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QUIMIOPREVENCIÓN, INMUNOTERAPIA Y GUIAS DE PRÁCTICA CLÍNICA EN CÁNCER DE PULMÓN

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Tesis doctoral

QUIMIOPREVENCIÓN, INMUNOTERAPIA Y GUIAS DE PRÁCTICA CLÍNICA EN CÁNCER DE PULMÓN

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"Si he visto más lejos, ha sido al pararme sobre los hombros de gigantes que me han guiado"

Isaac Newton

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BREVE PRESENTACIÓN PERSONAL

Soy Marcela Cortés, de nacionalidad chilena. De profesión Químico Farmacéutico y Magíster en Epidemiología Clínica. Desde el año 2002 trabajo como académica de pre y post grado en la facultad de Medicina de la Universidad Católica de la Santísima Concepción, y como epidemióloga clínica a cargo del Comité Ético Científico del Servicio de Salud de Talcahuano, VIII región de Chile.

Desde hace más de 20 años mi camino profesional se ha desarrollado en los ámbitos de la investigación clínica y la Medicina Basada en Evidencia, con múltiples actividades en distintas instituciones y países tales como: Ministerio de Salud, Organización Panamericana de la Salud (OMS/OPS), Unión Europea en FP7, Colaboración Cochrane y otras. Pero sin duda la más importante, fue el haberme desarrollado en el Centro Cochrane Iberoamericano. Con el generoso espíritu de colaboración de todos sus integrantes, en el curso de estos años, he participado en varias actividades de formación, docencia e investigación.

La primera revisión sistemática Cochrane en la que participé, fue publicada en el año 2008, marcando el inicio en este camino. Un ciclo que espero culminar, con la presentación de esta tesis doctoral.

CONFLICTOS DE INTERÉS

La autora de esta tesis declara no tener ningún conflicto de interés respecto al contenido del documento o en cada una de sus publicaciones.

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RESUMEN

Introducción:

El cáncer de pulmón es el cáncer más común en el mundo y principal causa de muerte por cáncer. Es una patología compleja y heterogénea que involucra tantos factores genéticos, ambientales, inmunológicos, microbiológicos y la respuesta individual de los pacientes. Así el diagnóstico y el tratamiento, plantean muchos desafíos para la salud pública y la práctica clínica.

Objetivos:

El objetivo general de esta tesis doctoral es determinar cuál es la evidencia disponible en el ámbito de la Quimioprevención, Inmunoterapia y la calidad de las recomendaciones terapéuticas en el cáncer de pulmón.

Métodos:

Se realizaron 3 estudios correspondientes a dos revisiones sistemáticas y una evaluación de la calidad de las guías de práctica clínica. Los tres estudios de esta tesis se centraron en el cáncer de pulmón. (Estudio 1: Determinar la evidencia en el ámbito de la Quimioprevención, con la revisión sistemática de fármacos para la prevención del cáncer de pulmón en personas sanas). (Estudio 2: Determinar la evidencia en el ámbito de la Inmunoterapia, con la realización de una revisión sistemática en vacunas terapéuticas para el cáncer de pulmón de células no pequeñas avanzado). (Estudio 3: Determinar la calidad de las guías de práctica clínica sobre el tratamiento del cáncer de pulmón de células no pequeñas (NSCLC) y describir sus recomendaciones).

Resultados:

En el estudio 1 se realizó una revisión sistemática que incluyó 12 estudios en los que se asignó a adultos sanos, suplementos vitamínicos o minerales comparados con placebo y seguimiento a largo plazo, para evaluar el riesgo de desarrollar cáncer de pulmón. Los resultados muestran que ninguno de los tratamientos comparados con placebo ha mostrado una diferencia en el riesgo de incidencia o mortalidad por cáncer de pulmón en personas sanas. En los fumadores y las personas expuestas al asbesto, la vitamina A aumenta la incidencia del cáncer de pulmón, la mortalidad por cáncer de pulmón y la mortalidad por todas las causas. La vitamina C aumenta la incidencia del cáncer de pulmón en las mujeres. La vitamina E aumenta el riesgo de sufrir accidentes cerebrovasculares hemorrágicos. La certeza de la evidencia es alta para las siguientes comparaciones con placebo: vitamina A, vitamina E, selenio y combinaciones de vitaminas A, C, E, selenio y zinc.

En el estudio 2 se realizó una revisión sistemática que incluyo a participantes mayores de 18 años con diagnóstico histológico de cáncer de pulmón de células no pequeñas, (NSCLC) en estado avanzado (estados IIIB o IV). Se encontraron 10 estudios con 2177 participantes con NSCLC avanzado. Se evaluaron siete tipos diferentes de vacunas. Tres vacunas se evaluaron en dos estudios cada una. La vacuna TG4010 basada en un vector, la vacuna contra el factor de crecimiento epidérmico y racotumomab. Las cuatro vacunas restantes se evaluaron en un único estudio. Los resultados encontrados muestran que ninguna de las vacunas aumentó el tiempo de supervivencia de los participantes, excepto el racotumomab, ligeramente en 1.4 meses. De la misma forma, ninguna de las vacunas mejoró el tiempo de supervivencia sin progresión, excepto la TG4010, que podría aumentarlo ligeramente en 0.8 meses. Las siete vacunas analizadas en gran medida parecen seguras en cuanto a efectos adversos graves excepto la vacuna SLR172 que, añadida a quimioterapia, aumentó la

proporción de personas que presentaron al menos un episodio adverso grave. La certeza de la evidencia varió de moderada a muy baja para las diferentes vacunas y desenlaces evaluados, principalmente porque los estudios eran pequeños y no hubo suficientes estudios para estar seguros de los resultados.

En el estudio 3 se evaluó críticamente la calidad metodológica de las recomendaciones de las guías de práctica clínica (GPC). Se incluyeron GPC con recomendaciones para el tratamiento del cáncer de pulmón no microcítico primario o metastásico en personas de 18 años o más. La calidad metodológica de cada GPC fue determinada de forma independiente por tres evaluadores utilizando el instrumento AGREE II (Appraisal of Guidelines for Research and Evaluation II). Se seleccionaron veintidós guías. El acuerdo entre los evaluadores fue muy bueno. Las puntuaciones medias por dominio AGREE II fueron: alcance y propósito 90,7% (que van del 64,8% al 100%), participación de los grupos de interés 76,9% (entre el 27,8% y el 96,3%), rigor del desarrollo 80,9% (osciló entre el 27,1% y el 92,4%), claridad de presentación 89,8% (que van del 50% al 100%), aplicabilidad 46,5% (rango del 12,5% al 87,5%) e independencia editorial 91,7% (que van del 27,8% al 100%). Entre todas las GPC evaluadas, seis fueron “recomendadas” por los revisores para uso en clínica, 12 GPC fueron recomendadas con modificaciones y cuatro GPC no fueron recomendadas. La mediana de la tasa global fue de 5 (mínimo 3, máximo 6) puntos.

Conclusión:

En el ámbito de la Quimioprevención, no hay evidencia de que los suplementos de vitaminas A, C, E, D, o selenio, solos o en diferentes combinaciones, prevengan la incidencia ni la mortalidad del cáncer de pulmón en personas sanas y en algunos grupos de personas expuestas, se detectaron efectos nocivos. En el ámbito de la Inmunoterapia, las vacunas terapéuticas para el cáncer de pulmón de

células no pequeñas avanzado no mejoran la supervivencia general, ni la supervivencia sin progresión, o lo hacen en un grado mínimo. Estas conclusiones se deben interpretar con cautela, ya que la evidencia de certeza muy baja a moderada impide establecer conclusiones sólidas, muchas vacunas se evaluaron en un único estudio con un escaso número de participantes y eventos. En la evaluación de la calidad de las GPC, que incluyen recomendaciones sobre las terapias para el NSCLC generalmente no proporcionan información explícita sobre fuentes de financiación, informes de costos, barreras, facilitadores, materiales adicionales y otros factores clave para garantizar la aplicación de sus recomendaciones.

ABSTRACT

Introduction:

Lung cancer is the most common cancer in the world and the main cause of cancer-related death. It is a complex and heterogeneous pathology that involves genetic, environmental, immunological, microbiological factors and the individual response of patients. Thus, diagnosis and treatment pose many challenges for public health and clinical practice.

Objectives:

The general objective of this doctoral thesis is to determine the available evidence in the field of Chemoprevention, Immunotherapy and the quality of therapeutic recommendations in lung cancer.

Methods:

Three studies were carried out, corresponding to two systematic reviews and an assessment of the quality of clinical practice guidelines. The three studies in this thesis focused on lung cancer. (Study 1: To determine the evidence in the field of Chemoprevention, with a systematic review of drugs for the prevention of lung cancer in healthy people). (Study 2: To determine the evidence in the field of immunotherapy, with the performance of a systematic review on therapeutic vaccines for advanced non-small cell lung cancer) (Study 3: To determine the quality of clinical practice guidelines on the treatment of non-small cell lung cancer (NSCLC) and describe their recommendations.)

Results:

In Study 1, a systematic review was performed that included 12 studies in which healthy adults were assigned to vitamin or mineral supplements compared with placebo and long-term follow-up, to evaluate the risk of developing lung cancer. The results show that none of the treatments compared

with placebo have shown a difference in the risk of incidence or mortality from lung cancer in healthy people. In smokers and people exposed to asbestos, vitamin A increases the incidence of lung cancer, mortality from lung cancer and mortality from all causes. Vitamin C increases the incidence of lung cancer in women. Vitamin E increases the risk of suffering hemorrhagic strokes. The certainty of the evidence is high for the following comparisons with placebo: vitamin A, vitamin E, selenium, and combinations of vitamins A, C, E, selenium, and zinc.

Study 2, was a systematic review that included participants aged 18 years or older with a histologically diagnosed advanced stage NSCLC (stage IIIB or IV). Ten studies were found with 2177 participants with advanced NSCLC. Seven different types of vaccines were evaluated. Three vaccines were evaluated in two studies each: the vector-based vaccine TG4010, the epidermal growth factor vaccine, and racotumomab. The remaining four vaccines were evaluated in a single study. The results found show that none of the vaccines increased the survival time of participants, except for racotumomab, which slightly increased it by 1.4 months. Similarly, none of the vaccines improved progression-free survival time, except for TG4010, which could slightly increase it by 0.8 months. The seven vaccines analysed largely appear to be safe in terms of serious adverse events, except for the SLR172 vaccine, which, when added to chemotherapy, increased the proportion of people who experienced at least one serious adverse event. The certainty of the evidence varied from moderate to very low for the different vaccines and outcomes assessed, mainly because the studies were small and there were not enough studies to be sure of the results.

In Study 3, the methodological quality of the recommendations in the clinical practice guidelines was critically assessed. CPGs with recommendations for the treatment of primary or metastatic non-small cell lung cancer in people aged 18 years or older were included. The methodological quality of each

CPG was independently determined by three evaluators using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. Twenty-two guidelines were selected. The agreement between the evaluators was very good. The mean scores per AGREE II domain were: scope and purpose 90.7% (ranging from 64.8% to 100%), stakeholder involvement 76.9% (ranging from 27.8% to 96.3%), rigor of development 80.9% (ranging from 27.1% to 92.4%), clarity of presentation 89.8% (ranging from 50% to 100%), applicability 46.5% (ranging from 12.5% to 87.5%) and editorial independence 91.7% (ranging from 27.8% to 100%). Among all the CPGs evaluated, six were "recommended" by the reviewers for clinical use, 12 CPGs were recommended with modifications and four CPGs were not recommended. The median overall rate was 5 (minimum 3, maximum 6) points.

Conclusion:

In the field of Chemoprevention, there is no evidence that vitamin A, C, E, D, or selenium supplements, alone or in different combinations, prevent the incidence or mortality of lung cancer in healthy people and in some groups of exposed people, harmful effects were detected. In the field of Immunotherapy, therapeutic vaccines for advanced non-small cell lung cancer do not improve overall survival, or progression-free survival, or do so to a minimal degree. These conclusions should be interpreted with caution, since the evidence of very low to moderate certainty prevents drawing firm conclusions, many vaccines were evaluated in a single study with a small number of participants and events. In assessing the quality of clinical practice guidelines, guidelines that include recommendations on therapies for NSCLC generally do not provide explicit information on funding sources, cost reporting, barriers, facilitators, additional materials, and other key factors to ensure implementation of their recommendations.

RESUM

Introducció:

El càncer de pulmó és el càncer més comú al món i principal causa de mort per càncer. És una patologia complexa i heterogènia que involucra tant factors genètics, ambientals, immunològics, microbiològics i la resposta individual dels pacients. Així, el diagnòstic i el tractament plantegen molts desafiaments per a la salut pública i la pràctica clínica.

Objectius:

L'objectiu general d'aquesta tesi doctoral és determinar quina és l'evidència disponible a l'àmbit de la Quimioprevenció, Immunoteràpia i la qualitat de les recomanacions terapèutiques al càncer de pulmó.

Mètodes:

Es van fer 3 estudis corresponents a dues revisions sistemàtiques i una avaluació de la qualitat de les guies de pràctica clínica. Els tres estudis d'aquesta tesi es van centrar en el càncer de pulmó. (Estudi 1: Determinar l'evidència a l'àmbit de la Quimioprevenció, amb la revisió sistemàtica de fàrmacs per a la prevenció del càncer de pulmó en persones sanes). (Estudi 2: Determinar l'evidència a l'àmbit de la Immunoteràpia, amb la realització d'una revisió sistemàtica en vacunes terapèutiques per al càncer de pulmó de cèl·lules no petites avançat). (Estudi 3: Determinar la qualitat de les guies de pràctica clínica sobre el tractament del càncer de pulmó de cèl·lules no petites (NSCLC) i descriure'n les recomanacions).

Resultats:

A l'estudi 1 es va realitzar una revisió sistemàtica que va incloure 12 estudis en què es va assignar a adults sans, suplements vitamínics o minerals comparats amb placebo i seguiment a llarg termini, per

avaluar el risc de desenvolupar càncer de pulmó. Els resultats mostren que cap dels tractaments comparats amb placebo no ha mostrat una diferència en el risc d'incidència o mortalitat per càncer de pulmó en persones sanes. Als fumadors i les persones exposades a l'asbest, la vitamina A augmenta la incidència del càncer de pulmó, la mortalitat per càncer de pulmó i la mortalitat per totes les causes. La vitamina C augmenta la incidència del càncer de pulmó a les dones. La vitamina E augmenta el risc de patir accidents cerebrovasculars hemorràgics. La certesa de l'evidència és alta per a les comparacions següents amb placebo: vitamina A, vitamina E, seleni i combinacions de vitamines A, C, E, seleni i zinc.

A l'estudi 2 es va realitzar una revisió sistemàtica que incloc a participants majors de 18 anys amb diagnòstic histològic, NSCLC en estadi avançat (estadis IIIB o IV). Es van trobar 10 estudis amb 2177 participants amb CPCNP avançat. Es van avaluar set tipus diferents de vacunes. Tres vacunes es van avaluar en dos estudis cadascuna: La vacuna TG4010 basada en un vector, la vacuna contra el factor de creixement epidèrmic i racotumomab. Les quatre vacunes restants es van avaluar en un únic estudi. Els resultats trobats mostren que cap de les vacunes va augmentar el temps de supervivència dels participants, excepte el racotumomab, lleugerament en 1,4 mesos. De la mateixa manera, cap de les vacunes va millorar el temps de supervivència sense progressió, excepte la TG4010, que podria augmentar-lo lleugerament en 0,8 mesos. Les set vacunes analitzades en gran mesura semblen segures quant a efectes adversos greus excepte la vacuna SLR172 que, afegida a quimioteràpia, va augmentar la proporció de persones que van presentar almenys un episodi advers greu. La certesa de l'evidència va variar de moderada a molt baixa per a les diferents vacunes i desenllaços avaluats, principalment perquè els estudis eren petits i no hi va haver prou estudis per estar segurs dels resultats.

A l'estudi 3 es va avaluar críticament la qualitat metodològica de les recomanacions de les guies de pràctica clínica. Es van incloure GPC amb recomanacions per la tractament del càncer de pulmó no microcític primari o metastàtic en persones de 18 anys o més. La qualitat metodològica de cada GPC va ser determinada de forma independent per tres avaluadors utilitzant l'instrument AGREE II (Appraisal of Guidelines for Research and Evaluation II). Es van seleccionar vint-i-dues guies. L'acord entre els avaluadors va ser molt bo. Les puntuacions mitjanes per domini AGREE II van ser: abast i propòsit 90,7% (que van del 64,8% al 100%), participació dels grups d'interès 76,9% (entre el 27,8% i el 96, 3%), rigor del desenvolupament 80,9% (oscil·là entre el 27,1% i el 92,4%), claredat de presentació 89,8% (que van del 50% al 100%), aplicabilitat 46,5% (rang del 12,5% al 87,5%) i independència editorial 91,7% (que van del 27,8% al 100%). Entre totes les GPC avaluades, sis van ser "recomanades" pels revisors per a ús a clínica, 12 GPC van ser recomanades amb modificacions i quatre GPC no van ser recomanades. La mitjana de la taxa global va ser de 5 (mínim 3, màxim 6) punts.

Conclusió:

A l'àmbit de la Quimioprevenció, no hi ha evidència que els suplements de vitamines A, C, E, D, o seleni, sols o en diferents combinacions, previnguin la incidència ni la mortalitat del càncer de pulmó en persones sanes i en alguns grups de persones exposades, es van detectar efectes nocius. A l'àmbit de la Immunoteràpia, les vacunes terapèutiques per la càncer de pulmó de cèl·lules no petites avançat no milloren la supervivència general, ni la supervivència sense progressió, o ho fan en un grau mínim. Aquestes conclusions s'han d'interpretar amb cautela, ja que l'evidència de certesa molt baixa a moderada impedeix establir conclusions sòlides, moltes vacunes es van avaluar en un únic estudi amb pocs participants i esdeveniments. En l'avaluació de la qualitat de les guies de pràctica clínica, que

inclouen recomanacions sobre les teràpies per la NSCLC generalment no proporcionen informació explícita sobre fonts de finançament, informes de costos, barreres, facilitadors, materials addicionals i altres factors clau per garantir l'aplicació de recomanacions.

1. INTRODUCCIÓN

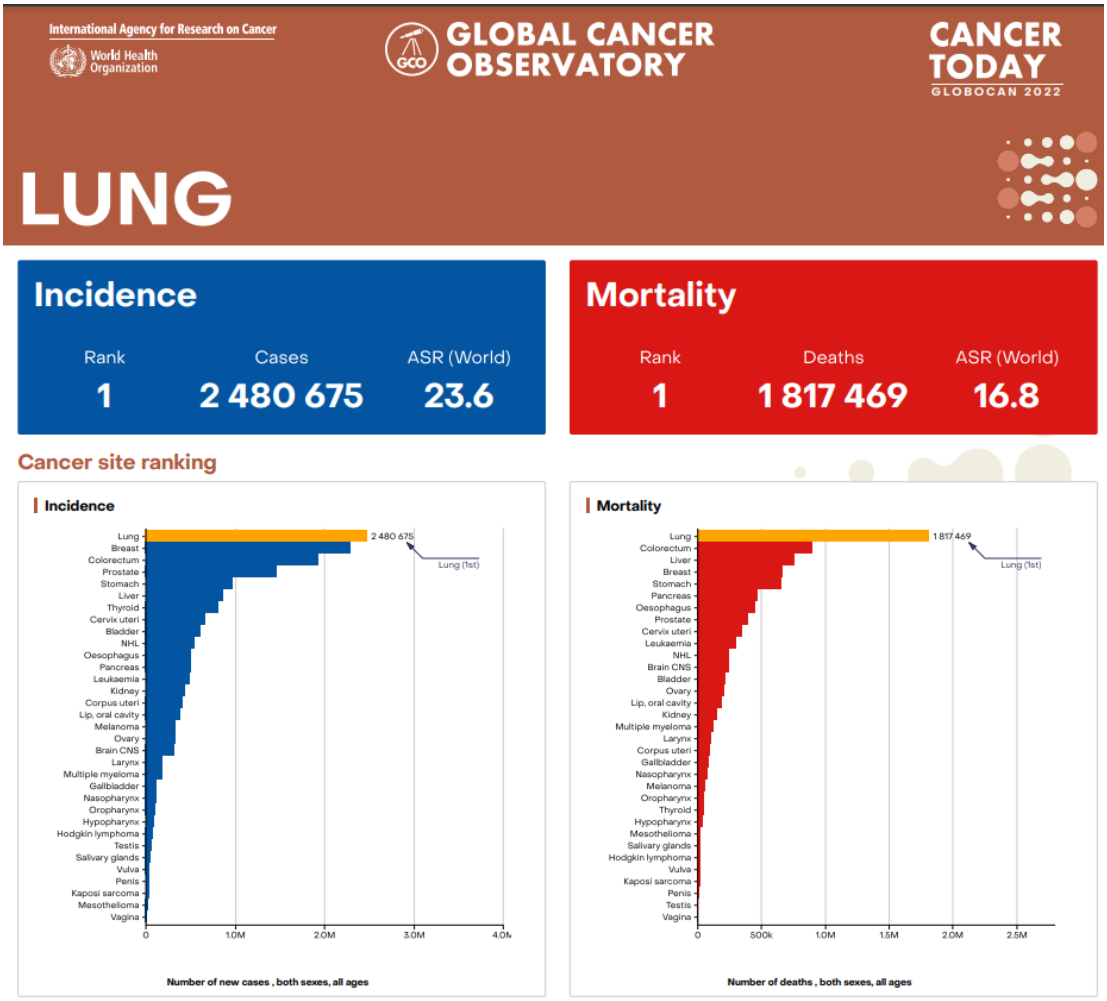
1.1 CÁNCER DE PULMÓN

1.1.1 Epidemiología

El cáncer de pulmón representa un problema prioritario de salud pública. Se trata de una enfermedad compleja y heterogénea que involucra factores genéticos, ambientales, inmunológicos y microbiológicos, así como la respuesta individual de los pacientes. Tanto el diagnóstico como el tratamiento del cáncer de pulmón plantean numerosos desafíos para la salud pública y la práctica clínica.

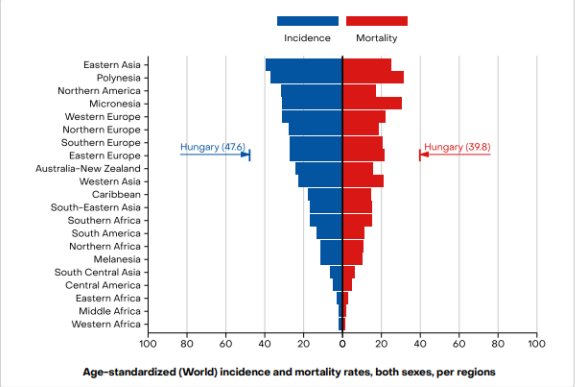
A nivel mundial, el cáncer de pulmón es el más común. Según los registros de la base de datos GLOBOCAN de la Agencia Internacional para la Investigación del Cáncer en 2022, se diagnosticaron 2.480.675 nuevos casos (1.572.045 en hombres y 908.630 en mujeres), lo que representa el 12,4% del total de todos los nuevos diagnósticos de cáncer. Además, fue la principal causa de muerte por cáncer, con un total de 1.817.469 fallecimientos (1.233.241 en hombres y 584.228 en mujeres), lo que equivale al 18,17% del total de muertes por esta enfermedad (GLOBOCAN 2024) (1, 2) (Fig. 1, 2).

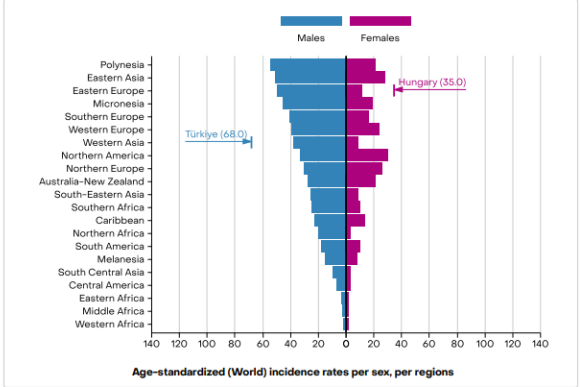
(Fig.1). *Global Cancer Observatory: Cancer Today: GLOBOCAN 2022*



Por otra parte, la razón hombre-mujer tiene variaciones importantes entre las regiones. (Fig 2).

(Fig.2) *Global Cancer Observatory: Cancer Today GLOBOCAN 2022 Estimates of Incidence and Mortality Worldwide per regions*





Se clasifica en dos grupos histológicos principales: el cáncer de pulmón de células no pequeñas (NSCLC) con el 85% y el cáncer de pulmón de células pequeñas (SCLC) con el 15% de los casos. Los NSCLC se dividen además en diferentes subtipos histológicos. Los tipos más comunes incluyen: el adenocarcinoma (de células glandulares) (40%), carcinoma de células escamosas (30%) y el de células grandes, con o sin características neuroendocrinas (10% a 15%). Los tumores carcinoides son neoplasias de células neuroendocrinas bien diferenciadas (células de Kulchitsky), mientras que el SCLC se origina a partir de células neuroendocrinas mal diferenciadas, lo que resulta en metástasis rápidas, una respuesta deficiente a la terapia y un pronóstico desfavorable. Tanto los carcinomas de células escamosas como los SCLC están asociados al tabaquismo, especialmente entre los hombres (3, 4).

La alta tasa de mortalidad asociada a este tipo de cáncer puede estar relacionada con la etapa clínica en el momento del diagnóstico. Solo el 15% de los pacientes son diagnosticados en una etapa temprana, mientras que la mayoría se identifica en estadios avanzados o con enfermedad metastásica. Según la octava edición de la clasificación de tumores, ganglios y metástasis (TNM) para el cáncer de pulmón, la supervivencia general a cinco años es del 92% para la etapa clínica IA1, 83% para IA2, 77% para IA3, 68% para IB, 60% para IIA, 53% para IIB, 36% para IIIA, 26% para IIIB, 13% para IIIC, 10% para IVA y 0% para IVB (3).

Estos resultados indican que las personas con cáncer de pulmón en etapas avanzadas tienen una esperanza de vida más corta en comparación con aquellas diagnosticadas en etapas anteriores. Además, esto genera una sobrecarga al sistema sanitario debido a los tratamientos combinados de quimioterapia y radioterapia, que tienen un bajo impacto en las tasas de supervivencia y mortalidad (5).

En contraste, el tratamiento quirúrgico para la enfermedad resecable y operable en etapas tempranas no solo puede ser curativo, sino que también proporciona tasas de supervivencia a cinco años después de la resección quirúrgica que oscilan entre el 30% y el 80%, en comparación con el 2% al 15% para las etapas avanzadas o metastásicas. Por lo tanto, es crucial tanto la prevención como la detección y tratamiento temprano para mejorar el pronóstico de los pacientes con cáncer de pulmón (6, 7).

1.1.2 Factores de Riesgo

La Agencia Internacional para la Investigación sobre el Cáncer (IARC) ha reconocido más de 30 agentes cancerígenos con suficiente evidencia de riesgo para el cáncer de pulmón, entre los cuales se encuentran el consumo de tabaco, el humo de tabaco de segunda mano, el aluminio, el amianto, el arsénico, el berilio, el cadmio y las emisiones de carbón, así como el radón, entre otros (8). Además, se ha determinado que la contaminación del aire por material particulado con un tamaño de partículas PM10 contribuye a la incidencia del cáncer de pulmón (9). Sin embargo, el consumo de tabaco ha sido señalado a lo largo del tiempo como el principal factor de riesgo para esta enfermedad.

