chang *et al*. [25], which showed high rates of sensitivity (98.9%) and specificity (98.7%), but adherence to referral was also 62.5%. Meanwhile, Chuang *et al*. [22], which showed rates of adherence to specialized consultations of 91.1%, they found that the probability of a positive patient having a potentially malignant lesion was 61% and mouth cancer of 22.7%. Thus, many cases may have gone unconfirmed or discarded due to non-attendance to specialized consultations in studies with low adherence to referral. As a result, the benefits of a screening program may be reduced when the acceptance rate for visual examination is low or few patients attend for the confirmation procedure of the diagnosis. It has been pointed out that the reason for these results is the distance of reference centers and the difficulty of transport due to lack of economic resources of the patients [12], the lack of community awareness of the importance of diagnosis, fear of the diagnosis being positive or fear of pain and discomfort with the exam [9]. These data suggest that oral cancer screening campaigns take place with community awareness campaigns about the importance of early diagnosis for patients' survival.

Oral cancer detection rates in screening programs are a measure that represents only a proportion related to positive cases of mouth câncer and are not valid as a population-based incidence or estimate of prevalence. Oral injuries are restricted to injuries determined in small samples, which does not allow a comprehensive view of the occurrence of these lesions in samples representative of the population [18]. In all the studies evaluated in this review that evaluated the effectiveness of screening programs showed effectiveness in reducing severe cases and increased diagnoses at early stages when programs happened over a subsequent

year. It is known that these results can affect the survival of patients, reducing the mortality and morbidity of cases [22]. Three of these studies that assessed survival, found an increase in survivability in 3, 5 or 10 years. And two studies that assessed mortality also found improvement in indexes. However, it was observed that the mortality rates were better when the studies evaluated patients three to four times in consecutive years, with a reduction of 81% mortality rate when high-risk patients participated in the 4 screening rounds [20].

The prevalence of the disease in a population plays an important role in evaluation of the usefulness of screening [4]. In south-central Asia, oral cancer is among the three most common types of cancer [29]. India has a high-rate incidence of oral cancer, mainly in the male population. The only test the clinical trial included in this review [20] was conducted in this country and showed that screening may be effective in the high-risk population that participates in more screenings. In 2016, the gross incidence rate of oral cancer in Taiwan was 32.46 per 100,000 people, the biggest in the world. And the incidence rate among men was 10.9 times higher than the women. Approximately 86% of Taiwan's oral cancer patients are usual betel nut chewers [30]. Three studies included in this review [22,23,25] were held in Taiwan. Two of them, Chang *et al*. [25] and Chuang *et al.* [22] showed that most of the screened population included in the program were male and while the studies by Chuang *et al.* [22] and Ho *et al*. [23] included only the highest risk population (betel smokers and chewers) for mouth cancer. Therefore, it is observed that screening programs that target high-risk populations can reduce in 21% the diagnosis of lesions at an advanced stage [22] and increase by 20.5% the early-stage diagnoses when the groups were screened more than three times in comparison with unscreened groups [23].

In Brazil, the implementation of actions for the prevention and early detection of mouth cancer was integrated into the flu vaccination campaign, which is defined as a priority for the population aged 60 years and over [19]. Bulgareli *et al*. [31] showed in his study the difficulties in carrying out these actions due to the longer time to take the oral exam in relation to the application of the vaccine, patient refusal, fear of the disease, shame of remove the prosthesis, lack of awareness of the patient regarding the importance of examination and early diagnosis. For Martins *et al*. [19] the linking of the campaigns was an important strategy for attracting this population, since many of them are edentulous people who find visits to the dentist unnecessary and the age group presents the higher incidence rates of oral cancer. The incidence of oral cancer in Brazil in elderly population over 60 years reaches 40% of positive cases [32]. However, three studies included in this review [12,18,19] did not present reduction rate of incidence and mortality, reduction of diagnoses at an advanced stage with increased

early-stage diagnoses and increased survival, which makes it difficult to assess effectiveness of these measures. Furthermore, detection rates were low. It is possible to suggest that these low detection rates may be related to the profile of the population being screened. Although the elderly population is considered at risk for the disease, the evaluation of non-elderly patients with high-risk habits could increase these detection rates of suspicious lesions.