El establecimiento de un vínculo causal entre el consumo de tabaco y el cáncer de pulmón ha desempeñado un papel fundamental en la ciencia, la medicina y la salud pública (10). Este proceso histórico no ha estado exento de controversias, desde la publicación del estudio epidemiológico sobre el cáncer realizado por Frederick L. Hoffman en 1931 (11) hasta el reconocimiento oficial en 1954 de los efectos causales del humo del tabaco (12). Posteriormente, se han llevado a cabo estudios que identifican el humo del tabaco como el principal factor de riesgo para el cáncer de pulmón (13, 14).

Además de los factores de riesgo mencionados, líneas de investigación en curso, como lo indica el estudio de asociación del genoma del adenocarcinoma de pulmón, han permitido identificar 24 loci de susceptibilidades relevantes. Las variantes de susceptibilidad conocidas representan el 13% del riesgo familiar estimado en poblaciones de Asia oriental, sin embargo, no mostraron evidencia de asociación en poblaciones europeas. Los autores concluyen en que se requieren estudios más amplios para investigar la arquitectura subyacente de la susceptibilidad al adenocarcinoma de pulmón en personas

que nunca han fumado, así como en individuos con antecedentes de tabaquismo y en diferentes poblaciones ancestrales (15).

El cáncer de pulmón en no fumadores (LCINS, por sus siglas en inglés) presenta características epidemiológicas, clínico-patológicas y moleculares distintas a las del cáncer de pulmón en quienes alguna vez fumaron. Entre los diversos factores de riesgo propuestos para el desarrollo del carcinoma pulmonar (LCINS), los factores ambientales cuentan con la evidencia más sólida. Además, aunque los estudios genéticos iniciales se centraron en gran medida en el cáncer de pulmón en su conjunto, investigaciones recientes también han identificado factores de riesgo genéticos específicos para el LCINS (16).

Múltiples factores epigenéticos, en particular la metilación del ADN, se han asociado con el desarrollo del cáncer de pulmón (CP), los estudios indican que esta metilación podría regular la expresión génica mediante la alteración de la estructura de la cromatina y la unión de factores de transcripción (TF) (17). La inestabilidad genómica es uno de los sellos distintivos del cáncer y está asociada a variaciones numéricas o estructurales en los cromosomas, tales como pérdidas o ganancias de fragmentos cromosómicos, translocaciones, deleciones y amplificaciones (18).

En comunicaciones recientes, se ha informado sobre un aumento en la incidencia de cáncer de pulmón en adultos jóvenes que, a diferencia de la población mayor, podría atribuirse a una interacción compleja entre la susceptibilidad individual y perfiles clínicos moleculares distintos, así como a factores de riesgo ambientales prevalentes que van más allá de la exposición al humo del tabaco, gas radón o contaminación del aire. Existe una brecha en la comprensión de los factores germinales no

modificables que contribuyen al cáncer de pulmón en adultos jóvenes, por lo tanto, es esencial perfeccionar las evaluaciones de riesgo, los enfoques de detección y las estrategias de tratamiento personalizadas (19).

1.1.3 Prevención

A pesar de que se han implementado numerosas estrategias preventivas para reducir la incidencia del cáncer de pulmón, se observa una tasa de supervivencia inferior a la de cualquier otro tipo de cáncer (20). Estas estrategias se han centrado principalmente en modificaciones del estilo de vida. Desde que se estableció la relación entre el tabaquismo y la incidencia del cáncer de pulmón, las intervenciones preventivas han estado orientadas a combatir el hábito de fumar. Las medidas destinadas a facilitar el abandono del tabaquismo incluyen, entre otras, la entrega de folletos informativos y otros medios de difusión (20).

En un estudio realizado en el contexto del cribado del cáncer de pulmón, se desarrolló un folleto elaborado con la colaboración de personas que actualmente fuman o que han sido fumadoras, con el objetivo de apoyar a los pacientes en su proceso para dejar de fumar. Este folleto contenía imágenes que ilustraban el daño causado en los pulmones y el corazón, junto con mensajes positivos diseñados para generar confianza e informar a los pacientes sobre los beneficios de cesar el consumo de tabaco. El estudio concluye que las intervenciones para dejar de fumar que incorporan imágenes personalizadas escaneadas de los pacientes, resaltando los beneficios individuales del abandono del hábito, combinadas con conversaciones de apoyo con un profesional capacitado, podrían motivar y sostener los intentos por dejar de fumar en aquellas personas que actualmente fuman y participan en

programas de detección del cáncer de pulmón. Además, se señala que es necesaria una evaluación adicional sobre la efectividad de esta estrategia (21).

Las medidas de salud pública destinadas a des normalizar el consumo de tabaco ha incluido envases neutros, la prohibición de publicidad, el aumento del precio y terapias sustitutivas. Se observa que muchas personas desean dejar el hábito, pero les resulta difícil (22).

El apoyo conductual proporciona una alternativa o complemento para ayudar a estas personas. Consiste en otorgar asesoramiento e información sobre el daño que provoca el tabaco y las opciones disponibles para facilitar el abandono del hábito de fumar. En una revisión sistemática (RS) con metaanálisis en red, se determinó con alta certeza de evidencia que la orientación y las recompensas económicas son efectivas para ayudar a las personas a dejar de fumar, mientras que se encontró certeza moderada sobre la efectividad de otros tipos de apoyo conductual, así como sobre quién proporciona dicho apoyo y cómo se lleva a cabo (23).

Las intervenciones conductuales han sido diseñadas para evaluar e implementar en diversos ámbitos. En una RS que incluyó a profesionales odontólogos y evaluar las intervenciones que ellos realizaban para promover el abandono del tabaquismo, tanto en la consulta como en el ámbito comunitario. Incluyeron 16 ensayos clínicos, todos emplearon intervenciones conductuales, y cuatro de ellos incorporaron terapia de reemplazo con nicotina (TRN) o cigarrillos electrónicos, como parte de la intervención. Los resultados concluyen, con un nivel de certeza de evidencia muy bajo, que solo con

el apoyo conductual, aumentan las tasas de abandono. De la misma forma, las tasas de abstinencia aumentan, cuando se combina el apoyo conductual con farmacoterapia, con un nivel de certeza de evidencia moderado. Se concluye que es necesario contar con más evidencia para determinar la magnitud del efecto beneficioso y poder establecer si la adición de intervenciones farmacológicas es más eficaz que el apoyo conductual por sí solo (24).

Dado que las poblaciones sin hogar presentan altas tasas de tabaquismo, se llevó a cabo una RS para evaluar las intervenciones dirigidas a la motivación e información de los servicios de apoyo disponibles para ellos, con el fin de lograr la abstinencia. En diez estudios que incluyeron a 1,634 participantes, no se encontró evidencia suficiente para evaluar los efectos de una intervención específica para el abandono del hábito de fumar en personas sin hogar (25).

La atención primaria representa un ámbito crucial para abordar la adicción al tabaco, sin embargo, la priorización del tema por parte de los profesionales varía considerablemente. En esta RS, se evaluó la efectividad de las intervenciones destinadas a dejar de fumar en los centros de atención primaria y si dicha efectividad se debe a una mejor implementación por parte de los profesionales sanitarios. Se incluyeron un total de 81 ensayos clínicos aleatorizados (ECA) con 112,159 participantes. Los resultados indican que, en algunos estudios, los datos presentaron una alta variabilidad, en otros, no se dispuso de suficientes datos, y en algunos casos, se identificaron problemas de calidad en los estudios incluidos. La confianza en la probabilidad de dejar de fumar fue moderada cuando, además del médico de atención primaria, se proporcionaba asesoramiento para cesar el consumo de tabaco,

se ofrecía medicación gratuita o se entregaba material impreso adaptado como parte del apoyo en la atención primaria. La confianza en la eficacia fue menor para intervenciones, como proporcionar información sobre los marcadores del riesgo individual de cáncer, así como en el conocimiento con el que contaban los trabajadores sanitarios sobre los tratamientos y estrategias destinadas a la deshabituación de fumar o en ofrecer recompensas por brindar apoyo en el proceso de cesación. Se concluye que es probable que estos resultados cambien a medida que se disponga de más evidencia (26).

En el ámbito de los pacientes con enfermedades mentales graves, y debido a una amplia variedad de factores, se observa una mayor probabilidad de dependencia del hábito de fumar en comparación con la población general. Se llevó a cabo RS para evaluar los efectos del asesoramiento sobre el abandono del hábito de fumar. Los autores concluyen que no existen pruebas de alta calidad que guíen a los profesionales sanitarios en relación con el asesoramiento para el cese del tabaquismo dirigido a sus pacientes, lo que indica que es un área que requiere mayor atención en la investigación (27).

Otra RS tuvo como objetivo determinar el efecto a largo plazo de los programas de tratamiento con incentivos, de manera independiente, en el abandono del hábito de fumar. Se incluyeron treinta y tres ensayos clínicos aleatorizados con una población mixta y más de 21,600 participantes. Luego de un largo seguimiento, los autores concluyen con alta certeza de evidencia que los incentivos, mejoran las tasas de abandono del hábito de fumar. Además, hay evidencia moderada que respalda que los

programas de incentivos dirigidos a mujeres embarazadas fumadoras mejoran las tasas de abandono del hábito, tanto al final del embarazo como después del parto (28).

Por otro lado, algunos profesionales de la salud y fumadores sostienen que fumar contribuye a la reducción del estrés y a la mitigación de otros síntomas relacionados con la salud mental, como la depresión y la ansiedad. Existe preocupación de que dejar de fumar pueda agravar estos síntomas. En una RS se investigó el impacto del cese del tabaquismo en la salud mental de las personas. Se incluyeron 102 estudios con más de 169,500 participantes. Los hallazgos indicaron que la salud mental no se deteriora como resultado del abandono del tabaquismo, con evidencia moderada a baja que sugiere que el cese del hábito tabáquico está asociado con mejoras pequeñas a moderadas en la salud mental (29).

En el ámbito de la terapia cognitiva, una RS evaluó la eficacia de las intervenciones basadas en la atención plena para facilitar el abandono del hábito de fumar. La atención plena, también conocida como 'mindfulness', es una técnica de meditación que busca lograr un mejor control sobre los pensamientos y emociones con el propósito de disminuir los impulsos de fumar y mejorar el estado de ánimo. No obstante, no se detectó un beneficio atribuible a estas intervenciones en cuanto a aumentar las tasas de abandono del hábito de fumar o a mejorar la salud mental y el bienestar (30).

En línea con el cambio conductual, en una RS, se evaluó si las intervenciones motivacionales (IM) son efectivas. Se incluyeron 37 ensayos con 15,000 personas fumadoras. Los resultados concluyeron que

no hay evidencia suficiente para demostrar que la IM ayuda a dejar el hábito tabáquico, en comparación con ninguna intervención. Además, se informó que las medidas de efecto del tratamiento presentaron baja certeza debido a imprecisión e inconsistencia. Existe muy poca evidencia acerca de la IM en relación con el abandono del hábito de fumar y la mejora del bienestar mental (31).

En una revisión sistemática más reciente en que se aborda el estado de ánimo bajo, asociado a la abstinencia de nicotina, proponen la evaluación de fármacos con propiedades antidepresivas para facilitar el abandono del hábito de fumar a largo plazo. Con la inclusión de 124 estudios y 48,832 participantes, se determina que el fármaco bupropión podría ayudar a las personas a dejar de fumar, pero también se pueden presentar eventos adversos, lo que podría conducir a la interrupción de su uso o requerir atención hospitalaria. Por otro lado, la nortriptilina también parece ser eficaz, aunque el bupropión podría demostrar una mayor efectividad. De hecho, el bupropión podría ser tan útil como la terapia de reemplazo de nicotina por sí sola para ayudar a las personas a dejar de fumar, pero menos efectivo en comparación con la terapia combinada de reemplazo de nicotina (es decir, un parche junto con otra forma) (32).

Para mitigar el placer que las personas suelen experimentar al fumar y los síntomas de abstinencia asociados al cese del consumo, esta revisión evalúa los agonistas parciales de los receptores de nicotina (APRN). El tratamiento más comúnmente utilizado en este grupo, es la vareniclina. Se ha informado que la eficacia de la vareniclina supera a la del bupropión. La citisina también puede contribuir al abandono del hábito tabáquico durante un periodo mínimo de seis meses. Es posible que

su efectividad sea comparable a la de la vareniclina no obstante, evidencia futura podría cambiar estos resultados. Se requieren estudios adicionales para evaluar su eficacia y seguridad (33).

En el ámbito de la quimio prevención, entendida como el uso de medicamentos, vitaminas o suplementos con el propósito de evitar o demorar la aparición del cáncer, se han propuesto diversos componentes con potencial quimiopreventivo, tales como inhibidores de la síntesis de poliaminas, retinoides, antiinflamatorios no esteroidales (AINE) e inhibidores de la ciclooxigenasa-2 (COX-2). En base a que las prostaglandinas desempeñan un papel promotor en el proceso carcinogénico, y el hallazgo de una mayor concentración intra tumoral en comparación con el tejido sano circundante, es que se ha sustentado el uso de los inhibidores de COX-2 (34).

La recomendación del consumo elevado de frutas y verduras como medida de prevención primaria se basa en el efecto de sustancias con propiedades antioxidantes. En este sentido, varios estudios epidemiológicos se han centrado en los flavonoides. El estudio realizado por García-Tirado en 2012 reporta un leve efecto protector del consumo de flavonoides (especialmente a dosis elevadas) frente al desarrollo del cáncer de pulmón, aunque señala que no todos los estudios corroboran esta afirmación (35). Otros estudios en el ámbito de la quimio prevención han reportado resultados contradictorios o no concluyentes (36-38).

Por otro lado, existen pocos métodos ideales para el diagnóstico temprano del cáncer de pulmón, debido a la heterogeneidad de las manifestaciones clínicas y las características patológicas. Esto

establece un escenario con limitadas oportunidades para la detección y el diagnóstico precoz, lo que resalta la importancia de realizar más investigaciones para desarrollar herramientas de estratificación de riesgos más efectivas. Estas herramientas deberían definir con mayor precisión qué personas presentan un riesgo muy alto para ser incluidas en programas de detección, así como identificar grupos de menor riesgo que pueden no requerir la misma frecuencia de seguimiento (39). Por lo tanto, es fundamental mejorar la eficacia de la prevención y el diagnóstico precoz, no solo prestando más atención al tratamiento, sino también brindando una atención de apoyo integral a los pacientes con cáncer de pulmón.

1.1.4 Tratamiento

El abordaje terapéutico comienza con la confirmación diagnóstica, iniciando con una tomografía computarizada (TC) con contraste del tórax, que incluye el cuello y el abdomen superior. Cuando la TC inicial demuestra metástasis a distancia o afectación de los ganglios linfáticos supraclaviculares o cervicales, el muestreo permite la estadificación y subtipificación patológica mediante análisis inmunohistoquímico y molecular. Por otro lado, se dispone de la tomografía por emisión de positrones combinada con tomografía computarizada (PET-CT) y ecografía endobronquial (EBUS) para el muestreo de los ganglios linfáticos mediastínicos, lo que ha permitido aumentar la precisión en la estadificación del cáncer de pulmón (40).

La Asociación Internacional para el Estudio del Cáncer de Pulmón (IASLC) publicó la octava edición basada en datos de 77,156 casos evaluables de carcinoma pulmonar no microcítico (NSCLC)

confirmados histológicamente, diagnosticados entre 1999 y 2010 a partir de 35 fuentes en 16 países. Los grupos de estadios se resumen en la siguiente tabla (41).

Tabla 1. Agrupamientos por estadios del cáncer de pulmón de la 8.ª edición de la Asociación Internacional para el Estudio del Cáncer de Pulmón (IASLC), 2018.

International Association for the Study of Lung Cancer (IASLC) 8th edition lung cancer stage groupings.

	N0	*N1*	*N2*	*N3*	*M1a*	*M1b*	*M1c*
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIIB	IIIA	IIIB	*IIIC*	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	*IIIC*	IVA	IVA	IVB

Gavin S Jones, and David R Baldwin Clin Med 2018;18:s41 - s46

Royal College of Physicians

Las opciones de tratamiento para el cáncer de pulmón se determinan principalmente en función del estadio de la enfermedad, sin embargo, también son relevantes otros factores, como el estado general de salud del paciente, su función pulmonar y ciertas características específicas del cáncer. En muchos casos, se puede emplear de manera conjunta más de un tipo de tratamiento. Entre las modalidades

terapéuticas disponibles se incluyen la cirugía, la ablación por radiofrecuencia, la radioterapia, la quimioterapia, la inmunoterapia y los procedimientos paliativos (42). Para cada alternativa se consideran factores como los resultados a corto, mediano y largo plazo, el grado de confianza en la evidencia y su aplicabilidad al paciente (43, 44). A pesar de los pequeños avances que se han podido registrar a corto plazo, como el uso más generalizado de la quimioterapia y la radioterapia (45), la supervivencia global del cáncer de pulmón sigue siendo muy baja a largo plazo. La probabilidad de supervivencia en esta patología es elevada únicamente durante el primer año. Los principales factores pronósticos son la comorbilidad, la presencia de dolor, hemoptisis y un diagnóstico tardío, los cuales están asociados con menores tasas de supervivencia. De manera similar, los factores pronósticos relacionados con las características de la neoplasia y el tratamiento quirúrgico adyuvante tienen un impacto significativo en la supervivencia (46).

Con la limitada eficacia de la quimioterapia y radioterapia, así como el avance en el conocimiento científico, el papel del sistema inmunológico ha emergido como una nueva oportunidad terapéutica. Se ha señalado que la activación de la inmunidad antitumoral endógena es fundamental en el tratamiento del cáncer. Además, se han identificado ciertos agentes quimioterapéuticos, como doxorrubicina, mitoxantrona, epirrubicina, idarrubicina, oxaliplatino y ciclofosfamida, que poseen la capacidad de estimular la inmunidad antitumoral al inducir la muerte celular inmunogénica (ICD) en las células tumorales. Esto sugiere que la quimioterapia inmunogénica tiene un gran potencial para mejorar la eficacia tanto de la quimioterapia como de la inmunoterapia, aunque su efectividad depende en gran medida de la dosis, el cronograma y el modelo tumoral (47).

El desarrollo de la inmunoterapia como tratamiento para el carcinoma pulmonar no microcítico (NSCLC), representa un nuevo enfoque que busca superar las limitaciones de las estrategias terapéuticas convencionales. Esta modalidad abarca una amplia gama de tratamientos diseñados para provocar la destrucción de células tumorales mediada por el sistema inmunológico (48, 49).

En este contexto, se ha demostrado que las células malignas pueden expresar proteínas mutadas que son reconocidas como antígenos extraños, así como sobre expresar proteínas normales o antígenos fetales, los cuales normalmente están ausentes en adultos sanos. Si estos antígenos asociados a tumores son identificados como extraños por el sistema inmunológico, este responde estimulando las células presentadoras de antígenos (APC), para provocar una respuesta inmune adaptativa (50).

Uno de los factores clave que permite el desarrollo de un proceso neoplásico en el organismo es la capacidad del tumor para evadir la detección inmunológica. Este efecto se logra mediante la supresión de la expresión del complejo mayor de histocompatibilidad (MHC) clase I en la superficie celular neoplásica, la pérdida o alteración de la expresión de antígenos asociados a tumores (TAA) por parte de las células neoplásicas, la inhibición de los mecanismos de reconocimiento de antígenos específicos de las células cancerosas y la expresión local de moléculas inmunes inhibidoras, como el factor de crecimiento tumoral (TGF-β) y el ligando Fas (51).

Sobre esta base, el descubrimiento de antígenos malignos específicos que desencadenen una respuesta inmune antitumoral y aumenten tanto el potencial como la especificidad de la respuesta inmune anticancerígena abre la posibilidad de desarrollar vacunas terapéuticas, junto con los inhibidores de puntos de control inmunológico y los anticuerpos monoclonales dirigidos contra

epítopes específicos de las células tumorales, que tienen como objetivo reforzar el sistema inmunológico en respuesta a las células cancerosas que expresan dichos antígenos. Las vacunas pueden administrarse en diferentes momentos desde el diagnóstico inicial del cáncer de pulmón o a medida que avanza la enfermedad, utilizando diversos mecanismos de acción. Pueden ser parte del tratamiento inicial (terapia de primera línea), aplicarse como terapia de segunda línea tras el fracaso o la aparición de efectos secundarios intolerables del tratamiento de primera línea, o emplearse como terapia de tercera línea cuando tanto la terapia de primera como la de segunda línea no son efectivas, dejan de serlo o no se toleran adecuadamente. También pueden utilizarse como terapia de mantenimiento en pacientes en los que el tumor no ha progresado tras la primera inducción de quimioterapia (52).

La estrategia de las vacunas terapéuticas se basa en el principio de que la exposición a un antígeno (en este caso, asociado a la célula tumoral) puede desencadenar una respuesta inmune adaptativa del organismo a través de vías humoral (linfocitos B) o celular (linfocitos T). La información sobre esta última estrategia en relación con el NSCLC es muy limitada, sin embargo, se ha descrito que podría ser una alternativa terapéutica viable para esta enfermedad (53).

1.2 SINTESIS DE LA EVIDENCIA CIENTÍFICA

La Medicina Basada en Evidencia (MBE) proporciona la mejor información disponible para orientar los tratamientos y cuenta con varios instrumentos que sintetizan dicha evidencia, entre los cuales se encuentran las revisiones sistemáticas (RS) y las guías de práctica clínica (GPC).

1.2.1 REVISIONES SISTEMÁTICAS

Las revisiones sistemáticas son un diseño de investigación clínica que aplica métodos estandarizados y validados científicamente con el objetivo de sintetizar toda la información disponible sobre una pregunta de investigación específica. Su valor en la toma de decisiones y en el desarrollo de directrices es ampliamente reconocido por consumidores, investigadores, pacientes y médicos (54).

La búsqueda y selección de estudios se realizan conforme a criterios de elegibilidad previamente diseñados para responder a la pregunta de investigación planteada. El objetivo es minimizar el sesgo mediante el uso de métodos explícitos y sistemáticos, los cuales están documentados en un protocolo (55).

Las revisiones sistemáticas Cochrane siguen un formato altamente estructurado. En general, las tareas incluyen capacitación, reuniones, desarrollo de protocolos, búsqueda de estudios, evaluación de citas e informes completos de los estudios para determinar su elegibilidad, evaluación del riesgo de sesgo en los estudios incluidos, recopilación de datos, búsqueda de datos faltantes y estudios no publicados, análisis de los datos, interpretación de los resultados, redacción de la revisión y mantenimiento actualizado (56). La mayoría de las revisiones Cochrane analizan la evidencia sobre los efectos de las intervenciones en atención sanitaria o social. Estas revisiones se centran principalmente en ensayos clínicos aleatorios, considerados como el diseño de investigación más sólido para evaluar los efectos relativos de las intervenciones. Otros tipos de revisiones incluyen: aquellas que evalúan la precisión de las pruebas diagnósticas, la investigación de pronóstico que proporciona información sobre la salud y el bienestar futuros de personas con enfermedades o

afecciones específicas, los resúmenes de revisiones (overviews) que compilan evidencia de múltiples revisiones sistemáticas en un solo documento, y las revisiones metodológicas que buscan responder preguntas sobre diversos aspectos relacionados con los métodos utilizados en revisiones sistemáticas, ensayos clínicos y otras evaluaciones en el ámbito de la atención sanitaria y social (57).

1.3 GUÍAS DE PRÁCTICA CLÍNICA

1.3.1 Relevancia de las guías de práctica clínica para la práctica

Las decisiones clínicas se toman en condiciones de incertidumbre. Sin embargo, a medida que avanzan las investigaciones en medicina, biomedicina y servicios de salud, la traducción de la evidencia científica reduce progresivamente esta incertidumbre en la práctica clínica. Los profesionales de la salud reconocen cada vez más que la atención médica debe fundamentarse en una combinación de evidencia científica, conocimientos adquiridos a partir de la experiencia clínica y las preferencias de los pacientes (58).

Las guías de práctica clínica (GPC) complementan este avance al establecer estándares de atención respaldados por evidencia científica sólida (58). Estas guías constituyen un compendio de recomendaciones diseñadas para optimizar la atención al paciente, basándose en una revisión sistemática de la evidencia y en una evaluación exhaustiva de los beneficios y riesgos asociados a las diferentes opciones de atención (59).

Las GPC facilitan la toma de decisiones tanto para médicos como para pacientes al traducir hallazgos complejos de investigaciones científicas en recomendaciones prácticas relevantes para la atención individualizada del paciente, evitando así un enfoque único que no se ajuste a las necesidades específicas de cada persona. No obstante, para alcanzar los objetivos relacionados con la mejora en la utilización de recursos y la calidad en la prestación de atención médica, es fundamental que las GPC sean de alta calidad tanto en contenido como en presentación. Se ha demostrado que las GPC deficientes pueden anular sus potenciales beneficios y conducir a prácticas subóptimas, ineficaces o incluso perjudiciales (60).

En este contexto, es necesario abordar los desafíos en el desarrollo de las directrices, tales como la promoción de prácticas metodológicas transparentes, la estandarización para conciliar directrices contradictorias y la atención a los conflictos de interés.

1.3.2 Evaluación de guías de práctica clínica

El concepto de que los estándares de calidad deben informar el desarrollo de las GPC es una preocupación generalizada a nivel mundial, subrayada por los crecientes llamados a establecer estándares internacionales que aceleren el desarrollo y la evaluación rigurosa de las GPC. Aunque existen diversas directrices para la evaluación del desarrollo de guías, como el enfoque de Clasificación de la Aplicabilidad, Desarrollo y Evaluación de las Recomendaciones (GRADE), que facilita la elaboración de guías de práctica clínica y proporciona criterios para orientar la evaluación de la implementación de las Recomendaciones Basadas en Evidencia. GRADE, además, garantiza que dicha información sea comprensible para personas de diferentes culturas con distintos niveles de

alfabetización y diversos idiomas (61, 62). No obstante, la herramienta preferente y ampliamente utilizada, además de validada, es la Evaluación de Guías para la Investigación y Evaluación (AGREE), que se ha convertido en el estándar para la evaluación de directrices (63).

El instrumento AGREE original fue publicado en 2003 con el objetivo de desarrollar una herramienta para evaluar la calidad de las recomendaciones y de los informes (64). A lo largo del tiempo, y a pesar de las persistentes preocupaciones sobre la calidad de las GPC, una revisión sistemática de estudios que evaluaron estas guías concluyó que, las puntuaciones de calidad medidas con el instrumento AGREE se han mantenido en niveles moderados a bajos durante las últimas dos décadas. Se insta a los desarrolladores de GPC, a continuar mejorando la calidad de sus productos (65).

Con el fin de optimizar sus propiedades de medición y avanzar en la labor relacionada con las directrices, el Consorcio AGREE Next Steps llevó a cabo un programa de investigación para alcanzar estos objetivos y crear la próxima versión de la herramienta, denominada AGREE II (66, 67). Esta nueva herramienta internacional para la evaluación de las GPC, ha sido validada y verificada en cuanto a su fiabilidad. Consta de 23 ítems organizados en 6 dominios: a) alcance y finalidad, b) participación de las partes interesadas, c) rigor del desarrollo, d) claridad de presentación, e) aplicabilidad, y f) independencia editorial (66, 67). El instrumento es sensible a las diferencias en aspectos importantes de las directrices, puede ser utilizado de manera consistente y sencilla por una amplia gama de profesionales provenientes de diversos ámbitos, y está diseñado como parte de una estrategia general de calidad destinada a mejorar la atención médica (66, 67).

2. JUSTIFICACIÓN

En la revisión presentada, se han identificado al menos tres áreas de incertidumbre que requieren una mayor clarificación:

A.- En el ámbito de la Quimioprevención, casi todos los ensayos de intervención clínica que han utilizado nutrientes aislados, como suplementos de vitamina A, vitamina E, vitamina C, ácido fólico, selenio y carotenoides, no han logrado demostrar efectos protectores contra el cáncer de pulmón. A pesar de la existencia de numerosos estudios sobre la función biológica celular de las vitaminas y su papel en la salud, se desconocen las consecuencias del consumo a largo plazo de estos nutrientes. Por lo tanto, considerando la posibilidad de que los suplementos vitamínicos o minerales puedan poseer propiedades quimiopreventivas o generar efectos adversos, es fundamental evaluar el uso de estos agentes.

B.- Como se describió anteriormente, la Inmunoterapia se ha convertido en un enfoque clínico de vanguardia para el tratamiento del cáncer, en el cual las vacunas terapéuticas representan una opción viable que estimula el sistema inmunológico para combatir antígenos tumorales. Por lo tanto, es fundamental evaluar los resultados clínicos de este tratamiento y determinar si las vacunas prolongan el tiempo de supervivencia de los pacientes y el tiempo sin progresión de la enfermedad, así como si están asociadas con efectos adversos.

C.- Las guías de práctica clínica (GPC) han avanzado, pero también presentan serias limitaciones en cuanto a métodos, alcance y contenido. No todas las GPC se desarrollan con un enfoque sistemático

basado en la evidencia, lo que conlleva el riesgo de generar recomendaciones sesgadas. Ante este escenario, es importante y necesario evaluar periódicamente el proceso de elaboración, la calidad e incluso el contenido de las guías, para asegurar que sus recomendaciones sean válidas y confiables. Esto también contribuye a diferentes procesos, como la elaboración o actualización de nuevas GPCs, así como a la identificación de posibles brechas en este campo que puedan influir en el proceso de toma de decisiones. Hasta la fecha, no se ha realizado una evaluación de la calidad de las GPCs, en cáncer de pulmón.

En consecuencia, la relevancia de esta tesis doctoral radica en la presentación y valoración de la evidencia científica disponible sobre la Quimioprevención, la Inmunoterapia y la calidad de las recomendaciones terapéuticas en el contexto del cáncer de pulmón. Esta evidencia puede ser útil en la atención sanitaria, proporcionando conocimientos que faciliten decisiones orientadas a mejorar aspectos fundamentales como la supervivencia y la calidad de vida de los pacientes con cáncer de pulmón. En este contexto, se ha formulado la siguiente pregunta de investigación: ¿Cuál es la evidencia sobre la eficacia de la Quimioprevención, la Inmunoterapia y la calidad de las recomendaciones terapéuticas en el cáncer de pulmón?

3. OBJETIVOS

3.1 OBJETIVO GENERAL

Determinar cuál es la evidencia disponible en el ámbito de la Quimioprevención, Inmunoterapia y la calidad de las recomendaciones terapéuticas en el cáncer de pulmón.

3.2 OBJETIVOS ESPECÍFICOS

1. Determinar la evidencia en el ámbito de la Quimioprevención, con la revisión sistemática de fármacos para la prevención del cáncer de pulmón en personas sanas.

2. Determinar la evidencia en el ámbito de la Inmunoterapia, con la realización de una revisión sistemática en vacunas terapéuticas para el NSCLC avanzado.

3. Determinar la calidad de las guías de práctica clínica sobre el tratamiento del NSCLC, y describir sus recomendaciones.

4. MÉTODOS

Esta tesis doctoral se presenta como un compendio de tres publicaciones científicas. Los métodos utilizados corresponden a cada uno de los estudios realizados. El diseño de cada estudio fue seleccionado cuidadosamente en función de la pregunta de investigación planteada. Con el objetivo de describir y evaluar la calidad de la evidencia científica sobre la Quimioprevención, se actualizó una revisión sistemática previa sobre fármacos para la prevención del cáncer de pulmón en personas sanas. En lo que respecta a la Inmunoterapia, se llevó a cabo una revisión sistemática centrada en vacunas terapéuticas para el tratamiento del NSCLC avanzado. Además, se realizó una evaluación crítica para determinar la calidad de las guías de práctica clínica que incluían recomendaciones sobre el tratamiento del NSCLC.

4.1 ESTUDIO 1. MEDICAMENTOS PARA PREVENIR EL CÁNCER DE PULMÓN EN PERSONAS SANAS (Revisión Sistemática)

Esta revisión sistemática tuvo como objetivo determinar si las vitaminas, los minerales y otros agentes potenciales, ya sea de forma aislada o en combinación, reducen la incidencia y la mortalidad por cáncer de pulmón en poblaciones sanas. Esta es la segunda actualización de la versión original, publicada en 2003 por miembros del Centro Cochrane Iberoamericano (96). En dicha revisión original no se encontraron diferencias significativas en relación con la vitamina A y el riesgo de incidencia o mortalidad por cáncer de pulmón, tanto en comparación con placebo como en la población general y en individuos de alto riesgo (fumadores y expuestos al amianto) (68). En la primera actualización de esta revisión, publicada en 2012 y cuya primera autora fue esta doctoranda, se incluyó un estudio adicional en los metaanálisis. Este cambio modificó los resultados, evidenciando un aumento en el

riesgo de mortalidad por cáncer de pulmón y por todas las causas entre aquellos que consumían vitamina A, específicamente en personas de alto riesgo (fumadores y expuestos al asbesto) (69, 70).

Estrategia de búsqueda y selección de estudios

Se llevaron a cabo búsquedas en CENTRAL, MEDLINE y EMBASE desde 1974 hasta mayo de 2019, y se examinaron las referencias incluidas en estudios y revisiones publicadas (96). Asimismo, se realizaron búsquedas en los siguientes registros de ensayos clínicos para identificar posibles ensayos no publicados o en curso: ClinicalTrials.gov , Plataforma de Registro Internacional de Ensayos Clínicos de la OMS (ICTRP) (96).

Se incluyeron ensayos controlados aleatorios (ECA) que compararon vitaminas o suplementos minerales con placebo, administrados a hombres y mujeres sanos de todas las edades, independientemente de su hábito de fumar u otros factores de riesgo asociados al cáncer de pulmón. Los fumadores y las personas expuestas al amianto fueron clasificados como individuos de alto riesgo, mientras que aquellos que no habían estado expuestos a tales factores se consideraron de bajo riesgo. Cuatro revisores seleccionaron de manera independiente los ensayos a incluir en la revisión, evaluaron su calidad metodológica y extrajeron los datos pertinentes (96). Las intervenciones consistieron en suplementación dietética con vitaminas y minerales específicos (como selenio y zinc), así como otros agentes potenciales, ya sean naturales o sintéticos, tales como retinoides, isotiocianatos, flavonoides, monoterpenos o productos farmacéuticos como la N-acetilcisteína, administrados solos o en combinación y en cualquier dosis. La administración se realizó en forma de cápsulas o tabletas para consumo por vía oral (96).

En esta revisión se consideraron los siguientes resultados primarios: incidencia de cáncer de pulmón, mortalidad por cáncer de pulmón y eventos adversos. Dado que la acción de los fármacos incluidos en esta revisión podría también influir en otros tipos de cáncer o enfermedades, se tomaron en cuenta los siguientes resultados secundarios: incidencia total de cáncer, mortalidad total por cáncer y mortalidad general. Se evaluó de manera independiente el riesgo de sesgo de cada estudio en los siguientes dominios: generación de secuencias, ocultamiento de la asignación, cegamiento de participantes y personal, resultados de la valoración, datos incompletos sobre resultados, e informes selectivos (71). El riesgo de sesgo para cada dominio fue evaluado según los criterios establecidos en el capítulo 8 del Manual Cochrane para revisiones sistemáticas de intervenciones (71). Los desacuerdos fueron resueltos mediante discusión y consenso (96).

Las medidas del efecto del tratamiento fueron los riesgos relativos (RR) y sus intervalos de confianza (IC) del 95% para los resultados dicotómicos (96). Cuando fue apropiado, se agruparon los resultados de grupos comparables de ensayos utilizando un modelo de efectos aleatorios (96). La unidad de análisis fue el participante. No se anticipó la posibilidad de realizar ensayos cruzados o ensayos grupales en este contexto. En caso de datos faltantes o incompletos, se intentó obtener la información contactando a los autores correspondientes. A aquellos autores que no respondieron se les envió una segunda carta; todos, excepto uno, proporcionaron la información y los datos adicionales requeridos sobre sus estudios (96). Se evaluó la heterogeneidad entre los ensayos utilizando el estadístico I^2. El valor de I^2 se interpretó según los siguientes umbrales: del 0% al 40% indica que la heterogeneidad podría no ser importante; entre el 30% y el 60% puede representar una heterogeneidad moderada; entre el 50% y el 90% puede reflejar una heterogeneidad sustancial; y del 75% al 100%, una heterogeneidad considerable (71). Se investigó la heterogeneidad sustancial ($I^2 > 50\%$) mediante análisis de subgrupos pre especificados (96).

Para la evaluación de sesgos de notificación, se planificó generar gráficos en embudo y llevar a cabo las pruebas de regresión lineal de Egger, con el fin de investigar los sesgos de informe de resultados. Esto se consideró únicamente cuando el número de ensayos incluidos en un metaanálisis específico fue suficiente (al menos diez ensayos). Se siguieron las recomendaciones establecidas en el Capítulo 10 del Manual Cochrane para revisiones sistemáticas de intervenciones (72).

En cuanto a la síntesis de datos, cuando se dispuso de un número adecuado de estudios clínicamente similares, se agruparon sus resultados en metaanálisis. Se realizaron metanálisis basados en la intención de tratar (ITT), siguiendo las directrices contenidas en el Capítulo 9 del Manual Cochrane para revisiones sistemáticas de intervenciones (71).

Se siguió el enfoque GRADE para la elaboración de las tablas de "Resumen de hallazgos", tal como se sugiere en los Capítulos 11 y 12 del Manual Cochrane para revisiones sistemáticas de intervenciones (71). Para cada resultado, se evaluó la certeza de la evidencia y se clasificó en una de las siguientes categorías: "alta", "moderada", "baja" o "muy baja". Esta evaluación tuvo en cuenta diversos factores, incluyendo el riesgo de sesgo de los estudios, la inconsistencia de los resultados, la falta de direccionalidad, la imprecisión y el sesgo de publicación (71). Cuando fue posible, se llevó a cabo un análisis de subgrupos para identificar grupos de alto y bajo riesgo (96).

Alto riesgo: incluye a aquellos individuos que son fumadores conocidos y/o aquellos que están expuestos a factores de riesgo ocupacional relacionados con el cáncer de pulmón, como el amianto.

Bajo riesgo: comprende a aquellos sin factores de riesgo conocidos para el cáncer de pulmón, como fumar o estar expuesto al amianto.

Además, cuando los datos disponibles lo permitieron, se llevaron a cabo análisis separados para hombres y mujeres. En los casos en que se observó una alta heterogeneidad entre los resultados de diferentes estudios, se realizaron análisis de sensibilidad eliminando un estudio a la vez y se exploraron posibles factores explicativos, como la dosis, el tiempo de tratamiento o la duración del seguimiento (96).

4.2 ESTUDIO 2. VACUNAS TERAPÉUTICAS PARA EL CÁNCER AVANZADO DE PULMÓN DE CÉLULAS NO PEQUEÑAS (Revisión Sistemática)

En la siguiente revisión sistemática Cochrane, cuyo objetivo fue evaluar la eficacia y seguridad de diferentes tipos de vacunas terapéuticas para personas con cáncer de pulmón de células no pequeñas avanzado (97), se llevó a cabo de acuerdo con el protocolo previamente publicado (53).

Estrategia de búsqueda y selección de estudios

Se realizaron búsquedas en CENTRAL, MEDLINE, Embase, Wanfang Data y China Journal Net (CNKI) hasta el 22 de agosto de 2023 (97). Además, se revisaron las listas de referencias de los estudios incluidos para identificar otros ensayos clínicos primarios. Se llevaron a cabo búsquedas en literatura gris y resúmenes de conferencias, incluyendo la Sociedad Estadounidense de Oncología Clínica (ASCO; www.asco.org), la Sociedad Europea de Oncología Médica (ESMO; www.esmo.org), la Asociación Americana para la Investigación del Cáncer (AACR;

www.aacr.org/Meetings/Pages/MeetingDetail.aspx) y el congreso sobre Inmunología e Inmunoterapia de Tumores y Cáncer (tumorimmunology.conferenceseries.com/) (97). También se buscaron erratas o retractaciones relacionadas con los ensayos incluidos, conforme a las orientaciones del Capítulo 4 del Manual Cochrane para Revisiones Sistemáticas de Intervenciones (73).

Se incluyeron ensayos controlados aleatorizados de grupos paralelos que evaluaron una vacuna terapéutica contra el cáncer, ya sea de forma aislada o en combinación con otros tratamientos, en adultos mayores de 18 años con NSCLC avanzado, sin importar la línea de tratamiento. No se incluyeron ensayos aleatorios grupales ni cuasi aleatorios (97). Los resultados primarios evaluados fueron: supervivencia global, supervivencia libre de progresión y eventos adversos graves relacionados con el tratamiento (97, 74, 75). Los resultados secundarios incluyeron las tasas de supervivencia a tres y cinco años, así como la calidad de vida relacionada con la salud (CVRS), medida mediante el EORTC QLQ-C30 (97, 76-79).

Evaluación de la calidad de los estudios y extracción de datos

En cuanto a la evaluación de la calidad de los estudios y la extracción de datos, cuatro revisores trabajaron de manera independiente para recopilar y analizar la información utilizando métodos y procedimientos metodológicos estándar establecidos por Cochrane (80). Se evaluaron todos los estudios potencialmente elegibles para su inclusión, sin considerar el idioma de publicación. Se utilizó Covidence [programa informático] para el cribado de títulos, resúmenes y textos completos (81). Se contactó a los autores de los estudios cuando fue necesario. Además, se elaboró un diagrama de flujo PRISMA para representar gráficamente el proceso (82).

Cuatro autores de la revisión extrajeron de manera independiente la información clínica y metodológica. Las discrepancias se resolvieron mediante consenso o consultando a otro autor de la revisión. En caso de que los informes no proporcionaran información adecuada o suficiente, se contactó a los autores del estudio para solicitar información adicional. Se evaluó el riesgo de sesgo en los estudios incluidos utilizando la herramienta Cochrane de riesgo de sesgo (RoB 1), tal como se describe en el Manual Cochrane para Revisiones Sistemáticas de Intervenciones (83). Para cada dominio de riesgo de sesgo, se asignó una calificación de bajo, poco claro o alto riesgo de sesgo, según las siguientes definiciones:

¿Se generó adecuadamente la secuencia de asignación?
¿Se ocultó adecuadamente la asignación?
¿El conocimiento sobre la intervención asignada fue adecuado?
¿Se abordaron adecuadamente los datos de resultados incompletos?
¿Los informes del estudio estuvieron libres de sesgos de selección?
¿Existieron otras fuentes potenciales de sesgo?

Se completó una tabla de riesgo de sesgo para cada estudio incluido y se resumieron los riesgos de sesgo entre los estudios, conforme a lo recomendado en el Capítulo 8 del Manual Cochrane para Revisiones Sistemáticas de Intervenciones (84).

Medidas del efecto del tratamiento.

Para evaluar la supervivencia general y la supervivencia libre de progresión, se midió el tiempo transcurrido hasta el evento utilizando el Hazard Ratio (HR) con un intervalo de confianza (IC) del 95%. Se extrajeron los HR y los errores estándar de los datos reportados o se estimaron a partir de otros datos o gráficos cuando fue posible (85). Se calcularon las proporciones de participantes que sobrevivieron a tres y cinco años, así como los porcentajes de participantes que experimentaron al menos un evento adverso grave, utilizando el Riesgo Relativo (RR) con un intervalo de confianza (IC) del 95%. Además, se aplicaron las diferencias de medias estandarizadas (SMD) para medidas que emplean diferentes escalas (85). En esta revisión se incluyeron únicamente ensayos aleatorios de grupos paralelos como unidad de análisis; por lo tanto, no se consideraron ensayos aleatorios grupales ni ensayos cruzados. Cuando los ensayos incluían múltiples comparaciones de intervenciones, se siguieron enfoques metodológicos estándar, tal como se recomienda en el capítulo 23 del Manual Cochrane para Revisiones Sistemáticas de Intervenciones (86).

Para abordar los datos faltantes, se estableció comunicación con los investigadores o patrocinadores del estudio. Con el fin de obtener los datos adicionales necesarios para el metaanálisis, se intentó estimar los valores a partir de los datos reportados (por ejemplo, estimar los Hazard ratios [HR] a partir de las curvas de supervivencia publicadas) (85). Para evaluar la heterogeneidad, se utilizó el estadístico I^2, cuyo valor se interpretó según los siguientes umbrales (87): una heterogeneidad del 0% al 40% podría no ser importante; del 30% al 60% puede representar una heterogeneidad moderada; del 50% al 90%, heterogeneidad sustancial; y del 75% al 100%, heterogeneidad considerable. Se investigó la heterogeneidad sustancial ($I^2 > 50\%$) mediante análisis de subgrupos pre especificados. Para la síntesis de datos, se empleó un metaanálisis para combinar los tamaños del efecto individual,

analizando los datos de cada comparación y sus resultados combinados con intervalos de confianza (IC) del 95%, utilizando RevMan Web 2022 [programa informático], mediante un modelo de efectos aleatorios (88). Se planificó realizar un análisis de subgrupos según las siguientes características clínicas: estadio clínico (III o IV), sexo de los participantes, tipo histológico del NSCLC (escamoso versus no escamoso), intervalo de tiempo entre la línea de tratamiento anterior y el inicio de la terapia con vacunas (tres, seis o doce meses), y estado funcional según el Eastern Cooperative Oncology Group (ECOG) (0 versus 1, o 0-1 versus 2) (89, 90).

No se realizó un análisis de subgrupos en dos situaciones: cuando las vacunas terapéuticas incluidas en esta revisión fueron evaluadas en un único ensayo clínico aleatorizado (ECA) y cuando el número final de participantes en los subgrupos era demasiado reducido, lo que no garantizaba un poder estadístico suficiente. Se llevó a cabo un análisis de sensibilidad para explorar la influencia sobre el tamaño del efecto, excluyendo estudios no publicados y aquellos de menor calidad (es decir, aquellos con alto riesgo de sesgo).

Se elaboraron tablas resumen de hallazgos utilizando los métodos y recomendaciones descritos en el Manual de uso del software GRADEpro GDT (91, 92). Se presentaron las tablas resumen de los hallazgos separado tanto para TG4010 y el factor de crecimiento epidérmico, dado que ambas vacunas fueron evaluadas en términos de eficacia y seguridad en dos ECAs cada una, y estos fueron lo suficientemente similares. Se incluyeron los siguientes resultados: supervivencia global, supervivencia libre de progresión, eventos adversos graves relacionados con el tratamiento, tasas de supervivencia a tres y cinco años, así como calidad de vida relacionada con la salud. Al evaluar la certeza de la evidencia por imprecisión, se consideró una mejora clínicamente relevante según el

cuestionario EORTC QLQ-C30 (93). Para la evaluación funcional del cáncer, se utilizó el cuestionario Therapy-Lung (FACT-L) (94). Cuando no fue posible la agregación de datos, se presentaron los resultados de estudios individuales en forma narrativa y se discutieron en el texto.

4.3 ESTUDIO 3. TRATAMIENTOS PARA EL CÁNCER DE PULMÓN DE CÉLULAS NO PEQUEÑAS: UNA EVALUACIÓN SISTEMÁTICA DE LA CALIDAD DE LAS GUÍAS DE PRÁCTICA CLÍNICA

El tercer estudio tuvo como objetivo evaluar la calidad metodológica de las guías de práctica clínica (GPC) que incluyen recomendaciones sobre tratamientos para el cáncer de pulmón de células no pequeñas (98).

Estrategia de búsqueda y selección de estudios

Se llevaron a cabo búsquedas en MEDLINE (a través de PubMed), así como en sitios web de desarrolladores de GPC, sociedades especializadas en cáncer de pulmón y organizaciones de oncología, con el fin de identificar GPC que proporcionan recomendaciones sobre tratamientos para el cáncer de pulmón de células no pequeñas. La última búsqueda se realizó el 6 de octubre de 2022 (98).

Los criterios de elegibilidad incluyeron GPC que ofrecieran recomendaciones para el manejo del carcinoma pulmonar no microcítico (NSCLC) primario o metastásico en personas mayores o iguales a 18 años. Las GPC debían contar con un capítulo metodológico explícito y describir cómo se formularon sus recomendaciones, tener una fecha de publicación dentro de los últimos 10 años, estar redactadas

en inglés o español, y presentar la versión más actualizada disponible. Se excluyeron las adaptaciones de GPC, así como aquellas que habían sido retractadas o archivadas por sus desarrolladores (98).

Evaluación de la calidad de los estudios y extracción de datos

La calidad metodológica de cada GPC fue determinada de forma independiente por tres evaluadores utilizando el instrumento Appraisal of Guidelines for Research and Evaluation II (AGREE II), que midió la calidad de cada GPC considerando 6 dominios: a) alcance y finalidad; b) participación de las partes interesadas; c) rigor del desarrollo; d) claridad de presentación; e) aplicabilidad; y f) independencia editorial (95).

Extracción y Análisis de datos

Se extrajeron datos sobre las características generales de cada GPC como título, año de publicación, organización autor, país, idioma, nivel de desarrollo, fuente de financiación, si se trataba o no de una actualización, métodos utilizados para formular las recomendaciones, nivel de evidencia y clasificación de las recomendaciones. Este proceso se llevó a cabo de forma independiente por dos autores. Las discrepancias se resolvieron por consenso y con la participación de un tercer autor si era necesario (98). Se realizó un análisis descriptivo de estas características utilizando tablas y una narrativa de síntesis. Los análisis estadísticos fueron realizados con el software SPSS® versión 27.0 (SPSS Inc. Chicago, IL) (98).

Inicialmente, se calculó el coeficiente Inter clase (ICC) con su intervalo de confianza del 95%, como indicador de concordancia entre evaluadores. Posteriormente se calcularon los puntajes de los dominios sumando todas las puntuaciones de los elementos individuales dentro de un dominio y se calculó el porcentaje de la puntuación máxima posible para ese dominio (98). Se calcularon las puntuaciones estandarizadas (rango, 0 % a 100 %) para cada dominio [(puntuación obtenida − puntuación mínima posible) / (puntuación máxima posible − puntuación mínima posible)] × 100%. Se asumió un umbral del 60% como indicador de calidad adecuada. Los valores de Mediana y mínimo-máximo, se calcularon para cada dominio y para cada GPC. Además, para determinar si la calidad metodológica de la GPC había mejorado en los últimos años, se compararon los puntajes de AGREE II con las GPC recientes (publicadas en los últimos 5 años) y GPC no recientes (publicadas antes del 2018) utilizando la prueba U de Mann-Whitney, con un nivel de significancia de 0,05 (98).

5. RESULTADOS

Los resultados de esta tesis doctoral corresponden a cada estudio realizado, los cuales han sido publicados en revistas científicas internacionales (96, 97, 98).

PUBLICACIONES CIENTÍFICAS QUE COMPRENDEN ESTE DOCTORADO

Publicación 1. Cortés-Jofré M, Rueda JR, Asenjo-Lobos C, Madrid E, Bonfill Cosp X. Drugs for preventing lung cancer in healthy people. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD002141. DOI: 10.1002/14651858.CD002141.pub3 (96).

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Publicación 2. Cortés-Jofré M, Rueda-Etxebarria M, Orillard E, Jimenez Tejero E, Rueda J-R. Therapeutic vaccines for advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews 2024, Issue 3. Art. No.: CD013377. DOI: 10.1002/14651858.CD013377.pub2 (97).

FI: 8, 4 (2024); Q1

Publicación 3. Cortés-Jofré M, Madera M, Tirado-Amador L, Asenjo-Lobos C, Bonfill-Cosp X. Treatments for non-small cell lung cancer: a systematic quality assessment of clinical practice guidelines. Clin Transl Oncol. 2023 May 30. doi: 10.1007/s12094-023-03223-4. Epub ahead of print. PMID: 37254015 (98).

FI: 2. 8 (2023); Q2

5.1 Publicación 1. Cortés-Jofré M, Rueda JR, Asenjo-Lobos C, Madrid E, Bonfill Cosp X. Drugs for preventing lung cancer in healthy people. Cochrane Database of Systematic Reviews 2020, Issue 3. Art. No.: CD002141. DOI: 10.1002/14651858.CD002141.pub3.

5.1.1 Resumen de los Resultados

En esta actualización de una RS previa (69), se identificaron tres ensayos nuevos para un total de 12 estudios. Seis analizaron vitamina A, tres estudios con vitamina C, tres combinados vitamina D3 + calcio, cuatro con vitamina E combinada con otros productos, uno suplementos de selenio y nueve estudiaron combinaciones de dos o más productos. Cuatro estudios incluyeron sólo hombres y cinco sólo mujeres (96).

La vitamina A produce poca o ninguna diferencia en la incidencia del cáncer de pulmón (RR 1,09; IC del 95%: 1,00 a 1,19; cinco ECA, 212314 participantes; evidencia de certeza alta) y la mortalidad por cáncer de pulmón (RR 1,06; IC del 95%: 0,81 a 1,38; tres ECA, 190118 participantes; evidencia de certeza alta) (96). Pero en los fumadores o trabajadores del asbesto, la vitamina A aumenta el riesgo de incidencia de cáncer de pulmón (RR 1,10; IC del 95%: 1,01 a 1,20; tres ECA, 43995 participantes; evidencia de certeza alta), mortalidad por cáncer de pulmón (RR 1,18; IC del 95%: 1,01 a 1,38; dos ECA, 29426 participantes; evidencia de certeza alta) y mortalidad por todas las causas (RR 1,09; IC del 95%: 1,05 a 1,13; dos ECA, 32883 participantes; evidencia de certeza alta) (96). La vitamina A aumenta el riesgo de efectos secundarios menores, como color amarillento de la piel y síntomas gastrointestinales menores (evidencia de certeza alta) (96).

Es probable que la vitamina C produzca poca o ninguna diferencia en la incidencia del cáncer de pulmón (RR 1,29; IC del 95%: 0,67 a 2,49; dos ECA, 14953 participantes; evidencia de certeza moderada) (96). En las mujeres, la vitamina C aumenta el riesgo de incidencia de cáncer de pulmón (RR 1,84; IC del 95%: 1,14 a 2,95; un ECA, 7627 participantes; evidencia de certeza alta) (96). En los hombres, la vitamina C produce poca o ninguna diferencia en la mortalidad por cáncer de pulmón (RR 0,81; IC del 95%: 0,53 a 1,23; un ECA, 7326 participantes; evidencia de certeza alta) (96).

La vitamina D + calcio puede dar lugar a poca o ninguna diferencia en la incidencia del cáncer de pulmón en mujeres posmenopáusicas (RR 0,90; IC del 95%: 0,39 a 2,08; tres ECA, 37 601 mujeres; evidencia de certeza baja) (96).

La vitamina E produce poca o ninguna diferencia en la incidencia del cáncer de pulmón (RR 1,01; IC del 95%: 0,90 a 1,14; tres ECA, 36 841 participantes; evidencia de certeza alta) o en la mortalidad por cáncer de pulmón (RR 0,96; IC del 95%: 0,77 a 1,18; dos ECA, 29214 participantes; evidencia de certeza alta), pero aumenta el riesgo de accidentes cerebrovasculares hemorrágicos (cociente de riesgos instantáneos [CRI] 1,74; IC del 95%: 1,04 a 2,91; un ECA, 14641 participantes; evidencia de certeza alta) (96).

El calcio produce poca o ninguna diferencia en la incidencia de cáncer de pulmón en mujeres posmenopáusicas (RR 0,65; IC del 95%: 0,13 a 3,18; un ECA, 733 participantes) o en el riesgo de cálculos renales (RR 1,94; IC del 95%: 0,20 a 18,57; un ECA, 733 participantes; evidencia de certeza baja) (96).