It is important to highlight some limitations of the present study, such as example, the inclusion of only one clinical trial [20]. Although it is the most adequate to assess the effectiveness of screening practice, the study showed high risk of bias. In addition, the cohort that was classified as high quality [22], also has restrictions due to the low repeated screening rate (21%) and the monitoring of selected participants be restricted to short periods of time. Another limitation was the large variability observed in the estimates of the effect of screening between studies, which made comparisons difficult. Only three studies compared the screened with unscreened group [20,22,23], an important analysis to evaluate the benefits and harms of a program. Improving survival and diagnostic stages of screened patients cannot be attributed solely to the screening, advances in medical knowledge and technology can contribute also to improve these rates [17] and no study considered these variables. The follow-up time for a program should be long enough to evaluate mortality and incidence and only two included studies showed follow-up by more than 10 years [17,20].

When health services educate and alert their population about the signs and symptoms of oral cancer, sensitizing the population to seek a professional when noticing the first signs, this strategy is called early diagnosis. And with the informed population, opportunistic screening can be effective in detecting cases [13] but according to Epstein [4] high-risk populations do not present for routine dental and medical evaluation. Monteiro *et al.* [11] showed that more cases were detected in an invited screening compared to an opportunistic screening. But he reports in his study that this could be resolved extending opportunistic screenings to patients seen at all health centers or hospitals, and that the screener could be dentists or other trained health professionals.

It is concluded that screening programs can increase the time of survival, increase diagnoses of early-stage injuries, decrease diagnoses in the advanced stage, especially when the program is constant. The reduction in the incidence of severe cases and mortality was observed with high-risk groups. So, strategies that increase rates of early detection of oral cancer, by including a larger number of high-risk individuals targeted, by campaigns, training of examiners and community sensitization should be considered when planning screening programs.

OTHER INFORMATION

For the preparation of this systematic review, the reference was used Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), composed of 27 guide items [33] and also guide items for the abstract. A protocol has been registered in OSF with the link osf.io/zg8nr. The approval of an ethics committee is not necessary in case of systematic reviews. Did not have funding and no conflict of interest.

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Figure 1: PRISMA flow diagram