El selenio en los hombres produce poca o ninguna diferencia en la incidencia del cáncer de pulmón (RR 1,11; IC del 95%: 0,80 a 1,54; un ECA, 17448 participantes; evidencia de certeza alta) y la mortalidad por cáncer de pulmón (RR 1,09; IC del 95%: 0,72 a 1,66; 1 ECA, 17 448 participantes; evidencia de certeza alta) pero aumenta el riesgo de dermatitis de grado 1 a 2 (RR 1,16; IC del 95%: 1,04 a 1,31; 1 ECA, 17 448 participantes; evidencia de certeza alta) y de alopecia (RR 1,28, IC del 95%: 1,07 a 1,53; un ECA, 17448 participantes; evidencia de certeza alta) (96).

La combinación de vitaminas A, C, E + selenio + zinc produce poca o ninguna diferencia en la incidencia del cáncer de pulmón (RR 0,64; IC del 95%: 0,28 a 1,48; un ECA, 12741 participantes; evidencia de certeza alta) (96).

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[Intervention Review]

Drugs for preventing lung cancer in healthy people

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ABSTRACT

Background

This is the second update of this Cochrane Review. Some studies have suggested a protective effect of antioxidant nutrients and higher dietary levels of fruits and vegetables on lung cancer.

Objectives

To determine whether vitamins and minerals and other potential agents, alone or in combination, reduce lung cancer incidence and lung cancer mortality in healthy populations.

Search methods

We searched CENTRAL, MEDLINE and Embase from 1974 to May 2019 and screened references included in published studies and reviews.

Selection criteria

We included randomised controlled trials (RCTs) comparing vitamins or mineral supplements with placebo, administered to healthy people with the aim of preventing lung cancer.

Data collection and analysis

Four review authors independently selected the trials to be included in the review, assessed their methodological quality and extracted data. For dichotomous outcomes we calculated risk ratios (RRs) and 95% confidence intervals (CIs) and pooled results using the random-effects model. We assessed the risk of bias using Cochrane's 'Risk of bias' assessment tool and certainty of evidence using the GRADE approach.

Main results

In this update, we identified three new trials for a total of 12 studies. Six analysed vitamin A, three vitamin C, three combined vitamin D3 + calcium, four vitamin E combined with other products, one selenium supplements and nine studied combinations of two or more products. Four studies included only men and five only women.

Vitamin A results in little to no difference in lung cancer incidence (RR 1.09, 95% CI 1.00 to 1.19; 5 RCTs, 212314 participants; high-certainty evidence) and lung cancer mortality (RR 1.06, 95% CI 0.81 to 1.38; 3 RCTs, 190118 participants; high-certainty evidence). But in smokers or asbestos workers vitamin A increases the risk of lung cancer incidence (RR 1.10, 95% CI 1.01 to 1.20; 3 RCTs, 43995 participants; high-

certainty evidence), lung cancer mortality (RR 1.18, 95% CI 1.01 to 1.38; 2 RCTs, 29426 participants; high-certainty evidence) and all-cause mortality (RR 1.09, 95% CI 1.05 to 1.13; 2 RCTs, 32883 participants; high-certainty evidence). Vitamin A increases the risk of minor side effects, such as yellowing of the skin and minor gastrointestinal symptoms (high-certainty evidence).

Vitamin C likely results in little to no difference in lung cancer incidence (RR 1.29, 95% CI 0.67 to 2.49; 2 RCTs, 14953 participants; moderate-certainty evidence). In women, vitamin C increases the risk of lung cancer incidence (RR 1.84, 95% CI 1.14 to 2.95; 1 RCT, 7627 participants; high-certainty evidence). In men, vitamin C results in little to no difference in mortality for lung cancer (RR 0.81, 95% CI 0.53 to 1.23; 1 RCT, 7326 participants; high-certainty evidence).

Vitamin D + calcium may result in little to no difference in lung cancer incidence in postmenopausal women (RR 0.90, 95% CI 0.39 to 2.08; 3 RCTs, 37601 women; low-certainty evidence).

Vitamin E results in little to no difference in lung cancer incidence (RR 1.01, 95% CI 0.90 to 1.14; 3 RCTs, 36841 participants; high-certainty evidence) or to lung cancer mortality (RR 0.96, 95% CI 0.77 to 1.18; 2 RCTs, 29214 participants; high-certainty evidence), but increases the risk of haemorrhagic strokes (hazard ratio (HR), 1.74, 95% CI 1.04 to 2.91; 1 RCT, 14641 participants; high-certainty evidence).

Calcium results in little to no difference in lung cancer incidence in postmenopausal women (RR 0.65, 95% CI 0.13 to 3.18; 1 RCT, 733 participants) or in risk of renal calculi (RR 1.94, 95% CI 0.20 to 18.57; 1 RCT, 733 participants; low-certainty evidence).

Selenium in men results in little to no difference in lung cancer incidence (RR 1.11, 95% CI 0.80 to 1.54; 1 RCT, 17448 participants; high-certainty evidence) and lung cancer mortality (RR 1.09, 95% CI 0.72 to 1.66; 1 RCT, 17448 participants; high-certainty evidence) and increases the risk for grade 1 to 2 dermatitis (RR 1.16, 95% CI 1.04 to 1.31; 1 RCT, 17448 participants; high-certainty evidence) and for alopecia (RR 1.28, 95% CI 1.07 to 1.53; 1 RCT, 17448 participants; high-certainty evidence).

The combination of vitamins A, C, E + selenium + zinc results in little to no difference in lung cancer incidence (RR 0.64, 95% CI 0.28 to 1.48; 1 RCT, 12741 participants; high-certainty evidence).

Authors' conclusions

Well-designed RCTs have shown no beneficial effect of supplements for the prevention of lung cancer and lung cancer mortality in healthy people. Vitamin A supplements increase lung cancer incidence and mortality in smokers or persons exposed to asbestos. Vitamin C increases lung cancer incidence in women. Vitamin E increases the risk of haemorrhagic strokes.

PLAIN LANGUAGE SUMMARY

Drugs for preventing lung cancer in healthy people

Review question

We reviewed the evidence assessing the relationship between vitamins or antioxidant intake and lung cancer prevention, mortality and adverse events for that cancer. This review updates our Cochrane Review on this topic published in 2012.

Background

Lung cancer is among the leading causes of cancer death throughout the world, and its prevention has become a public health priority. It has been suggested that vitamin supplements and some antioxidants may prevent lung cancer.

Study characteristics

This review includes 12 studies in which healthy adults were randomly assigned to receive vitamin supplements or placebo (a substance that has no physical effects) and were followed over time to evaluate their risk of developing lung cancer. The evidence is current to May 2019.

Key results

None of the treatments compared with placebo have shown a difference in the risk for lung cancer incidence or lung cancer mortality in healthy people. In smokers and people exposed to asbestos, vitamin A increases lung cancer incidence, lung cancer mortality and all-cause mortality. Vitamin C increases lung cancer incidence in women. Vitamin E increases the risk of haemorrhagic strokes.

The certainty of the evidence is high for the following comparisons against placebo: vitamin A; vitamin E; selenium; and combinations of vitamins A, C, E, selenium and zinc.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Vitamin A compared to placebo for preventing lung cancer in healthy people

Vitamin A compared to placebo for preventing lung cancer in healthy people

Patient or population: healthy people and healthy male physicians
Setting: outpatients
Intervention: vitamin A
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin A				
Incidence: lung cancer	Study population		RR 1.09 (1.00 to 1.19)	212314 (5 RCTs)	⊖⊖⊖⊖ High	Subgroup analysis shows increase in risk of lung cancer incidence in smokers and asbestos workers taking vitamin A
	9 per 1000	9 per 1000 (9 to 10)				
Mortality: lung cancer	Study population		RR 1.06 (0.81 to 1.38)	190118 (3 RCTs)	⊖⊖⊖⊖ High	Subgroup analysis shows increase in risk of lung cancer mortality in smokers and asbestos workers taking vitamin A
	3 per 1000	4 per 1000 (3 to 5)				
Adverse events: yellowing of the skin	Study population		RR 1.14 (1.07 to 1.21)	22071 (1 RCT)	⊖⊖⊖⊖ High	
	139 per 1000	159 per 1000 (149 to 168)				
Adverse events: minor gastrointestinal symptoms	Study population		RR 2.22 (1.80 to 2.74)	22071 (1 RCT)	⊖⊖⊖⊖ High	
	11 per 1000	25 per 1000 (20 to 31)				
Incidence: all cancers	Study population		RR 1.02 (0.97 to 1.07)	44267 (3 RCTs)	⊖⊖⊖⊖ High	
	132 per 1000	135 per 1000 (128 to 142)				
Mortality: all cancers	Study population		RR 1.02	22071	⊖⊖⊖⊖ High	

	34 per 1000	35 per 1000 (30 to 61)	(0.88 to 1.77)	(1 RCT)	
Mortality: all causes - smokers and asbestos workers	Study population 226 per 1000	246 per 1000 (237 to 255)	RR 1.09 (1.05 to 1.13)	32883 (2 RCTs)	⊕⊕⊕⊕ High

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

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 2. Vitamin C compared to placebo for preventing lung cancer in healthy people

Vitamin C compared to placebo for preventing lung cancer in healthy people

Patient or population: healthy male physicians, period: 1997 to 2007 and female health professionals, period: 1998 to 2005
Setting: outpatients
Intervention: vitamin C
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin C				
Incidence: lung cancer	Study population 11 per 1000	14 per 1000 (7 to 26)	RR 1.29 (0.67 to 2.49)	14953 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Incidence: lung cancer - men	Study population 15 per 1000	14 per 1000	RR 0.94 (0.64 to 1.38)	7326 (1 RCT)	⊕⊕⊕⊕ High	

		(9 to 20)				
Incidence: lung cancer - women	Study population		RR 1.84 (1.14 to 2.95)	7627 (1 RCT)	⊖⊖⊖⊖ High	
	7 per 1000	13 per 1000 (8 to 20)				
Mortality: lung cancer - men	Study population		RR 0.81 (0.53 to 1.23)	7326 (1 RCT)	⊖⊖⊖⊖ High	
	13 per 1000	11 per 1000 (7 to 16)				
Adverse events	Study population		Not available	1 RCT	⊖⊖⊖⊖ High	Numeric data not provided, but one study reported that there were no significant effects of either agent on minor bleeding or gastrointestinal tract symptoms, fatigue, drowsiness, skin discolouration, rashes, or migraine
	Not available	Not available				
Incidence: all cancers	Study population		RR 1.03 (0.94 to 1.13)	14953 (2 RCTs)	⊖⊖⊖⊖ High	
	170 per 1000	175 per 1000 (159 to 192)				
Mortality: all cancers	Study population		RR 1.11 (0.93 to 1.34)	14953 (2 RCTs)	⊖⊖⊖⊖ High	
	45 per 1000	49 per 1000 (41 to 60)				

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

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to inconsistency: high heterogeneity (I^2 = 78%).

Summary of findings 3. Vitamin D plus calcium compared to placebo for preventing lung cancer in healthy people

Vitamin D plus calcium compared to placebo for preventing lung cancer in healthy people

Patient or population: healthy postmenopausal women
Setting: outpatients
Intervention: vitamin D plus calcium
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin D plus calcium				
Incidence: lung cancer	Study population 7 per 1000	6 per 1000 (3 to 15)	RR 0.90 (0.39 to 2.08)	37061 (3 RCTs)	⊕⊕⊖⊖ Low [a, b]	
Mortality: lung cancer	Study population Not available	Not available	Not available	Not available		The studies did not evaluate this outcome.
Adverse events: renal calculi	Study population 8 per 1000	12 per 1000 (6 to 25)	RR 1.49 (0.70 to 3.17)	2931 (2 RCTs)	⊕⊕⊕⊖ Moderate [a]	
Adverse events: serum calcium above normal	Study population 2 per 1000	5 per 1000 (1 to 27)	RR 2.98 (0.60 to 14.74)	2197 (1 RCT)	⊕⊕⊖⊖ Low [a, b]	
Incidence: all cancers	Study population 76 per 1000	55 per 1000 (36 to 84)	RR 0.73 (0.48 to 1.11)	37061 (3 RCTs)	⊕⊕⊖⊖ Low [a, c]	
Mortality: all cancers	Study population		RR 0.91	34670	⊕⊕⊕⊖ Moderate [a]	

	20 per 1000	18 per 1000 (16 to 21)	(0.78 to 1.05)	(1 RCT)	
Mortality: all causes	Study population Not available	Not available	Not available	Not available	The studies did not evaluate this outcome.

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

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to two of the studies not providing information on several areas of risk of bias.
[b] Downgraded one level due to imprecision: very wide confidence interval.
[c] Downgraded one level due to high heterogeneity: I^2 = 77%.

Summary of findings 4. Vitamin E compared to placebo for preventing lung cancer in healthy people

Vitamin E compared to placebo for preventing lung cancer in healthy people

Patient or population: healthy people
Setting: outpatients
Intervention: vitamin E
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin E				
Incidence: lung cancer	Study population 30 per 1000	30 per 1000 (27 to 34)	RR 1.01 (0.90 to 1.14)	36841 (3 RCTs)	⊕⊕⊕⊕ High	

Mortality: lung cancer	Study population 12 per 1000	12 per 1000 (9 to 14)	RR 0.96 (0.77 to 1.18)	29214 (2 RCTs)	⊕⊕⊕⊕ High	
Adverse events: haemorrhagic stroke	Study population 3 per 1000	5 per 1000 (3 to 9)	HR 1.74 (1.04 to 2.91)	14641 (1 RCT)	⊕⊕⊕⊕ High	Reported no significant effects on minor bleeding or gastrointestinal tract symptoms.
Incidence: all cancers	Study population 142 per 1000	140 per 1000 (133 to 147)	RR 0.99 (0.94 to 1.04)	36832 (3 RCTs)	⊕⊕⊕⊕ High	
Mortality: all cancers	Study population 19 per 1000	21 per 1000 (19 to 24)	RR 1.11 (0.99 to 1.24)	54517 (2 RCTs)	⊕⊕⊕⊕ High	
Mortality: all causes	Study population 117 per 1000	120 per 1000 (116 to 125)	RR 1.03 (0.99 to 1.07)	69090 (3 RCTs)	⊕⊕⊕⊕ High	

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

CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 5. Calcium compared to placebo for preventing lung cancer in healthy people

Calcium compared to placebo for preventing lung cancer in healthy people

Patient or population: white healthy postmenopausal women over 55 years
Setting: outpatients
Intervention: calcium
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with calcium				
Incidence: lung cancer - women	Study population 10 per 1000	7 per 1000 (1 to 33)	RR 0.65 (0.13 to 3.18)	733 (1 RCT)	⊕⊕⊖⊖ Low [a,b]	
Mortality: lung cancer	Study population Not available	Not available	Not available	Not available		The study did not evaluate this outcome.
Adverse events: renal calculi	Study population 3 per 1000	7 per 1000 (1 to 64)	RR 1.94 (0.20 to 18.57)	733 (1 RCT)	⊕⊕⊖⊖ Low [a,b]	
Incidence: all cancers	Study population 69 per 1000	38 per 1000 (20 to 72)	RR 0.55 (0.29 to 1.03)	733 (1 RCT)	⊕⊕⊖⊖ Low [a,b]	
Mortality: all cancers	Study population Not available	Not available	Not available	Not available		The study did not evaluate this outcome.
Mortality: all causes	Study population Not available	Not available	Not available	Not available		The study did not evaluate this outcome.

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

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to the study not providing information on several areas of risk of bias.
[b] Downgraded one level due to imprecision: very wide confidence interval.

Summary of findings 6. Selenium compared to placebo for preventing lung cancer in healthy people

Selenium compared to placebo for preventing lung cancer in healthy people

Patient or population: healthy men
Setting: outpatients
Intervention: selenium
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with selenium				
Incidence: lung cancer	Study population 8 per 1000	9 per 1000 (6 to 12)	RR 1.11 (0.80 to 1.54)	17448 (1 RCT)	⊕⊕⊕⊕ High	
Mortality: lung cancer	Study population 5 per 1000	5 per 1000 (3 to 8)	RR1.09 (0.72 to 1.66)	17448 (1 RCT)	⊕⊕⊕⊕ High	
Adverse events: alopecia	Study population 24 per 1000	30 per 1000 (25 to 36)	RR 1.28 (1.07 to 1.53)	17448 (1 RCT)	⊕⊕⊕⊕ High	
adverse events: grade 1 to 2 dermatitis	Study population 59 per 1000	69 per 1000	RR 1.16 (1.04 to 1.31)	17448 (1 RCT)	⊕⊕⊕⊕ High	

		(62 to 78)			
Incidence: all cancers	Study population		RR 1.01 (0.92 to 1.11)	17448 (1 RCT)	⊕⊕⊕⊕ High
	95 per 1000	96 per 1000 (87 to 105)			
Mortality: all cancers	Study population		RR 1.02 (0.80 to 1.30)	17448 (1 RCT)	⊕⊕⊕⊕ High
	14 per 1000	15 per 1000 (11 to 19)			
Mortality: all causes	Study population		RR 0.98 (0.86 to 1.13)	17448 (1 RCT)	⊕⊕⊕⊕ High
	44 per 1000	43 per 1000 (38 to 50)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 7. Vitamins A, C, E + selenium + zinc compared to placebo for preventing lung cancer in healthy people

Vitamins A, C, E + selenium + zinc compared to placebo for preventing lung cancer in healthy people

Patient or population: healthy women, aged 35 to 60, and men, aged 45 to 60, living in France
Setting: outpatients
Intervention: vitamins A, C, E + selenium + zinc
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamins A, C, E + selenium + zinc				

Incidence: lung cancer	Study population 2 per 1000	1 per 1000 (1 to 3)	RR 0.64 (0.28 to 1.48)	12741 (1 RCT)	⊕⊕⊕⊕ High	
Mortality: lung cancer	Study population Not available	Not available	Not available	Not available		The study did not evaluate this outcome.
Adverse events	Study population Not available	Not available	Not available	Not available		No adverse data published
Incidence: all cancers	Study population 80 per 1000	77 per 1000 (67 to 88)	RR 0.96 (0.83 to 1.10)	12741 (1 RCT)	⊕⊕⊕⊕ High	
Mortality: all cancers	Study population Not available	Not available	Not available	Not available		The study did not evaluate this outcome.
Mortality: all causes	Study population 28 per 1000	25 per 1000 (20 to 31)	RR 0.88 (0.70 to 1.11)	12741 (1 RCT)	⊕⊕⊕⊕ High	

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

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

BACKGROUND

This review is an update of a previously published Cochrane Review (Cortes-Jofre 2012).

Description of the condition

Lung cancer is one of the most prevalent and lethal cancers in the world. It is classified into two main subtypes, small cell lung cancer and non-small cell lung cancer, the latter representing approximately 85% of all cases (Rahal 2017).

Lung cancer is the leading cause of death from male cancer and the second-leading cause of death in women around the world (Marshall 2013). In 2015, the global incidence was 2 million cases (1.3 for men and 0.6 for women), and overall mortality in the same year recorded 1.7 million deaths (1.2 in men and 0.5 in women) (Global 2017).

Geographic variation in incidence often reflects the national distribution of poverty and access to medical care, reflecting large historical and continuing differences in the prevalence of smoking (Siegel 2017).

Faced with this scenario, and considering the low average survival rate at five years after diagnosis for people diagnosed at a late stage (16.3%) (Marshall 2013), prevention emerges as an important strategy, focusing on known risk factors, such as smoking and exposure to environmental carcinogens: asbestos, arsenic, radon and polycyclic aromatic hydrocarbons, that predispose individuals to the development of lung cancer (Raaschou-Nielsen 2013).

Advances in cell and molecular biology have increased understanding of the multiple events that lead to the development of lung cancer. The development of new technologies, such as genomic profiling and genome-wide association studies has been helpful in the detection of new genetic variants, likely involved in lung cancer risk (Marshall 2013; Qu 2016; Sakoda 2011).

Description of the intervention

Cancer chemoprevention is the inhibition or reversal of carcinogenesis by intervention with pharmacologically active agents (Penny 2015) Several micronutrients have attracted the attention of the scientific community as potential cancer-preventive agents and among them diet-derived antioxidants have been studied intensively because of the protection they convey against oxidative stress (Benetou 2015).

Thus dietary supplements are commonly used to prevent chronic diseases, mainly cardiovascular disease and cancer and their use has increased over time, notably in the USA. A recent survey found that 77% of the USA adult population uses dietary supplements, the most predominant being multi vitamin/multi mineral supplements (CRN 2019). There are significant differences in dietary supplement intake within Europe with more prevalence in Northern countries than in Southern countries (Schwingshackl 2015), with for example, 2% of Greek men compared to 66% of Danish women taking dietary supplements.

How the intervention might work

Free radicals can lead to the development of cancer and cardiovascular disease by lipid peroxidation and DNA damage. Reactive oxygen species are ions or small molecules containing oxygen and an unpaired electron, and this free electron confers high reactivity to oxygen. Redox imbalance is induced by disequilibrium between the production and suppression of reactive oxygen species. Excess of oxidative damage can be controlled by exogenous antioxidants such as vitamins C and E, polyphenols, carotenes, flavonoids, omega-3, and N-acetylcysteine. These exogenous antioxidants deactivate excited oxygen molecules and organic free radicals, and in this way decrease the oxidative damage through distinct mechanisms of action (Hamishehkar 2016; Prevatto 2017).

It has been recognised that diet and nutrients play an important role in the development and progression of cancer, and many components of the diet are associated with the risk of cancer. With respect to lung cancer, it has been found that a high intake of vegetables, fruits, fish and soy may reduce the risk, while red meat and processed meat can increase it (Yang 2012). However, almost all trials of clinical intervention with isolated nutrients, such as supplements of vitamin A, vitamin E, vitamin C, folic acid, selenium and carotenoids, have not been able to demonstrate their protective effects against lung cancer (Wang 2015). Also high-dose beta-carotene supplementation appears to increase the risk of lung cancer among current smokers (Tanvetyanon 2008).

Since different foods are consumed in combinations, and interact with each other in a complex way, an integral diet analysis may better reflect dietary habits and provides a constructive tool for evaluating the overall effects of the total diet on human health (Cho 2006; Gnagnarella 2013).

No consistent evidence has been found that vitamin supplements affect cancer or mortality from all causes in healthy individuals without known nutritional deficiencies because the "multivitamin" preparations contain unbalanced formulations. The beta-carotene (presumably all-trans) used in studies has never been shown to be a safe supplement (Dror 2014; Fortmann 2014).

A systematic review that includes an uncontrolled trial in participants with early-stage non-small cell lung cancer suggested that beta-carotene could modulate the expression of biomarkers such as cyclins; two trials did not show a significant effect on atypia and sputum bronchial cell metaplasia/dysplasia, also associated with lung cancer. In addition, an observational study found no correlation between serum retinol and oxo-dGuo leukocytes, a marker of DNA damage. In conclusion, the beta-carotene retinoid may be promising for use among a subset of people, and deserves further study (Fritz 2011).

On the other hand, combined healthy foods could also reduce the risk of lung cancer, through antioxidants, polyphenols, fibre and minerals that they contain; in addition, their interrelations could synergistically improve their individual protective effects as a whole. Recent studies have shown that the dietary pattern could affect the structure and metabolome of the human intestinal microbiome and may contribute to the health or pathogenesis of disorders such as coronary vascular disease and inflammatory bowel disease (Albenberg 2014). However, the general effects of different dietary patterns on human health are not clear and still require more research (Sun 2016).

Why it is important to do this review

Most people believe that even if vitamins are not effective, at least they are safe. But in spite of a variety of research studies into the cellular biologic function of vitamins and interesting messages about their roles on health, the long-term health consequences of vitamin consumption are unknown (Hamishehkar 2016).

Given the continuing cancer burden, the relatively low impact of proven cancer treatment strategies in reducing lung cancer mortality, and the possibility that food-based or other components may have chemopreventive properties, it is essential to evaluate the use of these agents. Our aim was to review the evidence for the effectiveness of chemoprevention in lung cancer in healthy people.

OBJECTIVES

To determine whether vitamins and minerals and other potential agents, alone or in combination, reduce lung cancer incidence and lung cancer mortality in healthy populations.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) comparing any eligible intervention with placebo.

Types of participants

Healthy men and women of all ages, independent of their smoking status or other risk factors for lung cancer.
Smokers and those exposed to asbestos are considered as people at high risk; people not known to have been exposed to such risk factors are considered as people at low risk.

Types of interventions

Dietary supplementation with specific vitamins, minerals (selenium, zinc or others) and other potential agents, natural or synthetic, such as retinoids, isothiocyanates, flavonoids, monoterpenes, or pharmaceuticals such as N-acetyl cysteine, alone or in combination, at any doses. Administration could be in capsule or tablet form, to be consumed orally.

In this review we assessed the following comparisons.

- Vitamin A (beta-carotene or retinol) versus placebo
- Vitamin C (ascorbic acid) versus placebo
- Vitamin D plus calcium versus placebo
- Vitamin D plus calcium versus calcium alone
- Vitamin E (alpha-tocopherol) versus placebo
- Calcium versus placebo
- Selenium versus placebo
- Vitamin A plus vitamin E versus placebo
- Vitamin C plus vitamin E versus placebo
- Vitamin E plus selenium versus placebo
- Vitamins A and E plus selenium versus placebo
- Vitamins A, C, E plus selenium plus zinc versus placebo

Types of outcome measures

We considered the following primary outcomes in this review.

- Lung cancer incidence
- Lung cancer mortality
- Adverse events

Since the role of the drugs included in this review could also have an impact on other cancers or diseases, we also considered the following secondary outcomes.

- Total cancer incidence
- Total cancer mortality
- Total mortality

Search methods for identification of studies

Electronic searches

For this update, Cochrane Lung Cancer Information Specialists redesigned our search strategies for the following three main databases.

- CENTRAL (Appendix 1)
- MEDLINE (Appendix 2)
- Embase (Appendix 3)

The search string for MEDLINE was developed according to the Cochrane Highly Sensitive Search Strategy, sensitivity maximising version (2008 version) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.b of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We searched the three databases from 1974 to 2 May 2019.

We also searched the following clinical trials registries for possible unpublished or ongoing trials:

- ClinicalTrials.gov.
- WHO International Clinical Trials Registry Platform (ICTRP).

Searching other resources

We also searched and screened published meta-analyses and recent reviews addressing the topic of our review for RCTs from 1983 to May 2019.

Data collection and analysis

Selection of studies

In this update, four review authors (MC-J, JRR, CA and EM) independently evaluated the titles and abstracts obtained from the electronic search. They examined the full-text of the provisionally included studies to determine if the study met the inclusion criteria. We resolved disagreements by discussion and consensus.

All of the included studies presented their results in several articles, and in some cases postintervention follow-up data are also available. For all studies we used the most recently published data for each relevant outcome variable.

Data extraction and management

As in the first published version of this review, in this update we used a standardised form designed for the purposes of this review

to collect data. The extracted data included details of the methods of randomisation, comparisons of interest, the number and type of people originally randomised in each arm of the study, the losses to follow-up and the results of interest of each arm of the study.

In this update of the review, three review authors (MC-J, CA and JRR) extracted data from the new included studies, and the most relevant information about the study is presented in the Characteristics of included studies section. The same three review authors also extracted and analysed the most recent postintervention follow-up data of the trials already included in the first published versions of this review.

Assessment of risk of bias in included studies

Three review authors (MC-J, CA and JRR) independently assessed the risk of bias for each study for the following domains:

- sequence generation,
- allocation concealment,
- blinding of participants and personnel,
- outcome assessment,
- incomplete outcome data,
- selective reporting.

We judged each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We judged the risk of bias for each domain according to the criteria defined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion and consensus.

Measures of treatment effect

For each study, we calculated risk ratios (RRs) and their 95% confidence intervals (CIs) for dichotomous outcomes. Where appropriate, we pooled results of comparable groups of trials, using the random-effects model.

Unit of analysis issues

The unit of analysis was the participant. We did not anticipate the possibility of cross-over trials or cluster trials for this topic.