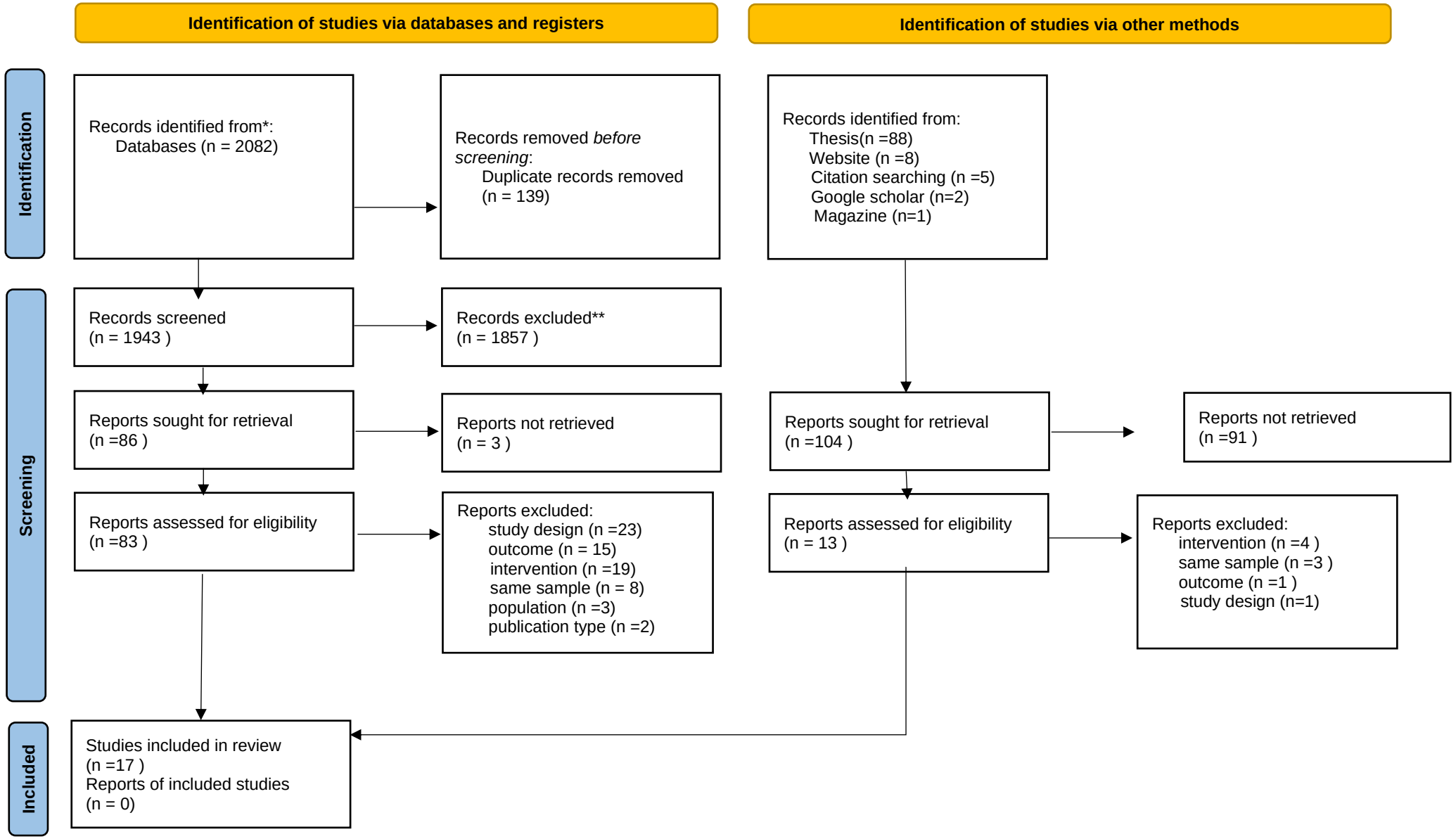

Table 1: General characteristics of the included studies

Author /Year	Country	Type of study	Study duration	N	Age group	Target population	% male	Type of screening	Screeners	Criteria for positive test	Reference standard	Outcome measures
Warnaku Lasuriya et al., 1984	Sri Lanka	accuracy	1 year	area 1: 29.295 area 2: 21.318	area 1: 20+ área 2: NR	general	area 1: 27.7% area 2: NR	area 1:organized (home visits) área 2: opportunistic	area 1: health professionals area 2: dentists e physicians	Stage 1: 'injury for observation' homogeneous leukoplakia, ulcerated leukoplakia Stage 2: 'injury for investigation' nodular leukoplakia, erythroplasia, oral submucosal fibrosis Stage 3: 'probable cancer or already treated': evident oral carcinoma, treated cancer	reexamination by the specialist, biopsy	screening positivity, adherence to referral, accuracy, detection rate
Mehta et al., 1986	Índia	accuracy	1 year	39.331	35+	high risk	NR	organized (home visits)	health professionals	nodular leukoplakia, submucosal	reexamina	screening positivity, adherence to

										fibrosis, ulcers and growths suggestive of oral cancer	tion by the dentist, biopsy	referral, accuracy, detection rate
Downer et al., 1995	UK	accuracy	1 year	309	40+	workers of a company	NR	organized (invitation)	dentists	white, red spot or ulcer of more than 2 weeks duration	reexamination by the specialist, biopsy	screening positivity, accuracy, detection rate
Jullien et al., 1995	UK	accuracy	1 year	2027	40+	general	44	opportunistic and organized (invitation)	dentists	white spot, red spot or an ulcer of more than two weeks	reexamination by the specialist, biopsy	screening positivity, accuracy, detection rate
Santana et al., 1997	Cuba	retrospective cohort	8 years	10167999 (1300000 /year)	NR	general	NR	opportunistic	stomato-logist	pre-malignant or malignant lesions	reexamination by the maxillofacial surgeon histopathological examination	screening positivity, adherence to referral, detection rate, diagnosis stage
Burzynski et al., 1997	US	retrospective cohort	4 years	1151	20+	general	38,49	organized (invitation)	dentistry students	reactive or infectious soft tissue neoplastic process	reexamination by dentists or physicians	screening positivity, detection rate

Mathew et al., 1997	Índia	accuracy	6 months	2069	35-64	general	32,7	organized (home visits)	health professionals	homogeneous, ulcerated, verrucous leukoplakia, erythroplasia, nodular leukoplakia, submucosal fibrosis and oral cancer	reexamination by the physicians	screening positivity, accuracy, detection rate
Nagao et al., 2000	Japan	retrospective cohort	3 years	19.056	male 40+ female 20+	general	31	organized (invitation)	graduate residents in dentistry, hospital dentists and dentists general	mucosal lesion consistent with clinical features of a carcinoma, leukoplakia, erythroplasia or lichen planus	reexamination by the specialist, biopsy	screening positivity, adherence to referral, accuracy, detection rate
Shibahara et al., 2011	Japan	retrospective cohort	20 years	3.429	avarege of 55+	general	24,7	organized (invitation)	specialist	NR	biopsy	screening positivity, detection rate, stage of diagnosis, 5-year survival rate

Chang et al., 2011	Taiwan	retrospective cohort	5 years	13.878	18+	patient of a tertiary reference center	100	opportunistic	Otorhinolaryngologists and dentists	ulcer that has not healed for more than 2 weeks, a persistent white lesion or red, a lesion that bled easily or an irregular superficial lesion within the oral cavity	biopsy	screening positivity, adherence to referral, detection rate, accuracy
Sartori; Frazão, 2012	Brazil	retrospective cohort	3 years	2980	50+	general	34.6	organized (invitation)	dentists	persistent lesion for more than 14 days - regardless of appearance	thorough examinatio, histopathological examination	screening positivity, accuracy, detection rate

Martins et al., 2012	=Brazil	retrospecti ve cohort	9 years	2.858.886 * sum of program years	60+	general	NR	organized (invitation)	primary care dentists	painless ulcers with more than 14 days of evolution; white or blackish lesions with ulcerated areas; reddish lesions with more than 14 days of evolution; fast-growing vegetative lesions (papules, nodules)	reexamina tion by the specialist, biopsy	screening positivity, detection rate
Sankaranaraya nan et al., 2013	India	randomi zed clinical trial	15 years	interventi on group: 96517 control group: 95356 **132814 were screened**	35+	general	NR	organized (home visits)	health professio nals	white lesions, ulcerated or white nodular lesions, verrucous lesions, red lesions, fibrosis oral submucosa, ulcers or growths suggestive of cancer	reexamina tion by the physicians and histopatholo gical examination	screening positivity, adherence to referral, detection rate, diagnostic stage, 5-year and 10-year survival, incidence, mortality

Monteiro et al., 2015	Portugal	prospective cohort	6 months	727	18+	general	38,1%	opportunistic and organized (invitation)	dental students and dentists	presence of potentially malignant disorder or oral cancer	reexamination by the specialist, biopsy	screening positivity, accuracy, detection rate
Voi et al., 2016	Brazil	retrospective cohort	5 years	57.682	40+	general	38%	organized (invitation)	dentist	code 1: reversible lesion, code 2: cancerizable lesion	reexamination by the specialist, biopsy	screening positivity, adherence to referral, detection rate
Chuang et al.,2017	Taiwan	retrospective cohort	6 years	2.334.299	18+	high risk	85,5	organized (invitation)	physicians and dentists	presence of potentially malignant lesions or oral cancer	histopathological examination	screening positivity, adherence to referral, detection rate, values positive predictors, diagnostic stage, incidence, mortality
Ho et al., 2019	Taiwan	retrospective cohort	4 years	NR	30+	high risk	NR	opportunistic and organized	physicians and dentists	NR	reexamination by the specialist, biopsy	adherence to referral,stage diagnostic, survival

Table 2: RoB 2 domains with authors´s judgment

SANKARANARAYANAN et al. 2013		
RoB2 - Domains	Authors´s judgment	Comments
Risk of bias arising from the randomization process	Some concerns	The allocation was chosen at random from six possible combinations of study groups in blocks of four. But no details of allocation concealment were provided.
Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial	Some concerns	Small number of clusters, randomization may become unbalanced. The proportion of smokers was slightly higher in the intervention group.
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention - mortality outcome)	Low risk	The nature of the intervention (visual inspection) does not allow for blinding of participants or health professionals. And for this outcome there is no interference.
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention -others outcomes)	High risk	Although blinding is not possible, the fact that participants and professionals know about the intervention can influence other outcomes.
Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	High risk	Only 59% of screened positive adhered to the referral.
Risk of bias due to missing outcome data	Some concerns	Less than 30% of suspected cases of oral cancer received a biopsy.
Risk of bias in measurement of the outcome	Some concerns	It is unclear whether dentists and physicians were trained and used standardized criteria to confirm positive screening.
Risk of bias in selection of the reported result	Low risk	The presented result seems to be in agreement with the analyzed data.
Overall risk of bias	High risk	