Dealing with missing data

In case of missing or incomplete data, we tried to obtain it by writing to the interested authors. Authors who did not respond were sent a second letter and all but one provided the required additional information and data on their studies.

Assessment of heterogeneity

We tested heterogeneity between trials with the I^2 statistic. We interpreted the I^2 value according to the following thresholds (Higgins 2011): 0% to 40% heterogeneity might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. We investigated substantial heterogeneity ($I^2 > 50\%$) by prespecified subgroup analysis.

Assessment of reporting biases

We planned to generate funnel plots and to perform Egger's linear regression tests to investigate reporting biases for considered outcomes when the number of trials included in a single meta-analysis is sufficient (at least 10 trials). We followed recommendations provided in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

When sufficient clinically similar studies were available, we grouped their results into meta-analyses and performed meta-analyses based on an intention-to-treat (ITT) analysis when they were available.

We performed meta-analyses according to the recommendations contained in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For the meta-analyses, a review author (JR) entered data into Review Manager 5 (Review Manager 2014), and a second review author (MC-J) reviewed the data to verify its accuracy.

'Summary of findings' tables

We followed the GRADE approach by creating 'Summary of findings' tables, as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For each outcome we rated the certainty of the evidence according to one of the following categories: 'high', moderate', 'low', or 'very low', after assessing and taking into account: risk of bias of the studies, inconsistency of results, indirectness, imprecision and publication bias.

For this update, we added the following seven 'Summary of findings' tables.

- Vitamin A (beta-carotene or retinol) compared to placebo (Summary of findings for the main comparison).
- Vitamin C compared to placebo (Summary of findings 2).
- Vitamin D plus calcium compared to placebo (Summary of findings 3).
- Vitamin E (alpha-tocopherol) compared to placebo (Summary of findings 4).
- Calcium compared to placebo (Summary of findings 5).
- Selenium compared to placebo (Summary of findings 6).
- Vitamins A, C, E + selenium + zinc compared to placebo (Summary of findings 7).

Subgroup analysis and investigation of heterogeneity

When available, we performed subgroup analyses for high and low risk groups.

- High risk: those known to be smokers and/or those known to be exposed to occupational risk factors of lung cancer, such as asbestos.
- Low risk: those with no known risk factors for lung cancer, such as smoking or asbestos.

Also, when available data allowed it, we conducted separate analyses for men and women.

Subgroup analyses are presented in the Data and analyses section. However, in the Effects of interventions section, or in the 'Summary of findings' tables, we presented results combined for all subgroups and presented separate data for subgroups in cases where there is relevant statistical heterogeneity.

Sensitivity analysis

In cases in which there is high heterogeneity among results of different studies, we conducted sensitivity analyses by removing one study at a time, and explored possible factors to explain it (e.g. doses, time of treatment, or length of follow-up).

RESULTS

Description of studies

Results of the search

We screened 10431 references. We removed 2256 duplicated. We discarded 8120 records after reading titles and abstracts and we excluded 55 studies after full-text assessment.

We found three new studies to include in our review (Brunner 2011; Lappe 2007; Lappe 2017), for a total of 12 included studies.

See PRISMA flow diagram Figure 1.

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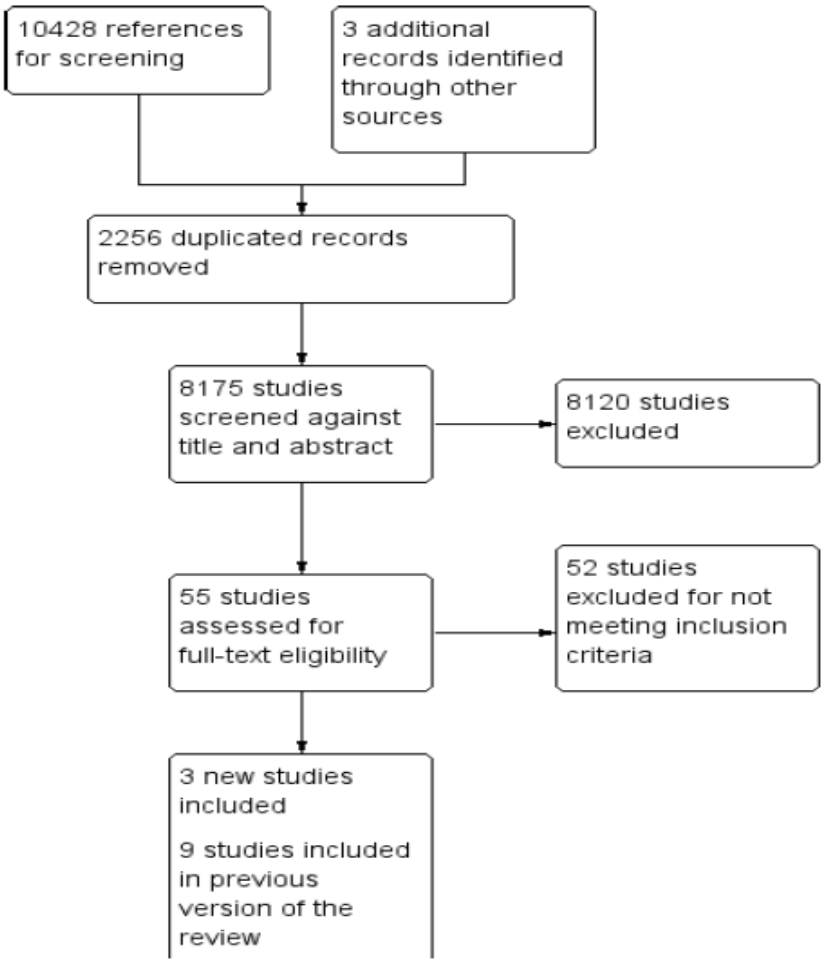
Figure 1. Bibliographic searches. Flow diagram of the selection of trial included in the meta-analysis.



Included studies

See Characteristics of included studies.

We included nine studies in the previous version of this review (ATBC 1994; Gaziano 2009; Hennekens 1996; Hercberg 2010; Kamangar 2006; Lee 2005; Lin 2009; Lippman 2009; Omenn 1996). In this new version, we included an additional three studies (Brunner 2011; Lappe 2007; Lappe 2017).

Only two of the trials were specifically designed to investigate the incidence of lung cancer as the primary outcome (ATBC 1994; Omenn 1996); most were looking primarily at the incidence of another cancer or all cancers.

Eight studies were conducted in the USA (Brunner 2011; Gaziano 2009; Hennekens 1996; Lappe 2007; Lappe 2017; Lee 2005, Lin 2009; Omenn 1996), one in the USA, Canada and Puerto Rico (Lippman 2009), one in China (Kamangar 2006), and two in Europe (ATBC 1994; Hercberg 2010).

Four studies included only men (ATBC 1994; Gaziano 2009; Hennekens 1996; Lippman 2009), and five only women (Brunner 2011; Lappe 2007; Lappe 2017; Lee 2005; Lin 2009). The age of participants at the start of treatment ranged from 35 to 84 years.

Two studies included only participants considered at high risk, namely smokers or those exposed to asbestos (ATBC 1994; Omenn 1996). One study included people deficient in many micronutrients (Kamangar 2006).

The type of supplements and doses varied across studies. Five studies analysed vitamin A, two vitamin C, three vitamin D3 plus calcium, five vitamin E, one selenium supplements, and nine studies were combinations of two or more products. Detailed data are presented in (Table 1).

The duration of treatments varied among the studies, ranging from two to 12 years and the length of follow-up ranged from six to 16 years (Table 2). Four studies were terminated prematurely: two of them when an interim analysis found a harmful effect associated with vitamins (beta-carotene + retinol) (ATBC 1994; Omenn 1996); another because the beta-carotene component was terminated early because of harmful results of an interim analysis in the Carotene and Retinol Efficacy Trial (CARET) (Lee 2005); and the fourth when the independent data and safety monitoring committee, after the second formal interim analysis (Lippman 2009), recommended the discontinuation of study supplements because the alternative hypothesis of no evidence of benefit from either study agent was convincingly demonstrated and there was no possibility of a benefit to the planned degree with additional follow-up (Table 2).

Excluded studies

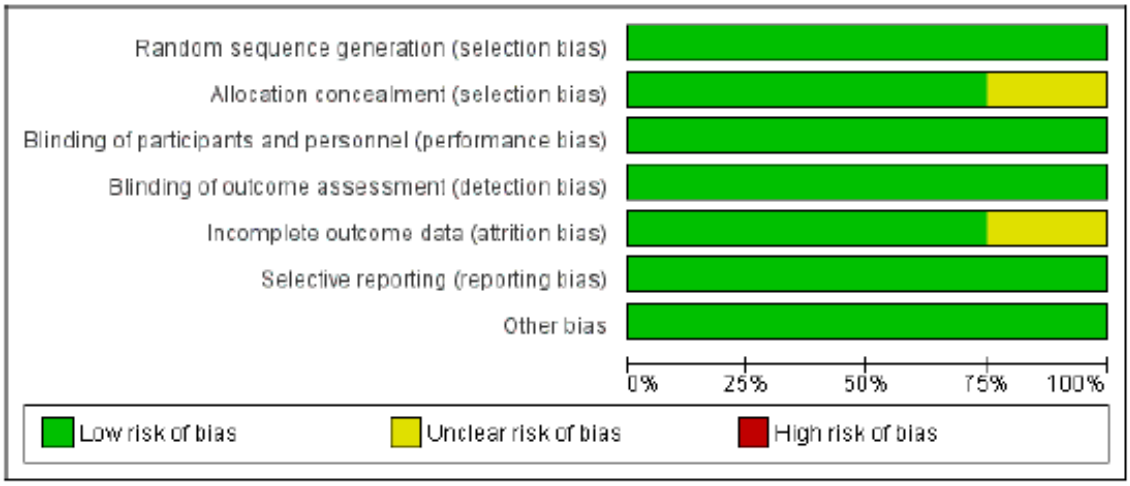
See Characteristics of excluded studies.

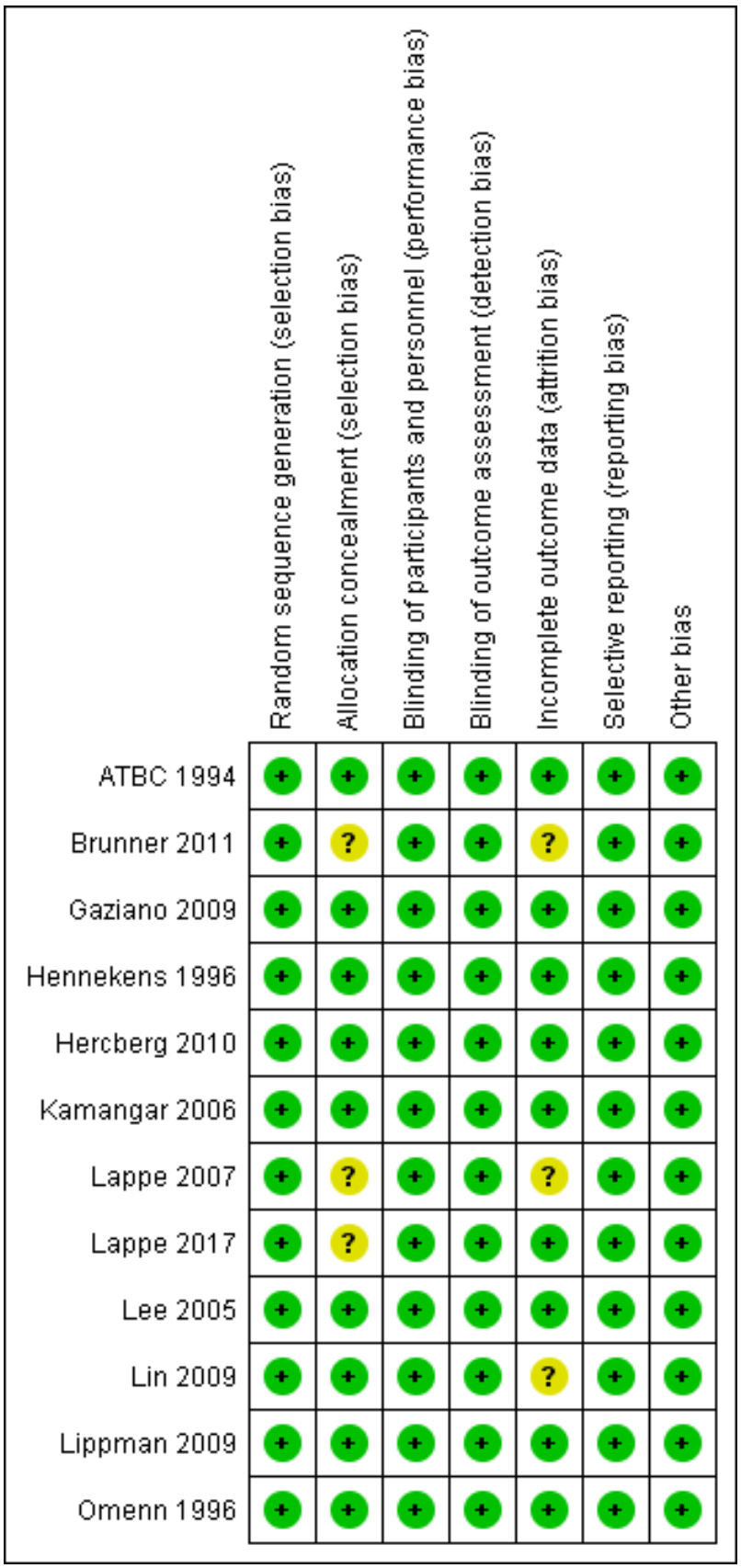
We excluded post-trial follow-up studies: Holick 2002, a cohort study from the ATBC 1994 Cancer Prevention Study; Wang 2014, a cohort study from the Physicians' Health Study II; Virtamo 2014, a cohort study from the ATBC Study; and Tao 2017, a cohort study from the Women's Health Initiative (WHI) calcium plus vitamin D supplementation (CaD) trial because they are observational studies. They commenced after the trials' planned period ended and the interventions (active compound or placebo) had stopped. Consequently, the comparison of the groups was uncontrolled, since participants were exposed to other factors (e.g. patient decisions, practice guidelines, etc.) that could introduce bias. Obtaining conclusions from a mixture of two different study designs could also compromise the validity of the results.

Risk of bias in included studies

We considered the risk of bias as low for eight of the included studies (ATBC 1994; Gaziano 2009; Hennekens 1996; Hercberg 2010; Kamangar 2006; Lee 2005; Lippman 2009; Omenn 1996). The remaining four studies did not provided information necessary for assessing the risk of bias in some domains. See individual and summarised results in Characteristics of included studies, Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
ATBC 1994
Brunner 2011
Gaziano 2009
Hennekens 1996
Hercberg 2010
Kamangar 2006
Lappe 2007
Lappe 2017
Lee 2005
Lin 2009
Lippman 2009
Omenn 1996

Allocation

We classified nine studies at low risk of allocation bias since all reported adequate random sequence generation procedures. The allocation concealment process can be considered adequate since allocation to treatment was done centrally. Three studies did not provided necessary information to assess concealment procedure (Brunner 2011; Lappe 2007; Lappe 2017).

Blinding

The risk of performance bias and detection bias was low in the included studies. Studies were double-blinded and those biases are unlikely since the primary outcomes of this review are incidence of cancer and mortality.

Incomplete outcome data

We classified nine studies as having a low risk of attrition bias. The risk was unclear for three studies because no information was provided on minimising attrition bias (Brunner 2011; Lappe 2017; Lin 2009). Only one study reported a relevant percentage of overall losses, but they were evenly distributed across the randomised groups (ATBC 1994).

Selective reporting

We considered the risk of bias from selective reporting to be low for all the included studies, since the studies reported all the outcomes stated as relevant in the protocols or methods' sections of the publications.

Other potential sources of bias

We considered the risk of bias for other potential sources of bias to be low for all the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Vitamin A compared to placebo for preventing lung cancer in healthy people; **Summary of findings 2** Vitamin C compared to placebo for preventing lung cancer in healthy people; **Summary of findings 3** Vitamin D plus calcium compared to placebo for preventing lung cancer in healthy people; **Summary of findings 4** Vitamin E compared to placebo for preventing lung cancer in healthy people; **Summary of findings 5** Calcium compared to placebo for preventing lung cancer in healthy people; **Summary of findings 6** Selenium compared to placebo for preventing lung cancer in healthy people; **Summary of findings 7** Vitamins A, C, E + selenium + zinc compared to placebo for preventing lung cancer in healthy people

Vitamin A (beta-carotene or retinol) versus placebo

Five studies compared vitamin A to placebo (ATBC 1994; Hennekens 1996; Kamangar 2006; Lin 2009; Omenn 1996).

Primary outcomes

Lung cancer incidence

The five studies, including 212314 people overall, evaluated the risk for lung cancer incidence in people taking vitamin A or placebo (ATBC 1994; Hennekens 1996; Kamangar 2006; Lin 2009; Omenn 1996). When pooling their results, a small increase in risk was observed (risk ratio (RR) 1.09, 95% confidence interval (CI) 1.00 to 1.19; I^2= 0%; 5 studies, 212314 participants; high-certainty evidence; Analysis 1.1; Summary of findings for the main comparison).

Data on lung cancer incidence for people at low risk were either available or provided by the authors for three studies (Hennekens 1996; Kamangar 2006; Lin 2009). There was no difference in risk between vitamin A and placebo (RR 0.99, 95% CI 0.69 to 1.42; I^2 = 7%; 3 studies, 168319 participants; high-certainty evidence; Analysis 1.1; Summary of findings for the main comparison).

Data on lung cancer incidence for people at high risk of developing lung cancer (smokers and those exposed to asbestos) were either available or provided by the authors of three studies (ATBC 1994; Hennekens 1996; Omenn 1996). In the high-risk group, vitamin A showed a higher risk for lung cancer incidence than placebo (RR 1.10, 95% CI 1.01 to 1.20, I^2 = 0%; 3 studies, 43995 participants Analysis 1.1).

Lung cancer mortality

Data on lung cancer mortality were either available or provided by the authors of three studies (ATBC 1994; Hennekens 1996; Kamangar 2006).

When pooling their results, no significant differences in risk were found between the groups (RR 1.06, 95% CI 0.81 to 1.38; I^2= 38%; 3 studies, 190118 participants; high-certainty evidence; Analysis 1.2; Summary of findings for the main comparison).

Considering the moderate statistical heterogeneity found, visual assessment of the forest plot shows that the results of Kamangar 2006 are different from the results of the other studies (see Analysis 1.2). When removing that study, the statistical heterogeneity fell to zero (I^2 = 0). The more distinctive feature of that study was that participants were deficient in many micronutrients.

Two studies provided data for people at low risk (Hennekens 1996; Kamangar 2006). There were no significant differences between vitamin A and placebo for lung cancer mortality (RR 0.71, 95% CI 0.35 to 1.44; I^2 = 20%; 2 studies, 160692 participants; high-certainty evidence; Analysis 1.2; Summary of findings for the main comparison).

Two studies provided data for people at high risk of developing lung cancer (ATBC 1994; Hennekens 1996). Those taking vitamin A had a higher risk for lung cancer mortality (RR 1.18, 95% CI 1.01 to 1.38, I^2 = 0%; 2 studies, 29426 participants Analysis 1.2).

Adverse events

Two of the studies included comments or data on adverse events in their publications (Hennekens 1996; Omenn 1996).

Omenn 1996 routinely monitored 13 symptoms (skin redness, dryness, itching, and yellowing; lip chapping; bone pain; nosebleeds; vomiting; frequency of bowel movements; weight loss; headaches; anxiety; and depression) and also included analysis of aspartate aminotransferase, alkaline phosphatase, triglycerides and total cholesterol. They reported having not found evidence of systemic toxicity in any organ except slight skin yellowing in some of those receiving beta-carotene (0.3% had yellowing of grade 3 or higher on the Carotene and Retinol Efficacy Trial (CARET) symptom-assessment scale).

Hennekens 1996 reported that during 12 years of treatment and follow-up no major side effects were significantly associated with assignment to beta-carotene supplementation.

Minor side effects included increases in yellowing of the skin (RR 1.14, 95% CI 1.07 to 1.21; 1 study, 22071 participants; high-certainty evidence; Analysis 1.3; Summary of findings for the main comparison) and minor gastrointestinal symptoms (RR 2.22, 95% CI 1.80 to 2.74; 1 study, 22071 participants; high-certainty-evidence; Analysis 1.3; Summary of findings for the main comparison).

Secondary outcomes

Total cancer incidence

Data on total cancer incidence were either available or provided by the authors of three studies (ATBC 1994; Hennekens 1996; Lin 2009).

Pooling the results of the studies, we did not find relevant differences between vitamin A and placebo (RR 1.02, 95% CI 0.97 to 1.07, I^2 = 0%; 3 studies, 44267 participants; high-certainty evidence; Analysis 1.4; Summary of findings for the main comparison).

Total cancer mortality

Hennekens 1996 was the only study that assessed total cancer mortality; it did not found any difference between vitamin A and placebo (RR 1.02, 95% CI 0.88 to 1.77; 1 study, 22071 participants; high-certainty evidence; Analysis 1.5; Summary of findings for the main comparison).

Total mortality

Data on total mortality were either available or provided by the authors for two studies that included only participants at high risk of developing lung cancer (ATBC 1994; Omenn 1996).

Pooling the results of the studies, we found a higher risk for vitamin A (RR 1.09, 95% CI 1.05 to 1.13, I^2 = 0%; 2 studies, 32883 participants; high-certainty evidence; Analysis 1.6; Summary of findings for the main comparison).

Vitamin C (ascorbic acid) versus placebo

Two studies compared vitamin C to placebo; one included 7326 men (Gaziano 2009), and the other 7627 women (Lin 2009).

Primary outcomes

Lung cancer incidence

Pooling data from those two studies showed no significant differences in lung cancer incidence (RR 1.29, 95% CI 0.67 to 2.49; I^2 = 78%; 2 studies, 14953 participants; moderate-certainty evidence; Analysis 2.1; Summary of findings 2).

Given the high heterogeneity found among results of the studies (I^2= 78 %), we conducted separate analyses for each study.

Gaziano 2009 found no differences in lung cancer incidence risk between vitamin C and placebo (RR 0.94, 95% CI 0.64 to 1.38; 1 study, 7326 participants (men only); high-certainty evidence; Analysis 2.1; Summary of findings 2).

Lin 2009 found a higher risk for those taking vitamin C (RR 1.84, 95% CI 1.14 to 2.95; 1 study, 7627 participants (women only); high-certainty evidence; Analysis 2.1; Summary of findings 2).

Lung cancer mortality

Only Gaziano 2009 provided data on this outcome and found no differences in lung cancer mortality between vitamin C and placebo (RR 0.81, 95% CI 0.53 to 1.23; 1 study, 7326 participants (men only); high-certainty evidence; Analysis 2.2; Summary of findings 2).

Adverse events

Gaziano 2009 evaluated potential adverse events of vitamin C compared to placebo and reported that there were no significant effects on minor bleeding (including haematuria, easy bruising, and epistaxis) or gastrointestinal tract symptoms (peptic ulcer, constipation, diarrhoea, gastritis, and nausea), fatigue, drowsiness, skin discolouration or rashes, or migraine.

Secondary outcomes

Total cancer incidence

Pooling data from the two studies (Gaziano 2009; Lin 2009), showed no significant differences in total cancer incidence (RR 1.03, 95% CI 0.94 to 1.13; I^2 = 35%; 2 studies, 14953 participants; high-certainty evidence; Analysis 2.3; Summary of findings 2).

Total cancer mortality

Pooling data from the two studies (Gaziano 2009; Lin 2009), showed no significant differences in total cancer mortality (RR 1.11, 95% CI 0.93 to 1.34; I^2 = 27%; 2 studies, 14953 participants; high-certainty evidence; Analysis 2.4; Summary of findings 2).

Total mortality

Only Gaziano 2009 provided data on this outcome and found no difference in total mortality between vitamin C and placebo (RR

1.06, 95% CI 0.97 to 1.15; 1 study, 7326 participants; high-certainty evidence; Analysis 2.5).

Vitamin D plus calcium versus placebo

Three studies compared vitamin D plus calcium versus placebo in postmenopausal women; followed up to four years in two studies (Lappe 2007; Lappe 2017), and seven years in one study (Brunner 2011), including a total of 37601 women.

Primary outcomes

Lung cancer incidence

Pooling data from the three studies, there was no difference in risk for lung cancer incidence (RR 0.90, 95% CI 0.39 to 2.08; I^2 = 34%; 3 studies, 37601 women; low-certainty-evidence; Analysis 3.1; Summary of findings 3).

Lung cancer mortality

None of the studies provided data for this outcome.

Adverse events

Two of the studies reported that during the course of the trials, there were no serious supplement-related adverse events (Lappe 2007; Lappe 2017).

There was no difference in risk for renal calculi (RR 1.49, 95% CI 0.70 to 3.17; I^2 = 0; 2 studies, 2931 participants; moderate-certainty evidence; Analysis 3.2; Summary of findings 3).

There was no difference in risk for serum calcium value above normal (RR 2.98, 95% CI 0.60 to 14.74; 1 study, 2197 participants; low-certainty evidence; Analysis 3.2; Summary of findings 3).

Secondary outcomes

Total cancer incidence

Pooling data from the three studies, there was no difference in risk for cancer incidence (RR 0.73, 95% CI 0.48 to 1.11; I^2= 77%; 3 studies, 37601 women; low-certainty evidence; Analysis 3.3; Summary of findings 3).

Given the high level of statistical heterogeneity found, we performed a sensitivity analysis, removing one study at a time. We found that when removing Lappe 2007, heterogeneity fell slightly, but was still high (I^2 = 67%), and that removing Lappe 2017, heterogeneity was even higher (I^2 = 83%). Removing Brunner 2011 and pooling Lappe 2007 and Lappe 2017, statistical heterogeneity decreased (I^2 = 39%). A significant difference favouring active treatment appeared (RR 0.59, 95% CI 0.37 to 0.94; 2 studies, 29312 participants; I^2 = 39%).

Heterogeneity among the three studies could come from two sources. First, the length of follow-up, which was much longer in Brunner 2011 (7 years) than in Lappe 2007 and Lappe 2017 (only 4 years); the shorter follow-up studies found more favourable results for the active treatment than the study with longer follow-up. Second, the doses of the treatment were different among the three studies: much smaller doses, 1000 mg of elemental calcium as calcium carbonate combined with 400 IU of vitamin D3 daily, in Brunner 2011; 1400 mg to 1500 mg supplemental calcium/day plus 1100 IU vitamin D3/day in Lappe 2007; and 2000 IU/day of vitamin D3 and 1500 mg/day of calcium in Lappe 2017. However, the dose-response gradient is unclear; when comparing Lappe 2007 and Lappe 2017, the potential protective effect is higher for the medium doses used in Lappe 2007.

Total cancer mortality

Total cancer mortality was only assessed in Brunner 2011 and that found no significant difference between active treatment and placebo (RR 0.91, 95% CI 0.78 to 1.05; 1 study, 34,670 women; moderate-certainty evidence; Analysis 3.4; Summary of findings 3).

Total mortality

None of the studies provided data for this outcome.

Vitamin D plus calcium versus calcium alone

One study compared vitamin D plus calcium to calcium alone in 891 postmenopausal women (Lappe 2017).

Primary outcomes

Lung cancer incidence

There was no difference in risk between vitamin D plus calcium and calcium alone (RR 0.33, 95% CI 0.03 to 3.19; 1 study, 891 participants; low-certainty evidence; Analysis 4.1).

Lung cancer mortality

The study did not evaluate this outcome.

Adverse events

The authors reported that during the course of the trial, there were no serious supplement-related adverse events, nor differences in adverse events between treatments.
There was no difference in risk for renal calculi between treatments (RR 0.33, 95% CI 0.03 to 3.19; 1 study, 891 participants; low-certainty evidence; Analysis 4.2).