Table 3: QUADAS 2 domains with authors´s judgment

Studies	RISK OF BIAS				CONCERNS REGARDING APPLICABILITY		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Warnakulasuriya et al., 1984	☹	☺	?	☹	☺	☺	☺
Mehta et al., 1986	☹	☺	?	☹	☺	☺	☺
Downer et al., 1995	☹	☺	☺	☹	☺	☺	☺
Jullien et al., 1995	☹	☺	☺	☹	☺	☺	☺
Mathew et al., 1997	☹	☺	☹	☹	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear

Table 4: Newcastle-Ottawa Scale with authors´s judgment

Newcastle- Ottawa	**SELECTION**				**COMPARABILITY**	**OUTCOME**			**QUALITY**
Author/ Year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	**ASSESSMENT**
Santana et al., 1997	*		*	*		*	*		low
Burzynski et al., 1997			*	*		*	*		low
Nagao et al., 2000	*		*	*	**	*	*		medium
Shibahara et al., 2011			*	*		*	*		low
Chang et al., 2011			*	*	**	*	*	*	medium
Sartori; Frazão, 2012	*		*	*		*	*	*	medium
Martins et al., 2012	*		*	*		*	*		low
Monteiro et al., 2015			*	*	**	*	*	*	medium
Voi et al., 2016			*	*	*	*	*		low
Chuang et al., 2017	*	*	*	*	**	*	*		high
Ho et al., 2019			*	*	**	*	*	*	medium

Table 5: Outcomes of interest of the review

Author/ Year	Incidence	Mortality	Survival 3 years▪ 5 years▪▪ 10 years▪▪▪	Diagnosis early stage [1] advanced stage [2]	Screening positivity	Adherence to referral	Accuracy	Detection rate of oral potentially malignant disorders ° and oral cancer*
Warnakulasuriya et al., 1984	NR	NR	NR	NR	area 1: 4,2% area 2: 0.6%	50,3%	Sensitivity 89%	area 1: 1,15 ° 0,01%* area 2: 0,14° 0,04% *
Mehta et al., 1986	NR	NR	NR	NR	1,3%	72%	Sensitivity 59% Specificity 98% PPV 31%	0,43% ° 0,06%*
Downer et al., 1995	NR	NR	NR	NR	4,5%	NR	Sensitivity 71% (95% CI 0.46-0.96) Specificity 99% (95% CI 0.98-1.00) PPV 86%	5,5% ° 0%*
Jullien et al., 1995	NR	NR	NR	NR	3%	NR	Sensitivity 74% (95 % CI 0,62-0,86) Specificity 99% (95 % CI 0,98-0,99) PPV 67% NPV 99%	2,5% ° 0,15%*
Santana et al., 1997	NR	NR	NR	1982:22,8%[1] 19,5%[2] 1988:48,2%[1] 17,1%[2]	1983-1988: 0.24% 1989-1990: 0.55%	1983-1988:24.35% 1989-1990: 27.1%	NR	1983-1988: 39,5%° 8,2%* 1989-1990: 38,3%° 9,1%*
Burzynski et al., 1997	NR	NR	NR	NR	1992: 14.55% 1995: 14.8%	NR	NR	1992: 3,36% ° 0%* 1995: 0,6% ° 0%*

Mathew et al., 1997	NR	NR	NR	NR	11,2%	NR	Sensitivity 94.3% (95% CI 0,90-0,97) Specificity 98.3% (95% CI 0,97-0,99) PPV 86,6% NPV 99,3%	10,2% ° 0,04%*
Nagao et al., 2000	NR	NR	NR	NR	1996: 5,4% 1998: 2,8%	68,5%	Sensitivity 92% Specificity 64% PPV 78%	O,4 % ° 0,01%*
Shibahara et al., 2011	NR	NR	1989 a 1998: 78,1%▪▪ 1999 a 2008: 86,3%▪▪	1989 a 1998: 36,2%[2] 1999 a 2008: 25,4%[2]	4,93%	NR	NR	0,84% ° 0,09%*
Chang et al., 2011	NR	NR	NR	NR	5,2%	62,5%	Sensitivity 98,9% Specificity 98,7% PPV 62,1% NPV 99,9%	0,09% ° 2,03% *
Sartori; Frazão, 2012	NR	NR	NR	NR	18%	NR	Sensitivity 91.7% (95% CI 85.3–95.6) Specificity 85.4% (95% CI 84.1–86.7) PPV 22.7% (95% CI 19.3–26.5) NPV 99.5% (95% CI 99.2-99.8)	1,68% ° 0,27% *
Martins et al., 2012	NR	NR	NR	NR	2001: 7,8% 2009:4,5%	NR	NR	2005: 0,02% * 2009: 0,01% *
Sankaranarayanan et al., 2013	21% reduction in advanced stage, 38% in high risk who had 4 exams	general: 38% reduction 3 rounds and 79% 4 rounds, high risk: 47% 3 rounds and 81% 4 rounds	control group: 43,4%▪▪ 30,6%▪▪▪ intervention group: 55,5%▪▪ 48,3%▪▪▪	control group: 27 %[1] intervention group: 39,4%[1]	1a: 7,3% 2a:2,6% 3a:2,1% 4a: 2,2%	59%	NR	1a 2,83% * 2a 1,19% * 3a 1,16% * 4a 0,39% * control and intervention group: 0,002%*