Secondary outcomes

Total cancer incidence

There was no difference in risk between treatments (RR 0.76, 95% CI 0.38 to 1.55; 1 study, 891 participants; moderate-certainty evidence; Analysis 4.3).

The other secondary outcomes were not reported in the study.

Vitamin E (alpha-tocopherol) versus placebo

Five studies accounting for a total of 94141participants compared vitamin E to placebo (ATBC 1994; Gaziano 2009; Lee 2005; Lin 2009; Lippman 2009). The certainty of evidence was high for all outcomes (see Summary of findings 4).

Primary outcomes

Lung cancer incidence

Three studies provided data on this outcome (ATBC 1994; Gaziano 2009; Lin 2009).

Pooled together their results showed no difference in risk for lung cancer incidence (RR 1.01, 95% CI 0.90 to 1.14; I^2 = 0%; 3 studies, 36841 participants; high-certainty evidence; Analysis 5.1; Summary of findings 4).

Lung cancer mortality

Two studies provided data for this outcome (ATBC 1994; Gaziano 2009).

Pooled together their results showed no difference in risk for lung cancer mortality between vitamin E and placebo (RR 0.96, 95% CI 0.77 to 1.18; I^2= 0%; 2 studies, 29214 participants; high-certainty evidence; Analysis 5.2; Summary of findings 4).

Adverse events

Gaziano 2009 assessed a number of potential side effects of vitamin E; there were no significant effects on minor bleeding or gastrointestinal tract symptoms. The authors reported that an excess number of haemorrhagic strokes was observed among those assigned to the vitamin E arm compared to placebo (39 versus 23 events; hazard ratio (HR) 1.74, 95% CI 1.04 to 2.91; 1 study, 14641 participants; high-certainty evidence; Summary of findings 4).

Secondary outcomes

Total cancer incidence

Three studies provided data for this outcome (ATBC 1994; Gaziano 2009; Lin 2009).

Pooled together, their results showed no difference in risk between vitamin E and placebo (RR 0.99, 95% CI 0.94 to 1.04; I^2= 0%; 3 studies, 36832 participants; high-certainty evidence; Analysis 5.3; Summary of findings 4).

Total cancer mortality

Two studies provided data for this outcome (Gaziano 2009; Lee 2005).

Pooled together, their results showed no difference in risk between vitamin E and placebo (RR 1.11, 95% CI 0.99 to 1.24; I^2= 0%; 2 studies, 54517 participants; high-certainty evidence; Analysis 5.4; Summary of findings 4).

Total mortality

Three studies provided data for this outcome (ATBC 1994; Gaziano 2009; Lee 2005).

Pooled together their results showed no difference in risk between vitamin E and placebo (RR 1.03, 95% CI 0.99 to 1.07; I^2 = 0%; 3 studies, 69090 participants; high-certainty evidence; Analysis 5.5; Summary of findings 4).

Calcium versus placebo

Lappe 2017 compared calcium to placebo in 733 postmenopausal women.

Primary outcomes

Lung cancer incidence

Lappe 2017 found no difference in risk for lung cancer incidence between calcium and placebo (RR 0.65, 95% CI 0.13 to 3.18; 1 study, 733 participants (postmenopausal women only); low-certainty evidence; Analysis 6.1; Summary of findings 5).

Lung cancer mortality

The study did not evaluate this outcome.

Adverse events

There was no difference in risk of renal calculi (RR 1.94, 95% CI 0.20 to 18.57; 1 study, 733 participants (postmenopausal women only); low-certainty evidence; Analysis 6.2; Summary of findings 5).

Secondary outcomes

Total cancer incidence

Lappe 2007 found no difference in risk between calcium and placebo for total cancer incidence (RR 0.55, 95% CI 0.29 to 1.03; 1 study, 733 participants (postmenopausal women only); low-certainty evidence; Analysis 6.3; Summary of findings 5).

The other secondary outcomes were not reported in this study.

Selenium versus placebo

A single study with 17,448 all-male participants (Lippman 2009), compared selenium to placebo.

Primary outcomes

Lung cancer incidence

There was no difference in risk between selenium and placebo (RR 1.11, 95% CI 0.80 to 1.54; 1 study, 17448 participants (men only); high-certainty evidence; Analysis 7.1; Summary of findings 6).

Lung cancer mortality

There was no difference in risk between selenium and placebo (RR 1.09, 95% CI 0.72 to 1.66; 1study, 17448 participants (men only); high-certainty evidence; Analysis 7.2; Summary of findings 6).

Adverse events

The authors evaluated several potential adverse events but they only found higher risk in selenium users for grade 1 to 2 dermatitis (RR 1.16, 95% CI 1.04 to 1.31; 1 study, 17448 participants (men only); high-certainty evidence; Analysis 7.3; Summary of findings 6) and for alopecia (RR 1.28, 95% CI 1.07 to 1.53; 1 study, 17448 participants (men only); high-certainty evidence; Analysis 7.3; Summary of findings 6).

Secondary outcomes

Total cancer incidence

There was no difference in risk between selenium and placebo (RR 1.01, 95% CI 0.92 to 1.11; 1 study, 17448 participants (men only); high-certainty evidence; Analysis 7.4; Summary of findings 6).

Total cancer mortality

There was no difference in risk between selenium and placebo (RR 1.02, 95% CI 0.80 to 1.30; 1 study, 17448 participants (men only); high-certainty evidence; Analysis 7.5; Summary of findings 6).

Total mortality

There was no difference in risk between selenium and placebo (RR 0.98, 95% CI 0.86 to 1.13; 1 study, 17448 participants (men only); high-certainty evidence; Analysis 7.6; Summary of findings 6).

Vitamin A + vitamin E versus placebo

Only one study compared vitamin A plus E to placebo (ATBC 1994), including 14565 participants, all of them male smokers (5+ cigarettes/day) or exposed to asbestos.

Primary outcomes

Lung cancer incidence

There was no difference in risk between vitamin A + vitamin E compared to placebo for lung cancer incidence (RR 1.10, 95% CI 0.97 to 1.24; 1 study, 14556 participants; high-certainty evidence; Analysis 8.1).

Lung cancer mortality

The study did not evaluate this outcome.

Adverse events

The authors did not publish separate data on adverse events for those taking both vitamins together.

Secondary outcomes

Total cancer incidence

There was no difference in risk between vitamin A + vitamin E and placebo for total cancer incidence (RR 1.04, 95% CI 0.97 to 1.11; 1 study, 14556 participants; high-certainty evidence; Analysis 8.2).

Total cancer mortality

The study did not evaluate this outcome.

Total mortality

The risk for total mortality was higher for vitamin A + vitamin E (RR 1.06, 95% CI 1.02 to 1.11; 1 study, 14556 participants; high-certainty evidence; Analysis 8.3).

Vitamin C + vitamin E versus placebo

One study compared vitamin C plus D to placebo in 7328 male physicians (Gaziano 2009).

Primary outcomes

Lung cancer incidence

There was no difference in risk between vitamin C + vitamin E and placebo for lung cancer incidence (RR 0.83, 95% CI 0.50 to 1.39; 1study, 7328 participants; high-certainty evidence; Analysis 9.1).

Lung cancer mortality

The study did not evaluate this outcome.

Adverse events

The authors reported that no significant differences were observed in adverse events, including haematuria, easy bruising, and nosebleeds for both active vitamins E and C compared with placebo. We judged the certainty of evidence as high for this outcome.

Secondary outcomes

Total cancer incidence

There was no difference in risk between vitamin C + vitamin E and placebo for lung cancer incidence (RR 1.03, 95% CI 0.91 to 1.16; 1 study, 7328 participants; high-certainty evidence; Analysis 9.2).

The other secondary outcomes were not reported in this study.

Vitamin E + selenium versus placebo

One study with 17,399 men compared vitamin E plus selenium with placebo (Lippman 2009).

Primary outcomes

Lung cancer incidence

There was no difference in risk between vitamin E plus selenium compared with placebo for lung cancer incidence (RR 1.16, 95% CI 0.84 to 1.61; 1 study, 17399 participants; high-certainty evidence; Analysis 10.1).

Lung cancer mortality

There was no difference in risk between vitamin E plus selenium compared with placebo for lung cancer mortality (RR 0.95, 95% CI 0.61 to 1.47; 1 study, 17399 participants; high-certainty evidence; Analysis 10.2).

Adverse events

The authors evaluated the risks for several potential adverse events, such as alopecia, dermatitis, halitosis, nail changes, fatigue and nausea, and they only found differences in risk for halitosis (RR 1.24, 95% CI 1.10 to 1.41; 1 study, 17399 participants; high-certainty evidence; Analysis 10.3).

Secondary outcomes

Total cancer incidence

There was no difference in risk between vitamin E plus selenium compared with placebo for total cancer incidence (RR 1.03, 95% CI 0.94 to 1.12; 1 study, 17399 participants; high-certainty evidence; Analysis 10.4).

Total cancer mortality

There was no difference in risk between vitamin E plus selenium compared with placebo for total cancer mortality (RR 0.94, 95% CI 0.73 to 1.20; 1 study, 17399 participants; high-certainty evidence; Analysis 10.5).

Total mortality

There was difference in risk between vitamin E plus selenium compared with placebo for total mortality (RR 0.94, 95% CI 0.82 to 1.08; 1 study, 17,399 participants; high-certainty evidence; Analysis 10.6).

Vitamins A plus E plus selenium versus placebo

One study compared vitamins A, E and selenium with placebo in 149773 participants recruited from a population with nutritional deficiencies (Kamangar 2006).

Primary outcomes

Lung cancer incidence

The study did not evaluate this outcome.

Lung cancer mortality

There was no difference in risk for lung cancer mortality (RR 0.55, 95% CI 0.26 to 1.14; 1 study, 149733 participants; high-certainty evidence; Analysis 11.1).

Adverse events data were not reported.

Secondary outcomes

None of our secondary outcomes were reported.

Vitamins A, C, E plus selenium plus zinc versus placebo

A single study with 12741 participants compared vitamins A, C, E, selenium and zinc to placebo (Hercberg 2010). The data allowed us to make separate analyses for males and females. Given that the results were similar for both subgroups and that there is no relevant statistical heterogeneity among them, we present here the combined results for both groups. However, detailed subgroup analyses are available in the Data and analyses section.

Primary outcomes

Lung cancer incidence

There was no difference in risk compared with placebo for lung cancer incidence (RR 0.64, 95% CI 0.28 to 1.48; 1 study, 12741 participants; high-certainty evidence; Analysis 12.1; Summary of findings 7).

Lung cancer mortality

The study did not evaluate this outcome.

Adverse events

The authors reported that there were data monitoring for safety, but they did not publish data on adverse events.

Secondary outcomes

Total cancer incidence

There was no difference in risk compared with placebo for total cancer incidence (RR 0.96, 95% CI 0.83 to 1.10; 1study, 12741 participants; high-certainty evidence; Analysis 12.2; Summary of findings 7).

Total cancer mortality

The study did not evaluate this outcome.

Total mortality

There was no difference in risk compared with placebo for total mortality (RR 0.88, 95% CI 0.70 to 1.11; 1 study, 12741 participants; high-certainty evidence; Analysis 12.3; Summary of findings 7).

DISCUSSION

Summary of main results

Available evidence for this review shows no reduction in either lung cancer incidence or lung cancer mortality after the use of different supplements of vitamins or minerals, either alone or combined.

Moreover, there is evidence that some of the treatments could even be harmful for some subgroups of people. Vitamin A supplements increase lung cancer incidence and mortality in smokers or persons exposed to asbestos. Vitamin C increases lung cancer incidence in women. Vitamin E increases the risk of haemorrhagic strokes.

See detailed data in the 'Summary of findings' tables for the seven main comparisons against placebo (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7).

Overall completeness and applicability of evidence

All of the comparisons undertaken in this review provided information on the effect of the intervention on lung cancer incidence, the main outcome of interest in this review. Analysis of the effect of the interventions on lung cancer mortality was possible for the following: vitamins A, C, E, selenium, vitamin E plus selenium, vitamin A plus E plus selenium.

For vitamin A, there was information from five studies, which separately investigated people at high risk (smokers and asbestos workers) and low risk. Lung cancer incidence data came from three studies for low-risk people and two studies for high-risk people. Lung cancer mortality data came from two studies for low-risk people and two studies for high-risk people. Two studies reported information on adverse events.

For vitamin C, there was information from single studies that investigated men and women separately. One study that included 7627 women found a statistically significant higher risk for lung cancer incidence in those taking vitamin C (risk ratio (RR) 1.84, 95% confidence interval (CI) 1.14 to 2.95), but not for total cancer incidence (Lin 2009). However, those results should be taken with caution given that they come from a single study and that the differences were not statistically significant for men, or for men and women pooled together. Only the study conducted in males reported on adverse events.

For vitamin E and lung cancer incidence, there was information from three studies which included different subgroups of people: 1) only people at high risk, 2) only men, and 3) only women. Lung cancer mortality data came from two studies: 1) in men, and 2) in people at high risk. Only one study reported on adverse events.

For vitamin D plus calcium, we assessed the incidence of lung cancer in three studies that included only women. None of the studies assessed lung cancer mortality. Two studies reported on adverse events.

For the vitamin D plus calcium versus placebo comparison, regarding total cancer incidence, pooling the results of the three published studies we found a non-statistically significant difference between treatments, but with high statistical heterogeneity (RR 0.73, 95% CI 0.48 to 1.11; I^2= 77%). Sensitivity analysis, removing one study at a time, showed contradictory results. Apart from random variation, there were some differences among those three studies that should be considered. First, differences in the duration of treatment and follow-up: seven years in Brunner 2011 and four years in Lappe 2007 and Lappe 2017. Brunner 2011, the study with longest follow-up and the largest sample size (34670 women), did not found differences among treatments (RR 0.98, 95% CI 0.91 to 1.05). Pooling the studies with shorter follow-up in Lappe 2007 and Lappe 2017 (2931 participants together), the 95% CI of the RR for total cancer incidence is wide 0.37 to 0.94, almost crossing 1. Second, differences in doses of the active products: 400 IU of vitamin D3 and 1000 mg of elemental calcium in Brunner 2011; 1100 IU of vitamin D3 and 1400 mg to 1500 mg of calcium in Lappe 2007; and 2000 IU of vitamin D3 and 1500 mg of calcium in Lappe 2017. Individual analysis of the results of the three studies found no clear gradient in the effect of the treatment on total cancer incidence

regarding vitamin D and calcium doses: the study with larger doses, i.e. Lappe 2017, showed a protective, non-statistically significant effect (RR 0.70, 95% CI 0.48 to 1.01), a much smaller effect than found in the other study conducted by the same author with smaller doses of vitamin D (RR 0.42, 95% CI 0.21 to 0.83; Lappe 2007).

It is unclear whether the effect differences found between Lappe's studies and Brunner's study are due to differences in doses of active treatments or differences in follow-up duration, or a combination of both factors.

For calcium, evidence came from a single study that included only women, and provided data on lung cancer incidence and total cancer incidence, but not on lung cancer mortality.

For selenium, evidence came from a single study that included only men, and provided data on lung cancer incidence; lung cancer mortality and adverse events.

For the combination of vitamins A, C, E, selenium and zinc, evidence came from a single study that provided separate information for men and women, and provided data on lung cancer incidence and adverse events, but not for lung cancer mortality.

For the remaining comparisons with combinations of two or more products, evidence came from single and separate studies in each case.

Certainty of the evidence

The source of evidence is direct, since studies were carried out on our target population groups (healthy people).

The studies included in this review were all randomised controlled trials (RCTs). We classified seven studies as being at low risk of bias in all domains, one at high risk for selective reporting bias and another for other biases, and five studies at unclear risk of bias in at least one domain (Figure 3). In cases of information coming from several studies, consistency of results varied. For vitamin A, in the case of lung cancer incidence amongst low-risk people, we found no statistically significant differences between placebo and active treatment (RR 0.99, 95% CI 0.69 to 1.42). Amongst high-risk people, the results showed a slightly higher risk for those taking vitamin A (RR 1.1, 95% CI 1.01 to 1.20.

Amongst the two studies that assessed lung cancer mortality, only one found significant differences between treatment and placebo (RR 1.18, 95% CI 1.01 to 1.38; ATBC 1994). A possible explanation is that the second study included high-risk people who were smokers (Hennekens 1996), whereas in ATBC 1994, they also included people exposed to asbestos.

For vitamin E, evidence for both incidence (RR 0.87 95% CI 0.59 to 1.29) and lung cancer mortality (RR 1.02 95% CI 0.67 to 1.56) amongst males, comes from two studies with consistent results of no significant differences between placebo and active treatment; for women, incidence of lung cancer was assessed by two studies with consistent results.

For vitamin D, three studies assessed lung cancer incidence and presented unclear risk of bias in: selection bias, performance bias, selective reporting and attrition bias. We found no statistical difference in their comparisons (RR 0.90, 95% CI 0.39 to 2.08).

Potential biases in the review process

We could not assess publication bias using funnel plots given that the number of published studies for each comparison was always five or less. We cannot completely discard the possibility of not having identified small studies, especially if they were conducted decades ago; it is only in recent years that it is compulsory, in most countries, to register any RCT involving a pharmacological product on humans.

Publication bias is unlikely to have occurred in the review process given that the published studies found unfavourable results for active treatments or showed no difference compared to placebo; it is quite unlikely that any relevant study remain unpublished, especially any with results favouring active interventions.

Agreements and disagreements with other studies or reviews

For vitamin A, the original version of this Cochrane Review published in 2003 found no differences in risk for lung cancer incidence or lung cancer mortality compared to placebo (Caraballoso 2003), neither for the overall population nor for high-risk people (smokers and exposed to asbestos). In the first update of the review published in 2012 (Cortes-Jofre 2012), we included an additional study in the meta-analyses (Omenn 1996) and the results changed showing an increase in the risk for lung cancer mortality and for all causes mortality for those taking vitamin A in high-risk people (smokers and exposed to asbestos).

In the current update, we included three new studies (37601 women) that evaluated vitamin D in the incidence of lung cancer (Brunner 2011; Lappe 2007; Lappe 2017); we did not find a difference in risk compared with placebo (RR 0.90, 95% CI 0.39 to 2.08).

Published systematic reviews on the effects of beta-carotene supplements or antioxidants reach conclusions similar to ours about the ineffectiveness of the use of these supplements to prevent lung cancer compared to placebo (Druesne-Pecollo 2010; Myung 2010).

One review found that consumption of vegetables and fruits is associated with a low risk of developing lung cancer (Wakai 2011), though this evidence comes from observational studies. Fruits and vegetables contain numerous components in addition to beta-carotene, and those observational studies generally evaluate foods rather than specific bioactive food components. It has been suggested that beta-carotene could be simply a marker for other protective dietary components, and that a systematic approach is needed to determine how combinations of vitamins and minerals may interact to influence cancer risk, and to increase our understanding of the potential benefits and risks of supplement use (Greenwald 2002).

Currently, cancer prevention is known to be directly related to the nature of carcinogenesis. Tumours develop over many years through a multi-step process that involves the accumulation of mutations in the genomes of cancer cells, along with contributing changes in the microenvironment, including the surrounding elements of the immune system (Dunn 2016).

So the history of antioxidants and cancer is a clear example of the need for transactional research, which is defined by the European

Society for Translational Medicine, as "an interdisciplinary branch of the biomedical field supported by three main pillars: bench side, bedside, and community" (Cohrs 2014).

By the time most of the RCTs began, there was a widespread belief in the scientific community that a diet rich in fruits and vegetables, both rich in antioxidants, could prevent cancer. That belief was based primarily on observational studies. The recently published basic research has cast doubt on the belief of the anticancer properties of antioxidants, and has warned that in some cases, its effect could in fact be carcinogenic (DeNicola 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that supplements of vitamins A, C, E, D, or selenium, either alone or in different combinations, prevent lung cancer or lung cancer mortality in healthy people. There is evidence for possible harmful effects of some interventions in some groups of people. In smokers and people exposed to asbestos, vitamin A increases lung cancer incidence, lung cancer mortality and all-cause mortality. Vitamin C increases lung cancer incidence in women. Vitamin E increases the risk of haemorrhagic strokes.

Implications for research

The main clinical trial registers do not include any new, ongoing or planned randomised controlled trials (RCTs) on supplementary vitamins, minerals and other antioxidants for the prevention of lung cancer in healthy people.

Research on the effect of vitamins, minerals and other antioxidants in the prevention of lung cancer in healthy people will probably require the selection of multiple pathways for carcinogenesis, given that the current available evidence does not support their use.

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* Indicates the major publication for the study

5.2 Publicación 2. Cortés-Jofré M, Rueda-Etxebarria M, Orillard E, Jimenez Tejero E, Rueda J-R. Therapeutic vaccines for advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews 2024, Issue 3. Art. No.: CD013377. DOI: 10.1002/14651858.CD013377.pub2 (97).

5.2.1 Resumen de los Resultados

En esta revisión se incluyeron 10 estudios con 2177 participantes. Los análisis de los desenlaces incluyeron solo a 2045 participantes (1401 hombres y 644 mujeres) (97). La certeza de la evidencia varió según la vacuna y el desenlace, oscilando entre moderada y muy baja (97).

TG4010: vacuna basada en un vector, TG4010, añadida a quimioterapia, en comparación con quimioterapia sola en el tratamiento de primera línea, podría dar lugar a poca o ninguna diferencia en la supervivencia global (cociente de riesgos instantáneos [CRI] 0,83; intervalo de confianza [IC] del 95%: 0,65 a 1,05; dos estudios, 370 participantes; evidencia de certeza baja) (97). Podría aumentar ligeramente la supervivencia sin progresión (CRI 0,74; IC del 95%: 0,55 a 0,99; un estudio, 222 participantes; evidencia de certeza baja) (97). Podría dar lugar a poca o ninguna diferencia en la proporción de participantes con al menos un evento adverso grave relacionado con el tratamiento, pero la evidencia es muy incierta ([RR] 0,70; IC del 95%: 0,23 a 2,19; dos estudios, 362 participantes; certeza de evidencia muy baja) (97).

Vacuna contra el factor de crecimiento epidérmico: La vacuna, comparada con el mejor tratamiento de apoyo como tratamiento de mantención alternativo después de la quimioterapia de primera línea,

podría dar lugar a poca o ninguna diferencia en la supervivencia global (CRI 0,82; IC del 95%: 0,66 a 1,02; un estudio, 378 participantes; certeza de evidencia baja) y en la proporción de participantes con al menos un evento adverso grave relacionado con el tratamiento (RR 1,32; IC del 95%: 0,88 a 1,98; dos estudios, 458 participantes; certeza de evidencia baja) (97).

La vacuna hTERT (vx-001) comparada con placebo como tratamiento de mantención después de la quimioterapia de primera línea podría dar lugar a poca o ninguna diferencia en la supervivencia global (CRI 0,97; IC del 95%: 0,70 a 1,34; un estudio, 190 participantes) (97).

Racotumomab: vacuna comparada con placebo como tratamiento de mantención alternativo tras la quimioterapia se evaluó en un estudio con 176 participantes. Podría aumentar la supervivencia global (CRI 0,63; IC del 95%: 0,46 a 0,87) (97). Podría dar lugar a poca o ninguna diferencia en la supervivencia sin progresión (CRI 0,73; IC del 95%: 0,53 a 1,00) y en la proporción de personas con al menos un evento adverso grave relacionado con el tratamiento (RR 1,03; IC del 95%: 0,15 a 7,18) (97).

Vacuna racotumomab versus docetaxel como tratamiento de mantención alternativo tras la quimioterapia se evaluó en un estudio con 145 participantes. El estudio no informó sobre las tasas de riesgo de supervivencia global ni el tiempo de supervivencia sin progresión, pero la diferencia en la mediana de los tiempos de supervivencia fue, menos de un mes (97). Racotumomab podría dar lugar a poca o ninguna diferencia en la proporción de personas con al menos un evento adverso grave relacionado con el tratamiento en comparación con docetaxel (RR 0,89; IC del 95%: 0,44 a 1,83) (97).

Vacuna peptídica personalizada: más docetaxel en comparación con docetaxel podría dar lugar a una diferencia escasa o nula en la supervivencia global (CRI 0,80; IC del 95%: 0,42 a 1,52) y la supervivencia sin progresión (CRI 0,78; IC del 95%: 0,43 a 1,42) (97).

La vacuna OSE2101 comparada con la quimioterapia, tras la quimioterapia o la inmunoterapia, se evaluó en un estudio con 219 participantes. Podría dar lugar a poca o ninguna diferencia en la supervivencia global (CRI 0,86; IC del 95%: 0,62 a 1,19) (97). Podría dar lugar a una pequeña diferencia en la proporción de personas con al menos un evento adverso grave relacionado con el tratamiento (RR 0,95; IC del 95%: 0,91 a 0,99) (97).

La vacuna SRL172 de Mycobacterium vaccae muerto, añadida a la quimioterapia, en comparación con la quimioterapia sola, podría no provocar diferencias en la supervivencia global y podría aumentar la proporción de personas con al menos un evento adverso grave relacionado con el tratamiento (RR 2,07; IC del 95%: 1,76 a 2,43; 351 participantes) (97).

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Therapeutic vaccines for advanced non-small cell lung cancer

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ABSTRACT

Background

New strategies in immunotherapy with specific antigens that trigger an anti-tumour immune response in people with lung cancer open the possibility of developing therapeutic vaccines aimed at boosting the adaptive immune response against cancer cells.

Objectives

To evaluate the effectiveness and safety of different types of therapeutic vaccines for people with advanced non-small cell lung cancer.

Search methods

We searched CENTRAL, MEDLINE, Embase, Wanfang Data, and China Journal Net (CNKI) up to 22 August 2023.

Selection criteria

We included parallel-group, randomised controlled trials evaluating a therapeutic cancer vaccine, alone or in combination with other treatments, in adults (> 18 years) with advanced non-small cell lung cancer (NSCLC), whatever the line of treatment.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcomes were overall survival, progression-free survival, and serious adverse events; secondary outcomes were three- and five-year survival rates and health-related quality of life.

Main results

We included 10 studies with 2177 participants. The outcome analyses included only 2045 participants (1401 men and 644 women). The certainty of the evidence varied by vaccine and outcome, and ranged from moderate to very low. We report only the results for primary outcomes here.

TG4010

The addition of the vector-based vaccine, TG4010, to chemotherapy, compared with chemotherapy alone in first-line treatment, may result in little to no difference in overall survival (hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.65 to 1.05; 2 studies, 370 participants; low-certainty evidence). It may increase progression-free survival slightly (HR 0.74, 95% CI 0.55 to 0.99; 1 study, 222 participants; low-certainty evidence). It may result in little to no difference in the proportion of participants with at least one serious treatment-related adverse event, but the evidence is very uncertain (risk ratio (RR) 0.70, 95% CI 0.23 to 2.19; 2 studies, 362 participants; very low-certainty evidence).

Epidermal growth factor vaccine

Epidermal growth factor vaccine, compared to best supportive care as switch maintenance treatment after first-line chemotherapy, may result in little to no difference in overall survival (HR 0.82, 95% CI 0.66 to 1.02; 1 study, 378 participants; low-certainty evidence), and in the proportion of participants with at least one serious treatment-related adverse event (RR 1.32, 95% CI 0.88 to 1.98; 2 studies, 458 participants; low-certainty evidence).

hTERT (vx-001)

The hTERT (vx-001) vaccine compared to placebo as maintenance treatment after first-line chemotherapy may result in little to no difference in overall survival (HR 0.97, 95% CI 0.70 to 1.34; 1 study, 190 participants).

Racotumomab

Racotumomab compared to placebo as a switch maintenance treatment post-chemotherapy was assessed in one study with 176 participants. It may increase overall survival (HR 0.63, 95% CI 0.46 to 0.87). It may make little to no difference in progression-free survival (HR 0.73, 95% CI 0.53 to 1.00) and in the proportion of people with at least one serious treatment-related adverse event (RR 1.03, 95% CI 0.15 to 7.18).