Monteiro et al., 2015	NR	NR	NR	NR	3,4%	NR	Sensitivity 96% Specificity 98% PPV 96% NPV 98%	3,03%° 0,27%*
Voi et al., 2016	NR	NR	NR	NR	2010: 1,72% 2014: 1,77%	55,6%	NR	2010: 10,8%° 2,33%* 2014: 9,74%° 2,6% *
Chuang et al., 2017	21% reduction in advanced stage and 17% overall	26% reduction	NR	not screened group: 39,6%[1] screened group: 46,5%[1]	1a: 0,77% Subseq: 0,97%	91,1%	PPV PMD: 61% OC: 22,7%	1a: 4,7% ° 1,8%* Subseq: 6,3% ° 1,3%*
Ho et al., 2019	NR	NR	not screened: 63,5%▪ screened: 71,4%▪	not screened: 27,8%[1] 44,5%[2] screened: 34% [1] 34,5%[2] + 3 screening: 48,3%[1]	NR	80%	NR	NR

Table 6: Assessment of the certainty of evidence (GRADE)

Certainty assessment								
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty	Importance
Mortality								
2	1 randomised trial, 1 observational study	serious limitations [1]	not serious	serious [7]	not serious	none	low	Screening must be able to significantly reduce mortality from oral cancer
Incidence								
2	1 randomised trial, 1 observational study	serious limitations [1]	not serious	serious [7]	not serious	none	low	The number of advanced-stage cancer cases should be lower in a population after adopting early detection strategies
Survival								
3	1 randomised trial, 2 observational study	serious limitations [1]	not serious	serious [8]	not serious	none	very low	Discovery in early stages of cancer increases survival
Diagnosis stage								
5	1 randomised trial, 4 observational study	serious limitations [1]	not serious	serious [8]	not serious	none	very low	Early diagnosis increases the chance of cure

Screening positivity								
16	1 randomised trial, 5 accuracy, 10 observational study	very serious limitations [2]	very serious [6]	very serious [9]	serious [12]	none	very low	The test used should identify individuals probably to have cancer.
Adherence to referral								
9	1 randomised trial, 2 accuracy, 6 observational study	serious limitations [3]	not serious	very serious [10]	not serious	none	very low	Poor referral compliance can reduce the benefits of finding cases and treating them early
Accuracy								
10	5 accuracy, 5 observational study	serious limitations [4]	not serious	serious [11]	serious [13]	none	very low	The test used must have high validity to be effective
Detection rate								
16	1 randomised trial, 5 accuracy, 10 observational study	serious limitations [5]	very serious [6]	very serious [9]	serious [12]	none	very low	By screening, the goal is to detect a greater number of malignant neoplasms at an early stage

Subitle: [1] randomization process was not clear in the clinical trial; [2] very different ways in which people were selected to participate; [3] 7/9 had a lower adhesion than 80%; [4] 3/8 performed the calculation of specificity per sample**;** [5] in only 2 the blinding was evident (they did not know the screening result); [6] heterogeneous studies, but with the same effect directions; [7] low-risk individuals with no habits constituted 56% of eligible subjects in the clinical trial; [8] cannot say that only screening causes the reduction; [9] severity of populations are different (general, high risk, hospital, work); [10] evaluated outcome is not of primary interest for decision; [11] 2/ 10 the comparator was not biopsy; [12] small number of events; [13] 4/10 had sensitivity less than 90%

5 CONSIDERAÇÕES FINAIS

Os resultados sugerem que quando a população rastreada está inserida em um programa contínuo e participa de mais de uma triagem periódica (anual ou bienal) ocorre uma identificação de lesões em estágios iniciais, diminuição de casos avançados, aumento da sobrevida e diminuição da mortalidade do câncer de boca. Os dados podem ser melhores quando a população de alto risco está totalmente incluída. Para melhoria dos resultados alcançados com esses programas, monitoramento das ações deve ser constante, principalmente em países com alta incidência do câncer de boca, tornando a estratégia de detecção precoce mais efetiva.