Racotumomab versus docetaxel as switch maintenance therapy post-chemotherapy was assessed in one study with 145 participants. The study did not report hazard rates on overall survival or progression-free survival time, but the difference in median survival times was very small – less than one month. Racotumomab may result in little to no difference in the proportion of people with at least one serious treatment-related adverse event compared with docetaxel (RR 0.89, 95% CI 0.44 to 1.83).

Personalised peptide vaccine

Personalised peptide vaccine plus docetaxel compared to docetaxel plus placebo post-chemotherapy treatment may result in little to no difference in overall survival (HR 0.80, 95% CI 0.42 to 1.52) and progression-free survival (HR 0.78, 95% CI 0.43 to 1.42).

OSE2101

The OSE2101 vaccine compared with chemotherapy, after chemotherapy or immunotherapy, was assessed in one study with 219 participants. It may result in little to no difference in overall survival (HR 0.86, 95% CI 0.62 to 1.19). It may result in a small difference in the proportion of people with at least one serious treatment-related adverse event (RR 0.95, 95% CI 0.91 to 0.99).

SRL172

The SRL172 vaccine of killed *Mycobacterium vaccae*, added to chemotherapy, compared to chemotherapy alone, may result in no difference in overall survival, and may increase the proportion of people with at least one serious treatment-related adverse event (RR 2.07, 95% CI 1.76 to 2.43; 351 participants).

Authors' conclusions

Adding a vaccine resulted in no differences in overall survival, except for racotumomab, which showed some improvement compared to placebo, but the difference in median survival time was very small (1.4 months) and the study only included 176 participants.

Regarding progression-free survival, we observed no differences between the compared treatments, except for TG4010, which may increase progression-free survival slightly. There were no differences between the compared treatments in serious treatment-related adverse events, except for SRL172 (killed *Mycobacterium vaccae*) added to chemotherapy, which was associated with an increase in the proportion of participants with at least one serious treatment-related adverse event, and OSE2101, which may decrease slightly the proportion of people having at least one serious treatment-related adverse event.

These conclusions should be interpreted cautiously, as the very low- to moderate-certainty evidence prevents drawing solid conclusions: many vaccines were evaluated in a single study with small numbers of participants and events.

PLAIN LANGUAGE SUMMARY

Do cancer vaccines help people with advanced non-small cell lung cancer?

Key messages

- The vaccines evaluated in this review do not improve peoples' survival, or progression-free survival, or do so to a negligible extent.

- Unwanted effects of the vaccines are not frequent.

What is lung cancer?

Lung cancer is one of the most common cancers worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for around 87% of lung cancers. Non-small cell lung cancer is often diagnosed when it is at an advanced stage, which is associated with high death rates and a short life expectancy.

How is non-small cell lung cancer treated?

Most of these cancers are treated first with chemotherapy – that is, medicine consisting of powerful chemicals to kill fast-growing cancer cells. New therapies to improve survival rates for people with NSCLC are focused on treatment with immunotherapy after chemotherapy. Cancer vaccines are a type of immunotherapy. Unlike vaccines to protect us from disease, cancer vaccines are for people who already have cancer. Therapeutic cancer vaccines aim to stimulate the immune system to recognise and destroy cancer cells.

What did we want to find out?

We wanted to find out whether vaccines lengthen people's survival time and time without disease progression, and whether they are associated with any unwanted effects.

What did we do?

We searched for studies that looked at therapeutic cancer vaccines alone or in combination with chemotherapy compared with supportive care, no treatment, or placebo (inactive or 'dummy' medicine) in people with advanced NSCLC.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 10 studies that involved 2177 participants with advanced NSCLC. The biggest study involved 419 people and the smallest study 50. Seven different types of vaccines were evaluated. Three vaccines were evaluated in 2 studies each: TG4010 vector-based vaccine; epidermal growth factor vaccine; and racotumomab. The remaining 4 vaccines were each evaluated in a single study.

Main results

- None of the vaccines increased participants' survival time, except racotumomab, which may improve it slightly compared to placebo. The median survival time for those in the racotumomab vaccine group was 8.2 months, compared to 6.8 months in the group that did not receive the vaccine. (The median is the middle value of a set of numbers.)

- None of the vaccines improved progression-free survival time, except TG4010, which may increase it slightly. The median progression-free survival time for people in the TG4010 vaccine group was 5.9 months, compared to 5.1 months in the non-vaccine group.

- The 7 different vaccines tested largely appear to be safe: there were no differences between the people given vaccines and those not given vaccines in terms of serious adverse (unwanted) events. However, 1 vaccine (SLR172) added to chemotherapy increased the proportion of people having at least 1 serious adverse event. A different vaccine (OSE2101) may result in a slight decrease in the proportion of people having at least 1 serious adverse event.

What are the limitations of the evidence?

Our confidence in the evidence varied from moderate to very low for the different vaccines and outcomes assessed, mainly because the studies were small and there were not enough studies to be sure of the results.

How up to date is this evidence?

The evidence is current to August 2023.

SUMMARY OF FINDINGS

Summary of findings 1. TG4010 added to chemotherapy compared to chemotherapy alone in first-line treatment

TG4010 added to chemotherapy compared to chemotherapy alone in first-line treatment

Patient or population: adults with advanced non-small cell lung cancer (NSCLC)
Setting: outpatients
Intervention: TG4010 added to chemotherapy
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with TG4010 added to chemotherapy				
Overall survival	**HR 0.83** (0.65 to 1.05)			370 (2 RCTs)	⊕⊕⊖⊖ Low[a]	TG4010 vaccine may result in little to no difference in overall survival.
Progression-free survival	**HR 0.74** (0.55 to 0.99)			222 (1 RCT)	⊕⊕⊖⊖ Low[a]	TG4010 vaccine may slightly increase progression-free survival.
Participants with at least one serious adverse event	251 per 1000	**176 per 1000** (58 to 551)	**RR 0.70** (0.23 to 2.19)	362 (2 RCTs)	⊕⊖⊖⊖ Very low[b]	TG4010 vaccine may result in little to no difference in the number of participants that have at least one serious adverse event but the evidence is very uncertain.
Survival rates at 3 years	68 per 1000	**68 per 1000** (20 to 224)	**RR 1.00** (0.30 to 3.31)	148 (1 RCT)	⊕⊕⊖⊖ Low[a]	TG4010 vaccine may result in little to no difference in survival rates at 3 years.
Survival rates at 5 years	Neither study assessed this outcome (and none of the participants were alive at five years).					
Health-related quality of life	Neither study assessed this outcome.					

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

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] For the outcomes of overall survival, progression-free survival, and survival rates at 3 years, we downgraded the certainty of the evidence by two levels for imprecision (the confidence interval includes the threshold of clinical relevance and no clear conclusions can be drawn).
[b] For serious adverse events, we downgraded the certainty of the evidence by two levels for imprecision, and one level for inconsistency (high I^2 statistic).

Summary of findings 2. Epidermal growth factor versus best supportive care for switch maintenance after first-line treatment

Epidermal growth factor versus best supportive care for switch maintenance after first-line treatment

Patient or population: adults with advanced non-small cell lung cancer (NSCLC)
Setting: outpatients
Intervention: epidermal growth factor vaccine
Comparison: best supportive care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with epidermal growth factor vaccine added to chemotherapy				
Overall survival	**HR 0.82** (0.66 to 1.02)			378 (1 RCT)	⊕⊖⊖⊖ Low[a]	Epidermal growth factor vaccine may result in little to no difference in overall survival.
Progression-free survival	Neither study assessed this outcome.					
Participants with at least one serious adverse event	151 per 1000	**200 per 1000** (133 to 299)	**RR 1.32** (0.88 to 1.98)	458 (2 RCTs)	⊕⊖⊖⊖ Low[a]	Epidermal growth factor vaccine may result in little to no difference in the rate of participants that have at least one serious adverse event.
Survival rates at 3 years	87 per 1000	**126 per 1000** (72 to 222)	**RR 1.45** (0.82 to 2.54)	458 (2 RCTs)	⊕⊖⊖⊖ Low[a]	Epidermal growth factor vaccine may result in little to no difference in survival rates at 3 years.

Survival rates at 5 years	23 per 1000	**77 per 1000** (23 to 256)	**RR 3.40** (1.02 to 11.27)	378 (1 RCT)	⊕⊕⊖⊖ Low[a]	Epidermal growth factor vaccine may result in a small difference in survival rates at 5 years.
Health-related quality of life Assessed with EORTC QLQ-C30 global health status score at 6 months	The mean health-related quality of life score at 6 months was **54.9**, as assessed with EORTC QLQ-C30 global health status	**MD 7.9 higher** (0.49 lower to 16.29 higher)		86 (1 RCT)	⊕⊖⊖⊖ Very low[b]	Epidermal growth factor vaccine may result in little to no difference in health-related quality of life but the evidence is very uncertain.

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

CI: confidence interval; **EORTC QLQ-C30:** European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; **HR:** hazard ratio; **MD:** mean difference; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] For the outcomes of overall survival, participants with at least one serious adverse event, and survival rates at three and five years, we downgraded the certainty of the evidence by two levels for imprecision (the confidence interval contains the threshold of clinical relevance and no clear conclusions can be drawn).
[b]We downgraded the certainty of the evidence by two levels for risk of bias (lack of blinding, incomplete outcome data) and by one level for imprecision.

BACKGROUND

Description of the condition

Lung cancer is the most common cancer worldwide. In records from the GLOBOCAN database of the International Agency for Research on Cancer in 2022, lung cancer ranked as the most commonly diagnosed cancer, with an incidence of 2,480,675 new cases (1,572,045 in men and 908,630 in women), representing 12.4% of the total of all new cancers (GLOBOCAN 2024). It was also the main cause of death from cancer, accounting for 1,817,469 deaths (1,233,241 in men and 584,228 in women), representing 18.7% of total cancer deaths (GLOBOCAN 2024).

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, making up 87% of all lung cancers, while small cell lung cancer (SCLC) represents about 13% of all lung cancer cases (Goldstraw 2016).

Most people with NSCLC are diagnosed at an advanced stage (stage IIIB or IV), according to the TNM stage classification for lung cancer (Appendix 1). Of people diagnosed with NSCLC, about 17.6% of non-small cell lung cancers are stage IIIB when diagnosed, and 40% are stage IV (Lemjabbar-alaoui H 2015).

New strategies in immunotherapy target immune-modulating mechanisms that help tumour cells defend themselves against the immune system (Remon 2017). This approach targets immune checkpoint pathways, which include blockade of the inhibitory receptors, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1), and its ligand, PD-L1. Immune checkpoint inhibitors are now an important part of the therapeutic armamentarium for NSCLC, both in locally advanced and metastatic stages.

For people with unresectable locally advanced stages, the usual recommendations are curative radiotherapy combined with chemotherapy and anti-PD-L1 treatment as consolidation treatment (Antonia 2017; Antonia 2018).

The treatment of advanced lung cancer consists of platinum-based doublet chemotherapy with anti-PD-1 treatment (immunotherapy), independent of the PD-L1 status (Paz-Ares 2018; Gandhi 2018). In the case of a PD-L1 tumour proportion score of 50% or higher, an anti-PD-1 monoclonal antibody as monotherapy can be proposed (Reck 2016). In cases of epidermal growth factor receptor (EGFR) activating mutations or ALK (anaplastic lymphoma kinase) translocation, patients receive an EGFR or ALK tyrosine kinase inhibitor. New data are likely to expand the role of immunotherapy in combination with other therapies in the coming years (Ramamurthy 2017).

With the development of immune checkpoint inhibitors, research has led to a better understanding of the interactions between the immune system and cancer cells and the mechanisms by which cancer evades the immune response. Immunotherapy represents a broad class of treatments designed to elicit immune-mediated destruction of tumour cells (Domingues 2014). It has been shown that malignant cells can express mutated proteins that can be recognised as foreign antigens, over-expressed normal proteins, or expressed foetal antigens, which are normally absent in healthy adults. If these tumour-associated antigens are recognised as foreign by the immune system, they can activate them by stimulating antigens-presenting cells (APC), and eliciting a targeted adaptive immune response (Rosenberg 1999). The discovery of specific malignant antigens that trigger an anti-tumour immune response in people with lung cancer opens the possibility of developing therapeutic vaccines aimed at boosting the adaptive immune response against cancer cells that express those antigens.

Therapeutic vaccines can be given at different moments, from the initial diagnosis of advanced lung cancer or as the disease progresses:

- as part of the initial treatment (first-line treatment);
- as second-line treatment after failure or non-tolerated side effects of first-line treatment;
- as third-line treatment when both first- and second-line treatment do not work, stop working, or are not well-tolerated;
- as an ongoing maintenance treatment given to help keep cancer from coming back after a good response to first- or second-line treatment;
- as switch maintenance, in patients in which the tumour did not progress with first induction chemotherapy, using a vaccine with a different mechanism of action.

Description of the intervention

Therapeutic vaccines stimulate the immune system to target cancer cells by boosting the innate and adaptive immune response (Zhou 2016). These vaccines may induce cellular and humoral immune responses against tumour-specific or associated antigens. However, there are several obstacles, such as tolerance, poorly-defined immunogenic tumour antigens, and several suppression mechanisms, which decrease the effectiveness of the immune system, mainly by protecting the tumour-suppressive micro-environment, especially in advanced-stage NSCLC (Vesely 2011).

Several clinical trials that examine vaccination strategies have been developed for people with advanced NSCLC, looking primarily at allogeneic whole-cell vaccines, protein-based vaccines, peptide vaccines, anti-idiotype vaccines, and viral-based vaccines (Declerck 2014; Yang 2016; Zhou 2016; Zhu 2017).

How the intervention might work

There are data to support the hypothesis that cancer vaccines can induce a specific anti-tumour immune response in people with cancer (Leone 2013). This is achieved through the administration of either immunogenic tumour-associated antigens or cells in conjunction with immunoadjuvants that enhance the immune response (Mountzios 2016). The immune system plays a dual role in cancer development: it can promote tumour growth by mechanisms that interfere with immune surveillance, but it can also suppress tumour growth by activating innate and adaptive immune mechanisms (Schreiber 2011; Vesely 2013).

Therapeutic cancer vaccines try to elicit an effective immune response; in this setting, innate and adaptive immune cells recognise antigens in transformed cells and destroy them (Monteiro 2016; Vesely 2011). The tumour antigens are taken up, processed, and presented to T cells by specific antigen-presenting cells, such as dendritic cells and macrophages. Peptides derived from these antigens are then presented in the context of class I major histocompatibility complex molecules to CD8+ T cells (anti-tumour cytotoxic T cells) and in the context of class II major

histocompatibility complex molecules to CD4+ T cells. The antigen-presenting cells, mainly dendritic cells, express co-stimulatory molecules, such as CD80 and CD86, which provide the signals required to activate tumour antigen-specific CD8+ T cells, and tumour antigen-specific CD4+ helper T cells, in a process called cross-presentation. The helper T cells may secrete cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin (IL-2), and interferon-gamma (IFN-γ) that can activate macrophages and natural killers to kill tumour cells. Helper T cells can also help in the activation and differentiation of B cells to plasma cells, promoting the production of specific anti-tumour antigen antibodies. Antibodies may kill tumour cells by activating complementary, antibody-dependent cell cytotoxicity, or other mechanisms (Mittal 2014; Pardoll 2015; Schreiber 2011; Vesely 2013).

TG4010

TG4010 is formed by an attenuated vaccinia Ankaravirus, genetically modified to express the coding sequences of the mucin-1 (MUC1) antigen and interleukin-2 (Suzuki 2014; Quoix 2017). IL-2 plays a key role in activating the adaptive and innate immune response, especially T cells and natural killer cells in tumour-associated environments. TG4010 has been shown to induce adaptive responses in participants with NSCLC in several studies (Hillman 2017; Schaedler 2017; Tosch 2017).

CIMAvax-EGF

CIMAvax-EGF vaccine is made from human recombinant epidermal growth factor (EGF) linked to P64, a carrier recombinant protein of the meningitis B bacteria, and an oily adjuvant (Ascarateil 2015). The mechanism of action of CIMAvax-EGF is based on the formation of antibodies against the epidermal growth factor, a self-protein overexpressed in NSCLC. Its overexpression has been associated with poor prognosis, lower survival, and resistance to treatment in cancer. The vaccine induces antibodies that remove EGF, thus blocking the EGF–EGFR interaction. The response against this self-protein is due to a chemical bond between recombinant epidermal growth factor and the P64k protein derived from *Neisseria meningitidis* bacteria (Saavedra 2016; Saavedra 2017).

hTERT (vx-001) vaccine

The hTERT (human telomerase reverse transcriptase) (vx-001) vaccine is made with "optimised cryptic peptides", a family of tumour antigens derived from universal tumour antigens. Vx-001 comprises two 9-amino acid peptides, the optimised Vx-001/TERT572Y and the wild-type (WT) Vx-001/TERT5. Vx-001 targets TERT (telomerase reverse transcriptase). Optimised cryptic peptides are recognised by the immune system as foreign and are strongly immunogenic (Gridelli 2020).

Racotumomab

Racotumomab (anti-idiotype vaccine) is a murine monoclonal antibody IgG1 directed to membrane glycoconjugates expressed in aggressive solid tumours. It was developed as a mirror image of the idiotype of another antibody against N-glycolyl-containing molecules, such as the N-glycolyl GM3 ganglioside (NeuGcGM3 ganglioside) (Hernandez 2021). These glycolipids are generally not expressed in healthy individuals. The vaccine develops antibodies against that ganglioside and induces complementary, independent, oncotic necrosis for tumour cells(Hernandez 2008; Hernandez 2011).

Personalised peptide vaccination (PPV)

The earlier generations of peptide vaccines were composed of one to several human leukocyte antigen (HLA)-class I-restricted peptides of a single HLA-type. Personalised peptide vaccination (PPV) includes vaccine antigens selected and administered based on pre-existing host immunity before vaccination: 12 peptides for HLA-A2, 14 peptides for HLA-A24, nine peptides for HLA-A3 supertype, and four peptides for HLA-A26 (Takayama 2016).

OSE2101

The vaccine includes modified HLA-A2+-restricted neoepitopes that target tumour-associated antigens frequently overexpressed in NSCLC (human epidermal growth factor receptor 2 (HER2/neu), carcinoembryonic antigen (CEA), melanoma antigen genes 2 and 3 (MAGE 2 and 3), and p53) and generate a specific cytotoxic T cell response, stimulating killer T cells, allowing them to detect and kill cancer cells (Besse 2023).

SRL172 - killed *Mycobacterium vaccae*

SRL172 is a suspension of killed *Mycobacterium vaccae*, a rapidly growing mycobacterium that normally grows as an environmental saprophyte (O'Brien 2004). It has several functions relevant to its activity in cancer, including activation of antigen-presenting cells (APCs), Th1 adjuvant properties, suppression of pre-existing Th2 responses (via activation of regulatory T cells), and activation of natural killer (NK) cells (O'Brien 2004).

Why it is important to do this review

The evaluation of potential therapies aimed at treating advanced non-small cell lung cancer has a crucial role in guiding future medical treatment to improve the survival rates of this deadliest malignant disease. As previously described, immunotherapy has become a cutting-edge clinical approach to treating cancer (Domingues 2014). Therapeutic vaccines represent a viable immunotherapy option that stimulates the immune system to fight against tumour antigens. Thus, a review of current clinical trials is important to evaluate the clinical outcomes of this treatment.

Existing systematic reviews in this area are scarce and have limitations. A recent Cochrane review assessed the effect of vaccines in people with non-small cell lung cancer, but it did not include studies on people with advanced stages (Zhu 2021). Two reviews that did include studies in people with advanced lung cancer are now rather dated and do not include recently published studies (Dammeijer 2016; Wang 2015). Furthermore, the Dammeijer 2016 and Wang 2015 reviews did not address the health-related quality of life of the participants, which is paramount for people with advanced lung cancer, and they also pooled studies examining different types of vaccines.

Thus, this review is important because it provides an up-to-date synthesis and analysis of the current evidence on the effects of therapeutic vaccines in people with advanced non-small cell lung cancer, covers health-related quality of life, and evaluates separately the specific effects of each type of vaccine.

The present review focuses only on therapeutic vaccines for advanced NSCLC, whatever the line of treatment or maintenance treatment.

OBJECTIVES

To evaluate the effectiveness and safety of different types of therapeutic vaccines for people with advanced non-small cell lung cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We included only parallel-group, randomised controlled trials (RCTs) in which participants were assigned to interventions by chance. We did not include cluster-randomised trials or quasi-randomised trials.

Types of participants

We included participants older than 18 years with histologically-confirmed, advanced-stage NSCLC (stages IIIB or IV), whatever the line of treatment.

We excluded studies if, in addition to participants with advanced NSCLC, they also included participants with non-advanced NSCLC (cancer stages lower than IIIB) and did not provide separate data for participants with advanced NSCLC.

Types of interventions

Therapeutic cancer vaccine interventions targeting tumour-associated antigens. Therefore, we included the following interventions in this review.

- Therapeutic cancer vaccines alone or in combination with chemotherapy versus supportive care, no treatment, or placebo
- Therapeutic cancer vaccines alone or in combination with chemotherapy versus chemotherapy alone, as stated in current treatment guidelines.

Vaccines can be used as first- or second-line treatments or as maintenance treatment post-induction treatment.

We excluded studies that gave both groups vaccines and studies with multicomponent interventions which would preclude isolating for the effect of the vaccine.

We also excluded studies that gave vaccines withdrawn by their manufacturers for being ineffective in treating advanced NSCLC, as these are unavailable for use in clinical practice: tecemotide, belagenpumatucel-L, and melanoma antigen gene (MAGE)-A3 peptide vaccines.

Types of outcome measures

We considered the following outcomes in this review.

Primary outcomes

- Overall survival: defined as the interval between the date of randomisation and the date of death from any cause.
- Progression-free survival: defined as the interval between the date of randomisation and the appearance of new lesions, or the progression of the primary tumour, preferably according to RECIST criteria for studies done after the year 2009 (Response Evaluation Criteria in Solid Tumour (RECIST 2009)), or death.
- Serious treatment-related adverse events, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Freites-Martinez 2021).

Secondary outcomes

- Survival rates: proportion of participants in a study who were still alive at: (1) three years and (2) five years.
- Health-related quality of life (HRQoL), measured with standard and psychometrically validated instruments with application in cancer, such as the 30-item European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 (Aaronson 1993; Damm 2013; Smith 2014)). Improvement was defined as a 10-point or greater increase in functional scores or a 10-point or greater decrease in symptom scores of the EORTC QLQ-C30 questionnaire (Maringwa 2011). For the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire, a 2- to 3-point change in the Lung Cancer Subscale (LCS) and a 5- to 6-point change in the Trial Outcome Index (TOI) are considered minimally important differences (Cella 2002).

Search methods for identification of studies

The Cochrane Lung Cancer Information Specialist designed and ran our search strategies for the three main databases (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase).

Electronic searches

We searched for eligible trials, without language restrictions, in:

- The Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, from inception to 22 August 2023;
- MEDLINE (via PubMed from 1966 to 22 August 2023);
- Embase (from 1974 to 22 August 2023);
- Wanfang Data (from 2017 to July 2022);
- China Journal Net (often referred to as CNKI) (from 2017 to July 2022).

The search strategy combined terms from the Medical Subject Heading (MeSH), free-text terms, and appropriate indexing terms relevant to other information sources. Our MEDLINE search string was developed according to the Cochrane Highly Sensitive Search Strategy, sensitivity-maximizing version (2008 version) as referenced in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2023). Our search strategies are presented in Appendix 2 (CENTRAL), Appendix 3 (MEDLINE), Appendix 4 (Embase), Appendix 5 (Wanfang Data), and Appendix 6 (China Journal Net).

Searching other resources

We reviewed the reference lists of the included studies to identify other primary clinical trials.

We searched the grey literature by conducting a manual search for potentially eligible trials in abstracts from the following conference proceedings for the years 2020 to 2023:

- American Society of Clinical Oncology (ASCO; www.asco.org/), up to 22 September 2023;
- European Society of Medical Oncology (ESMO; www.esmo.org), up to 22 September 2023;
- American Association for Cancer Research (AACR; www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=54#.WsZl0C7waM9), up to 22 September 2023;
- Tumor & Cancer Immunology and Immunotherapy (tumorimmunology.conferenceseries.com/), up to 22 September 2023.

We searched for errata or retractions from included trials, according to the guidance in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2023).

Data collection and analysis

Four review authors (MC-J, JR, MR-E, EJ) performed the data collection and analysis, using standard Cochrane methodological procedures (Higgins 2023a). We assessed all potentially eligible studies for inclusion, regardless of the language of publication.

Selection of studies

Four review authors (MC-J, JR, MR-E, EJ) independently screened articles by titles and abstract; we retrieved full-text documents that possibly met the review's inclusion criteria. Three review authors (MC-J, JR, MR-E) independently screened the full-text articles for eligibility. We used Covidence to manage duplication detection and full-text evaluation. We contacted study authors when necessary to help us make a decision about the inclusion of a study and to request additional data. A consensus was reached regarding the inclusion or exclusion of a trial. We reported the reasons for excluding a trial. We created a PRISMA flowchart to show the process graphically (Moher 2009).

Data extraction and management

Four review authors (MC-J, JR, MR-E, EJ) independently extracted clinical and methodological information. Two review authors (JR, MR-E) independently extracted quantitative data for effect sizes, using a standard data collection form. We resolved any discrepancies regarding the extracted data by consensus or by consulting another review author.

We used a standardised form designed for this review to collect data for each included study, and we extracted the following information.

- Methods: design of the study, setting and year, duration of follow-up, publication status (published or unpublished).
- Participants: main characteristics (sex, age), number randomised to trial arms, and baseline clinical characteristics (clinical stage or severity at inception, time since first-line treatment).
- Interventions: details of experimental intervention and comparison, dosage, and timing.
- Outcomes: primary and secondary outcomes of the study as reported in publications, obtained from trial protocols, or both.
- Other: trial registration code; funding; conflicts of interest reported.

If reports did not provide appropriate or sufficient information, we contacted study authors, requesting additional information.

Assessment of risk of bias in included studies

Three review authors (MC-J, JR, MR-E), working in two-person subgroups, independently assessed the methodological quality of each study using the Cochrane risk of bias (RoB 1) tool, described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we could not resolve disagreements through discussion, we consulted a third review author.

For each risk of bias domain, we assigned a rating of low, unclear, or high risk of bias, based on the following definitions.

- Was the allocation sequence adequately generated? We considered randomisation adequate (low risk of bias) if the allocation sequence was generated from a table of random numbers or by computer. We judged a study to have an unclear risk of bias if the study report stated that the trial was randomised, but did not describe the method.
- Was allocation adequately concealed? We deemed allocation concealment to be adequate (low risk of bias) if the report stated that it was undertaken using sequentially pre-numbered, sealed opaque envelopes, or by a centralised system. We judged a study to have an unclear risk of bias if the study report stated that the allocation was concealed, but did not describe the method.
- Was knowledge of the allocated intervention adequately prevented during the study? Effective blinding of participants can be difficult to apply to trials of anticancer treatment because of the known potential toxicity of chemotherapy. We evaluated the risk of bias separately for personnel, participants, and outcomes assessors, and for each outcome, when applicable. We considered that lack of blinding of participants and personnel could be a source of performance bias and detection bias for subjective outcomes (quality of life and progression-free survival), but not for objective outcomes (overall survival, survival rates at three and five years, and severe adverse events).
- Were incomplete outcome data adequately addressed? We examined whether imbalance across intervention groups could be seen in the numbers or reasons for missing data, the type of measures undertaken to handle missing data, and whether the analysis was carried out on an intention-to-treat (ITT) basis.
- Were reports of the study free of the suggestion of selective outcome reporting? We evaluated whether each predefined outcome was measured, analysed, and reported.
- Were there any other potential sources of bias?