Sendo assim, são fatores que devem ser considerados no planejamento de um programa nacional de controle do câncer de boca: a frequência da triagem, a idade mínima dos indivíduos incluídos na triagem, estratégias efetivas de encaminhamento que aumentem a adesão dos pacientes às consultas de confirmação do diagnóstico, incluindo campanhas de sensibilização da comunidade da importância do diagnóstico inicial. Além de uma organização dos serviços que possibilite o envio de convites para a triagem inicial e a convocação dos indivíduos para repetir a triagem em anos posteriores; seguir aqueles com anormalidades identificadas; monitorar e avaliar o programa.

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ANEXO A - Estratégia de busca em bases de dados eletrônicas

Base de dados	Estratégia de busca	Resultados
PUBMED	(((((((((Mouth Neoplasm[MeSH Terms]) OR (Mouth Neoplasm[Text Word])) OR (Oral Neoplasms[Text Word])) OR (Mouth Cancer[Text Word])) OR (Oral Cancer[Text Word])) OR (Squamous Cell Carcinoma of Head and Neck[MeSH Terms])) OR (Squamous Cell Carcinoma of Head[Text Word] AND Neck[Text Word])) OR (Oral Squamous Cell Carcinoma[Text Word])) OR (Oral Potentially Malignant Disorders[Text Word])) AND ((((((((((Mass Screening[MeSH Terms]) OR (Mass Screening[Text Word])) OR (Diagnostic Screening Programs[MeSH Terms])) OR (Diagnostic Screening Programs[Text Word])) OR (Conventional Oral Examination[Text Word])) OR (Visual Inspection[Text Word])) OR (Visual Examination[Text Word])) OR (Visual Screen[Text Word])) OR (Screening Program[Text Word])) OR (Cancer Screening[Text Word]))	884
COCRHANE		
	#1 MeSH descriptor: [Mouth Neoplasms] explode all trees	
	#2 (Mouth Neoplasm) (Word variations have been searched)	
	#3 (Oral Neoplasms) (Word variations have been searched)	
	#4 (Mouth Cancer) (Word variations have been searched)	
	#5 MeSH descriptor: [Squamous Cell Carcinoma of Head and Neck] explode all trees	
	#6 (Squamous Cell Carcinoma of Head and Neck) (Word variations have been searched)	994
	#7 (Oral Squamous Cell Carcinoma) (Word variations have been searched)	
	#8 (Oral Potentially Malignant Disorders) (Word variations have been searched)	
	#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	
	#10 MeSH descriptor: [Mass Screening] explode all trees	
	#11 (Mass Screening) (Word variations have been searched)	
	#12 MeSH descriptor: [Diagnostic Screening Programs] explode all trees	
	#13 (Diagnostic Screening Programs) (Word variations have been searched)	
	#14 (Conventional Oral Examination) (Word variations have been searched)	
	#15 (Visual Inspection) (Word variations have been searched)	
	#16 (Visual Examination) (Word variations have been searched)	

	#17 (Visual Screen) (Word variations have been searched) #18 (Screening Program) (Word variations have been searched) #19 (Cancer Screening) (Word variations have been searched) #20 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 #21 #9 AND #20	
EMBASE	(('mouth tumor' OR 'mouth cancer' OR 'oral potentially malignant disorder') AND ('mass screening' OR 'visual inspection' OR 'visual examination' OR 'cancer screening')) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	192
LILACS	tw:((tw:(mouth neoplasms OR (squamous cell carcinoma of head AND neck) OR neoplasias bucais)) AND (tw:(mass screening OR diagnostic screening programs OR (programas de rastreamento)))) AND (db:("LILACS"))	12

ANEXO B - Domínios para avaliar o risco de viés segundo o sistema RoB2

Domain 1a: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1a.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1a.2 Was the allocation sequence concealed until clusters were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1a.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 1b: Risk of bias arising from the timing of identification or recruitment of participants in a cluster-randomized trial

Signalling questions	Comments	Response options
1b.1 Were all the individual participants identified and recruited (if appropriate) before randomization of clusters?		Y/PY/PN/N/NI
1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention assigned to the cluster?		NA/Y/PY/PN/N/NI
1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between intervention groups?		Y/PY/PN/N/NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the timing of identification and recruitment of participants?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1a Were participants aware that they were in a trial?		Y / PY / PN / N / NI
2.1b. If Y/PY/NI to 2.1a: Were participants aware of their assigned intervention during the trial?		NA / Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias		NA / Favours experimental / Favours

due to deviations from intended interventions?		comparator / Towards null /Away from null / Unpredictable

Domain 3: Risk of bias due to missing outcome data

Signalling questions	Comments	Response options
3.1a Were data for this outcome available for all clusters that recruited participants?		Y / PY / PN / N / NI
3.1b Were data for this outcome available for all, or nearly all, participants within clusters?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1a or 3.1b: Is there evidence that the result was not biased by missing data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3a If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware that a trial was taking place?		NA / Y / PY / PN / N / NI
4.3b If Y/PY/NI to 4.3a: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3b: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**Comments**	**Response options** Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

ANEXO C - Domínios para avaliar o risco de viés segundo o sistema QUADAS 2

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used,	Were the reference standard	Did all patients receive a reference standard?

	Did the study avoid inappropriate exclusions?	was it pre-specified?	results interpreted without knowledge of the results of the index test?	Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

ANEXO D - Domínios para avaliar a qualidade metodológica segundo o sistema Newcastle-Ottawa Scale (NOS)

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ⁻

b) somewhat representative of the average _____ in the community ⁻

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ⁻

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) ⁻

b) structured interview ⁻

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ⁻

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) ⁻

b) study controls for any additional factor ¯ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment ¯

b) record linkage ¯

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) ¯

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ¯

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ¯

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

ANEXO E - Domínios para avaliar a certeza da evidência segundo o sistema GRADE

Domínio	Descrição	Pontuação
Certeza da evidência		
Risco de viés	• Ausência de sigilo da alocação; • Ausência de mascaramento (cegamento); • Seguimento incompleto; • Relato seletivo dos desfechos; • Seleção e inclusão inadequada de participantes; • Falhas para controlar adequadamente os fatores de confusão.	Se houver limitações graves reduzir 1 nível, se for muito grave reduzir 2 níveis
Inconsistência	• Diferenças elevadas nas estimativas dos efeitos (ex.: risco relativo) dos estudos individuais; • Sobreposição dos intervalos de confiança; • Inconsistência (I2) e teste de inconsistência (I2) e do teste de heterogeneidade [TG1].	Se a inconsitência for grave reduzir 1 nível, se for muito grave reduzir 2 níveis
Evidência indireta	• quando a questão da pesquisa não é respondida diretamente pelos estudos disponíveis seja por diferenças na população, nas intervenções, comparações ou desfechos.	Se a evidência indireta for grave reduzir 1 nível, se for muito grave reduzir 2 níveis
Imprecisão	• amplitude do intervalo de confiança referente ao efeito absoluto < 95%; • pequeno número de eventos.	Se a imprecisão for grave reduzir 1 nível, se for muito grave reduzir 2 níveis
Viés de publicação	• estratégia de busca pouco abrangente; • um valor estatisticamente significativo no teste de Egger e assimetria identificada visualmente no gráfico em funil; • estudos que apresentem conflitos de interesse.	Se houver alta probabilidade reduzir em 1 nível

ANEXO F - PRISMA 2020 check list

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each	

Section and Topic	Item #	Checklist item	Location where item is reported
assessment		study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision	

Section and Topic	Item #	Checklist item	Location where item is reported
		(e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included	

Section and Topic	Item #	Checklist item	Location where item is reported
materials		studies; data used for all analyses; analytic code; any other materials used in the review.	

ANEXO G - PRISMA 2020 abstract check list

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	
Synthesis of results	6	Specify the methods used to present and synthesise results.	
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	
Interpretation	10	Provide a general interpretation of the results and important implications.	

Section and Topic	Item #	Checklist item	Reported (Yes/No)
OTHER			
Funding	11	Specify the primary source of funding for the review.	
Registration	12	Provide the register name and registration number.	