We completed a risk of bias table for each included study and summarised risks of bias across studies, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023b).

Measures of treatment effect

For overall survival and progression-free survival, we measured the effect of treatment on time-to-event outcomes using the hazard ratio (HR) with a 95% confidence interval (CI). We extracted HRs and standard errors from the reported data or estimated them from other data or graphs if possible (Tierney 2007). We measured the proportions of participants surviving at three and five years, and the percentages of participants with at least one serious adverse event using the relative risk or risk ratio (RR) with 95% CI. For

continuous outcomes (HRQoL), we used mean differences (MDs) for measures using the same scale, and standardised mean differences (SMDs) for measures using different scales.

Unit of analysis issues

We included only parallel-group randomised trials in this review, and thus, there was no unit of analysis issues related to the inclusion of cluster-randomised trials or cross-over trials.

If trials included several intervention comparisons, we followed standard methodological approaches, as recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023c).

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). Also, for studies with full texts available, we attempted to obtain more information from study authors if details relevant to our analysis had not been reported. In future updates, if we cannot obtain additional data necessary for meta-analysis, we will try to estimate values from reported data (for example, estimating the HR from published survival curves (Tierney 2007)). We conducted the main analyses as 'available-data analysis', using ITT data from the included studies where they were available, and any reported data otherwise.

Assessment of heterogeneity

We used the I^2 statistic to assess heterogeneity amongst trials for each meta-analysis. The I^2 statistic describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error. We interpreted the I^2 value according to the following thresholds (Deeks 2023): 0% to 40% heterogeneity might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. We investigated substantial heterogeneity ($I^2 > 50\%$) by prespecified subgroup analysis.

Assessment of reporting biases

To address reporting bias and related small-study effects, we planned to draw funnel plots for each meta-analysis when advisable. If the required statistical conditions were met (i.e. inclusion of about 10 studies in a meta-analysis), we planned to use asymmetry tests (Page 2023). In future updates of this review, if there are sufficient studies, for dichotomous outcomes we will test asymmetry with the Harbord test if Tau^2 is less than 0.1 (Harbord 2006), and with the Rücker test if Tau^2 is more than 0.1 (Rücker 2008); and for continuous outcomes, we will use the regression asymmetry test (Egger 1997).

Data synthesis

We used meta-analysis to combine individual effect sizes when event percentages were available or could be calculated. We used Review Manager Web to analyse data for each comparison and outcome (RevMan Web 2022), using a random-effects model. This model assumes between-study variability in the observed effect beyond that due to random error. We presented all combined effect estimates with 95% CI.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses according to the following clinical characteristics:

- clinical stage (III or IV);
- sex of participants;
- NSCLC histological type (squamous versus non-squamous);
- time interval between the previous treatment line and beginning therapy with vaccines (three, six, or 12 months);
- Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1, or 0-1 versus 2) (Oken 1982; Prasad 2018).

However, ultimately, we did not attempt subgroup analyses for two reasons: (1) four of the therapeutic vaccines included in this review were evaluated in a single RCT; three vaccines were evaluated in two studies each, and in those cases, we did not find heterogeneity amongst their results; and (2) the final numbers of participants in the subgroups were too small for all proposed subgroup analyses and thus did not guarantee enough statistical power.

Sensitivity analysis

If relevant, in future updates of the review, we will conduct sensitivity analyses to assess whether the results are robust to decisions made during the review process. We will perform sensitivity analyses to explore the influence on the effect size by: (1) excluding unpublished studies; and (2) excluding lower-quality studies (i.e. those at high risk of bias).

Summary of findings and assessment of the certainty of the evidence

We present separate summary of findings tables for TG4010 and epidermal growth factor (Summary of findings 1; Summary of findings 2), as both of these vaccines were evaluated for efficacy and safety in two RCTs each, and these were sufficiently alike for pooling of results to make sense. We did not pool results from the two RCTs that examined racotumomab as one study compared racotumomab to placebo, whilst the other compared it to docetaxel. We created the summary of findings tables using the methods and recommendations described in the GRADE Handbookand using GRADEpro GDT software (GRADEpro GDT; Schünemann 2013). For the summary of findings tables, we used the five GRADE considerations (study limitations (i.e. risk of bias); consistency of the effect (heterogeneity if I^2 was higher than 50%); imprecision (if the confidence interval contains the threshold of clinical relevance and no clear conclusions can be drawn); indirectness; and publication bias) to assess the certainty of the body of evidence.

We included the following outcomes: overall survival, progression-free survival, serious treatment-related adverse events, survival rates at three and five years, and health-related quality of life.

When assessing the certainty of the evidence for imprecision, we considered a clinically relevant improvement for the EORTC QLQ-C30 questionnaire to be a 10-point or greater increase in functional scores or a 10-point or greater decrease in symptom scores (Maringwa 2011). For the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire, a 2- to 3-point change in the Lung Cancer Subscale (LCS) and a 5- to 6-point change in the Trial Outcome Index (TOI) are considered minimally important differences (Cella 2002).

When data aggregation was not possible, we presented the results of individual studies narratively and discussed them in the text.

RESULTS

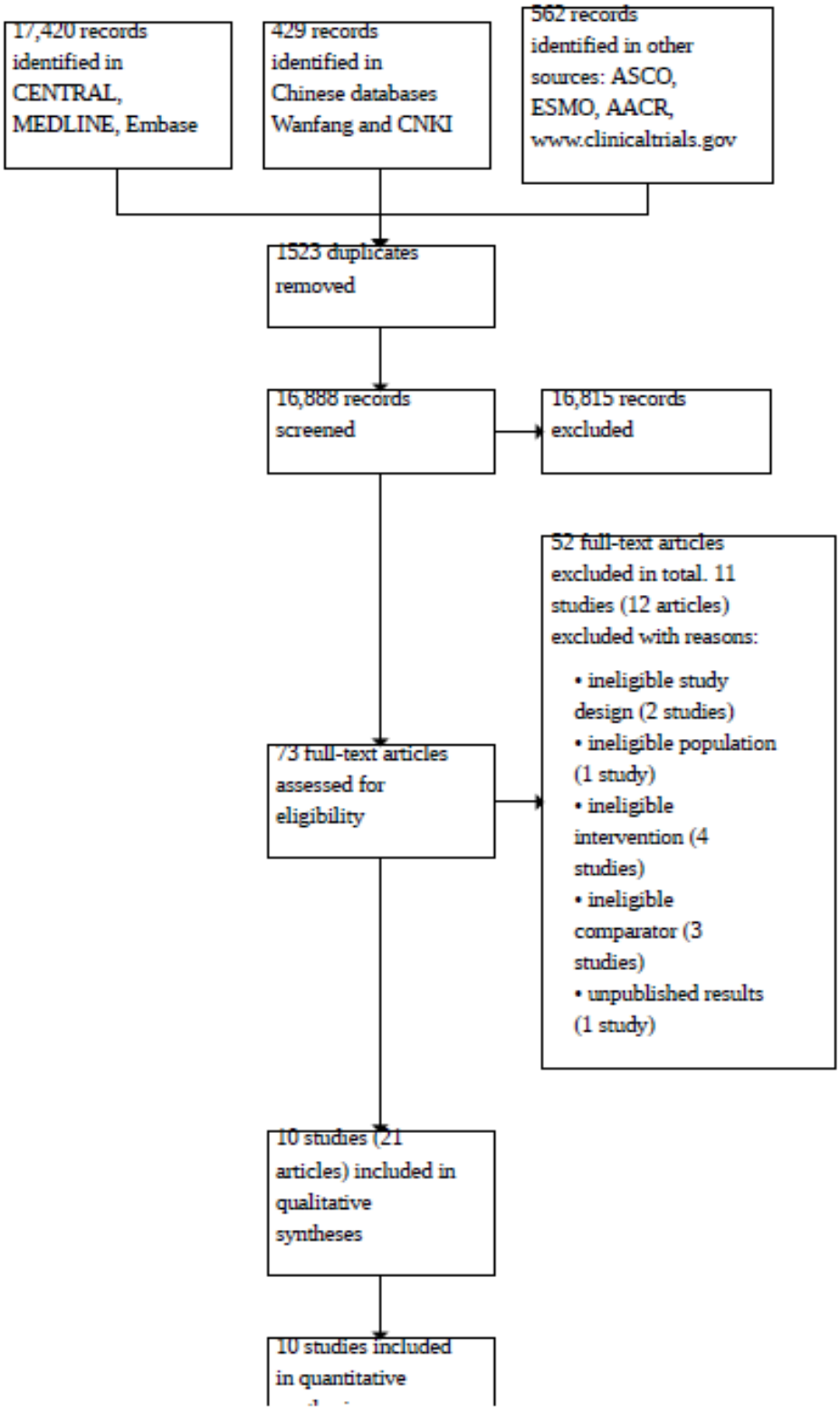
Description of studies

Details are available in Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We identified 18,411 records through electronic database searches. After the removal of duplicates, we screened 16,888 records by titles and abstracts and discarded 16,815 as irrelevant to the review. We retrieved the remaining 73 records in full text for further assessment. Of these, we included 10 studies (21 references) in the review, and we excluded 11 studies (12 references) with reasons. We discarded the remaining 40 references as irrelevant to the review (see Figure 1).

Figure 1. Study flow diagram



Included studies

Four studies were conducted in European countries (Gridelli 2020; O'Brien 2004; Quoix 2011; Quoix 2016); four studies were conducted in Cuba (Alfonso 2014; Hernandez 2021; Neninger 2008; Rodriguez 2016); one study was conducted in several different European countries, Israel, and the USA (Besse 2023); and the remaining study was conducted in Japan (Takayama 2016). Taken together, the 10 studies randomised a total of 2177 participants. Our outcome analyses included only 2045 participants (1401 men and 644 women).

Two studies assessed TG4010, a vector-based vaccine (Quoix 2011; Quoix 2016); two studies assessed an epidermal growth factor vaccine (Neninger 2008; Rodriguez 2016); two studies assessed racotumomab-alum (Alfonso 2014; Hernandez 2021); and one study each assessed hTERT (vx-001) (Gridelli 2020), a personalised peptide vaccine (Takayama 2016), OSE2101 (Besse 2023), and SRL172 (killed *Mycobacterium vaccae*) (O'Brien 2004).

In two studies, vaccines were part of first-line treatment (Quoix 2011; Quoix 2016); in four studies, participants received the vaccines as maintenance treatment after finishing first-line chemotherapy (Alfonso 2014; Gridelli 2020; Hernandez 2021; Takayama 2016). In two studies, the vaccine was used for switch maintenance after first-line treatment (Neninger 2008; Rodriguez 2016); in one study, participants had previously received one line of immune checkpoint blockers (Besse 2023); and one study included participants in first-line or maintenance treatment (O'Brien 2004).

In the included studies, whatever the line of treatment (first- or second-line), all participants received chemotherapy or a usual anticancer treatment and were then randomised to receive a therapeutic vaccine added to it.

Eight of the included studies were prospectively registered in publicly accessible clinical trial registers. We found no registry information for two studies (Neninger 2008; O'Brien 2004).

In terms of the review's prespecified outcomes, seven studies reported data on rates of overall survival (Alfonso 2014; Besse 2023; Gridelli 2020; Quoix 2011; Quoix 2016; Rodriguez 2016; Takayama 2016), and three on rates of progression-free survival (Alfonso 2014; Quoix 2011; Takayama 2016). All included studies provided data on severe adverse events. Six studies provided data on survival percentages at three years and five years (Alfonso 2014; Besse 2023; Gridelli 2020; Neninger 2008; Quoix 2011; Rodriguez 2016), and only four reported on health-related quality of life (Besse 2023; O'Brien 2004; Quoix 2011; Rodriguez 2016).

Two studies were terminated prematurely. The Rodriguez 2016 trial on epidermal growth factor vaccine CIMAvax-EGF was stopped before reaching the intended sample size, at the second interim analysis, after the Cuban National Regulatory Agency approved the vaccine for marketing. The sponsor of the Besse 2023 study on OSE2101 stopped the trial prematurely in April 2020 at the recommendation of an independent data monitoring committee, due to the risk that the coronavirus disease 2019 (COVID-19) pandemic posed to data integrity.

Excluded studies

We excluded 64 full-text articles in total at the full-text screening stage. Following the guidance in the *Cochrane Handbook of Systematic Review of Interventions* (Lefebvre 2023), we selected 11 excluded studies (12 articles in total) that readers might plausibly expect to see amongst the included studies, and we have listed these, together with reasons for exclusion, in the Characteristics of excluded studies table. We discarded the remaining 52 articles as irrelevant to the review. We excluded the 11 studies for the following reasons:

- ineligible study design: single-arm studies (two studies: Saavedra 2017; Sebastian 2014);
- ineligible participants: planned to include people with stage IIIA cancer (as well as higher stages); study results not published (one study: Wu 2011).
- ineligible intervention: (1) vaccine given as part of a multicomponent intervention, which precluded assessing the separate effect of the vaccine (two studies: Cohen 2014; Ramalingam 2014); (2) vaccine withdrawn by manufacturers (two studies: Butts 2014; Katakami 2017).
- ineligible comparison: comparison of different schedules or maintenance schemes for the same vaccine (three studies: Gray 2018; Ramlau 2008; Saavedra 2021);
- unpublished results (one study: Govindan 2014).

Risk of bias in included studies

In most cases, we assessed the risk of bias in the included studies using information published in full-text papers, available in trial protocols publicly accessible from clinical trial registries, or both. We requested additional information from more than 30 authors; only three responded with partial information on their studies (Besse 2023; Hernandez 2021; Neninger 2008). For those studies whose authors did not respond to our requests, we deemed the risk of bias for some domains to be unclear.

In Figure 2, we present a graph displaying our global assessment of the risk of bias for each domain for all included trials, presented as percentages. In Figure 3, we present a summary of our judgements about each risk of bias domain for each included study. For detailed explanations of our judgements for each study, see the risk of bias tables in the Characteristics of included studies section.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

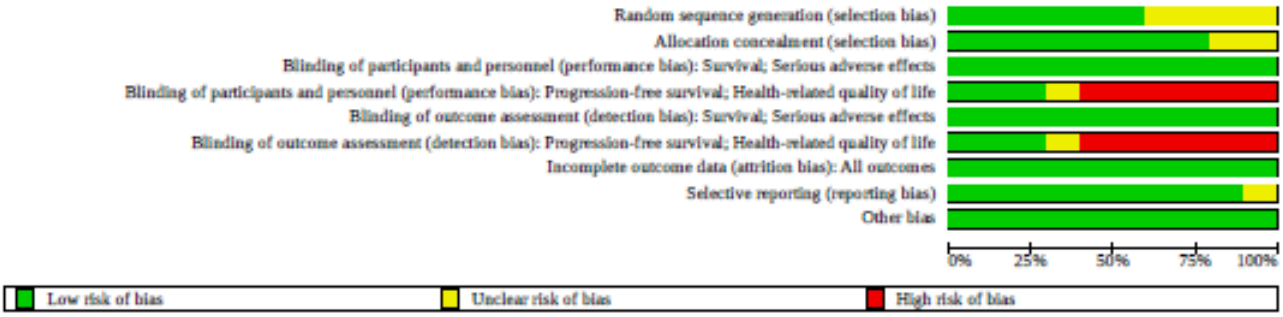


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

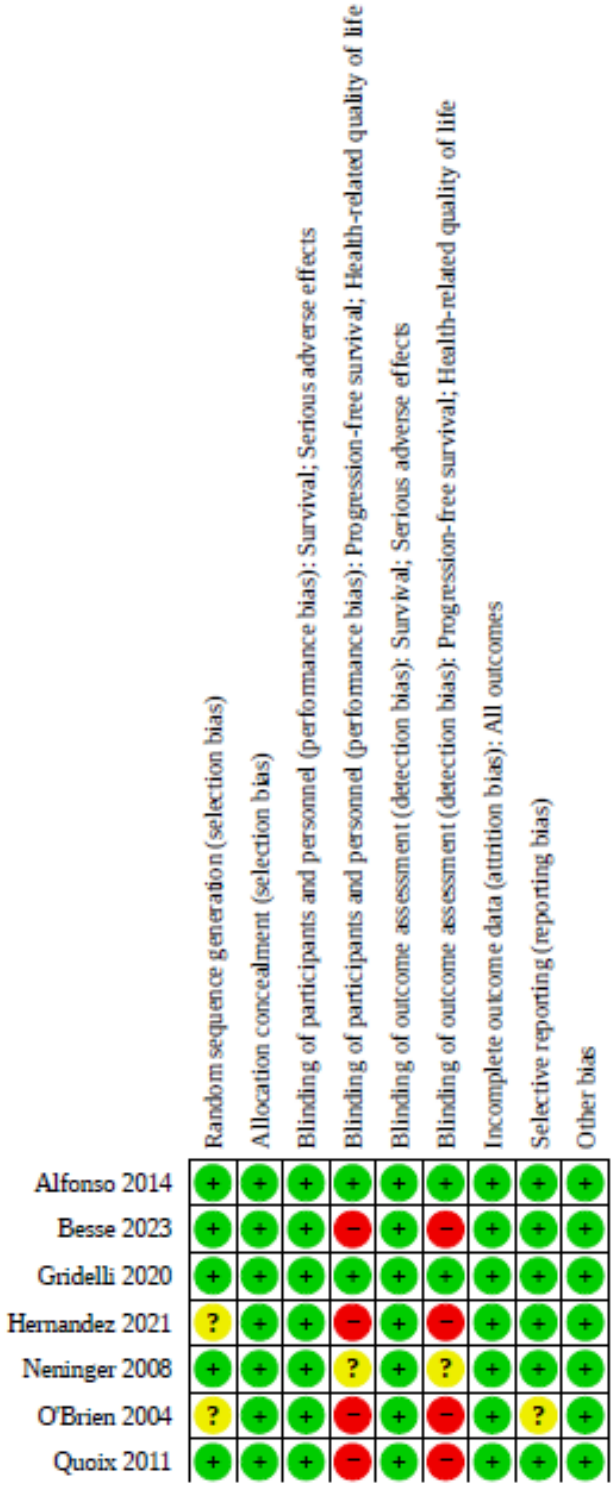
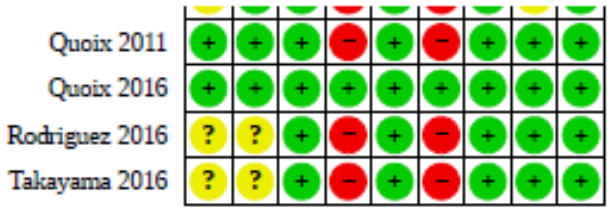


Figure 3. (Continued)



Allocation

Six included studies used adequate methods of sequence generation and allocation concealment, and therefore we considered them at low risk of selection bias (Alfonso 2014; Besse 2023; Gridelli 2020; Neninger 2008; Quoix 2011; Quoix 2016).

For the remaining four studies, we did not find relevant information on sequence generation procedures, allocation concealment, or both, and we classified them as being at unclear risk of selection bias. We sent emails requesting additional information (where we had contact information for corresponding authors or contact persons in clinical trials registers), but we received no replies.

Blinding

Blinding of participants and personnel (performance bias)

In three included studies, participants and personnel were blinded (Alfonso 2014; Gridelli 2020; Quoix 2016); we judged these to be at low risk of performance bias for subjective outcomes.

Six included studies had an open-label design (Besse 2023; Hernandez 2021; Quoix 2011; O'Brien 2004; Rodriguez 2016; Takayama 2016). We considered these, by default, to be at high risk of performance bias for the review's subjective outcomes of progression-free survival and HRQoL, if they measured these outcomes in their studies: Takayama 2016 assessed only progression-free survival; Rodriguez 2016 and O'Brien 2004 assessed only HRQoL; and Besse 2023, Hernandez 2021, and Quoix 2011 evaluated both outcomes. However, we considered that the non-blinding of participants and personnel was not a source of bias for the review's objective outcomes related to death (overall survival and survival rate at three and five years) and for severe adverse events.

One study did not report blinding (Neninger 2008).

Blinding of outcome assessors (detection bias)

We considered that the lack of blinding of outcome assessors could be a source of high risk of detection bias for the same cases described above for performance bias.

Incomplete outcome data

We did not detect a risk of attrition bias in any of the included studies. There were few losses to follow-up in the studies.

Selective reporting

For the studies registered in publicly-accessible clinical trials registers, we compared the outcomes described in the registries with those reported in study publications, and we judged them as having a low risk of reporting bias. For studies that were not prospectively registered, we checked whether their publications reported on all outcomes that could reasonably be expected to be assessed in these types of trials.

Most of the studies did not provide sufficient detail about their statistical methods, which impeded a proper evaluation of selective reporting bias.

Other potential sources of bias

For those studies that provided sufficient information, we checked for possible baseline differences between the intervention and comparator groups. We did not detect any potential bias related to baseline differences.

We did not conduct publication bias analysis using funnel plots since there were insufficient studies for each treatment comparison (Page 2023).

Effects of interventions

See: **Summary of findings 1** TG4010 added to chemotherapy compared to chemotherapy alone in first-line treatment; **Summary of findings 2** Epidermal growth factor versus best supportive care for switch maintenance after first-line treatment

Comparison 1. TG4010 plus chemotherapy compared to chemotherapy alone in first-line treatment

Two studies with 370 participants analysed the effects of a vector-based vaccine, TG4010, as part of first-line treatments (Quoix 2011; Quoix 2016). Participants had stage IIIB or IV non-small cell lung cancer without a known activating EGFR mutation and with MUC1 expression in at least 50% of tumoural cells, previously untreated.

The Quoix 2011 study was conducted in 23 centres in France, Poland, Germany, and Hungary. It included 148 participants: 107 men and 41 women. Of these, 74 were randomised to vaccine plus chemotherapy and 74 to chemotherapy alone. Twelve participants had stage IIIB cancer and 136 had stage IV cancer. Their mean age was 58 years. They were followed up for 50 months.

The Quoix 2016 study was conducted in 45 centres in France, Belgium, the UK, Italy, Spain, Hungary, Poland, Israel, and the USA. It included 222 participants: 142 men and 80 women. Of these, 111 were randomised to vaccine plus chemotherapy and 111 to chemotherapy alone. All participants had stage IV cancer. Their mean age was 61 years. They were followed up for 36 months.

See Summary of findings 1.

Primary outcomes

Overall survival

Pooled results showed that adding TG4010 to first-line chemotherapy may result in little to no difference in overall survival compared with chemotherapy alone (HR 0.83, 95% CI 0.65 to 1.05; I^2 = 0%; 2 studies, 370 participants; low-certainty evidence; Analysis 1.1). We downgraded the certainty of the evidence by two levels for imprecision. Median survival for the vaccine and no-vaccine groups was 10.7 months versus 10.3 months, respectively, in Quoix 2011, and 12.7 months and 10.6 months in Quoix 2016.

Progression-free survival

Only Quoix 2016 evaluated this outcome and found that adding the TG4010 vaccine may slightly increase participants' progression-free survival compared with chemotherapy alone (HR 0.74, 95% CI 0.55 to 0.99; 1 study, 222 participants; low-certainty evidence; Analysis 1.2). We downgraded the certainty of the evidence by two levels for imprecision. Median progression-free survival for the vaccine and non-vaccine groups in the study was 5.9 versus 5.1 months, respectively.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

Both studies evaluated the percentages of participants who had at least one serious adverse event. Pooled results showed that adding the TG4010 vaccine to first-line chemotherapy may result in little to no difference in the proportion of participants with at least one serious adverse event compared with chemotherapy alone, but the evidence is very uncertain (RR 0.70, 95% CI 0.23 to 2.19; I^2 = 75%; 2 studies, 362 participants; very low-certainty evidence; Analysis 1.3). We downgraded the certainty of the evidence by two levels for imprecision and one level for heterogeneity.

Quoix 2011 provided detailed data on the number of serious adverse events in each treatment group, and reported 88 serious adverse events in the 73 participants who received the vaccine and 99 in the 72 participants who did not receive the vaccine.

Secondary outcomes

Survival rates at three and five years

Only Quoix 2011 provided data on this outcome and found that adding the TG4010 vaccine to first-line chemotherapy may result in little to no difference in the survival rate at three years (RR 1.0, 95% CI 0.30 to 3.31; 1 study, 148 participants; low-certainty evidence; Analysis 1.4). We downgraded the certainty of the evidence by two levels for imprecision. None of the participants in the study were alive at five years.

Health-related quality of life (HRQoL)

None of the studies provided data to compare scores on a health-related quality of life scale between groups before and after the treatments.

Quoix 2011 assessed HRQoL, using the Functional Assessment of Cancer Therapy-Lung (FACT-L) at baseline and every six weeks, measuring the "Time until definitive deterioration" (TUDD) of the four well-being dimensions of the FACT-L (physical (PWB), functional (FWB), emotional (EWB), and social well-being (SWB)) and the Lung Cancer Subscale (LCS) domains for a 5-point minimal clinically important difference. The study reported that "no difference of TUDD of HRQOL has been found between treatment arms".

Comparison 2. Epidermal growth factor vaccine versus best supportive care for switch maintenance after first-line treatment

Two studies carried out in Cuba, which included 485 participants in total, compared adding an epidermal growth factor vaccine between one and two months after finishing chemotherapy to best supportive care (Neninger 2008; Rodriguez 2016).

The Neninger 2008 study included 80 participants: 59 men and 21 women. Forty participants were randomised to the vaccine and 40 to best supportive care. Fifty participants had stage IIIB cancer and 30 had stage IV. Their mean age was 56 years. They were followed up for 50 months.

The Rodriguez 2016 study included 405 participants: 264 men and 141 women. Of these, 270 were randomised to vaccine and 135 to control; 257 participants had stage IIIB and 134 had stage IV. Their mean age was not reported. They were followed up for 84 months. The Rodriguez 2016 trial on epidermal growth factor vaccine CIMAvax-EGF was stopped before reaching the intended sample size, at the second interim analysis, after the Cuban National Regulatory Agency approved the vaccine for marketing.

See Summary of findings 2.

Primary outcomes

Overall survival

Only Rodriguez 2016 reported a hazard ratio for overall survival, showing that epidermal growth factor vaccine may result in little to no difference in overall survival compared with best supportive care (HR 0.82, 95% CI 0.66 to 1.02; 1 study, 378 participants; low-certainty evidence; Analysis 2.1). We downgraded the certainty of the evidence by two levels for imprecision. Median survival times in the vaccine and control groups were 6.5 months versus 5.3 months, respectively (Neninger 2008), and 10.8 versus 8.9 months (Rodriguez 2016).

Progression-free survival

Neither study assessed this outcome.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

Pooled results showed that adding the vaccine may result in little to no difference in the proportion of people with at least one serious adverse event compared with best supportive care (RR 1.32, 95% CI 0.88 to 1.98; 2 studies, 458 participants; low-certainty evidence; Analysis 2.2). We downgraded the certainty of the evidence by two levels for imprecision.

Secondary outcomes

Survival rates at three and five years

Both studies provided data necessary to calculate survival rates at three years. Only Rodriguez 2016 followed participants for five years.

Survival rate at three years: pooled results showed that the vaccine may result in no difference in the survival rate at three years compared with best supportive care (RR 1.45, 95% CI 0.82 to

2.54; 2 studies, 458 participants; low-certainty evidence; Analysis 2.3). We downgraded the certainty of the evidence by two levels for imprecision.

Survival rate at five years: results showed that the vaccine may increase the survival rate slightly at five years compared with best supportive care (RR 3.40, 95% CI 1.02 to 11.27; 1 study, 378 participants; low-certainty evidence; Analysis 2.4). We downgraded the certainty of the evidence by two levels for imprecision.

Health-related quality of life (HRQoL)

Rodriguez 2016 analysed the effect of the treatments on the HRQoL of the participants, evaluated with the EORTC QLQ-C30 questionnaire at three to six months of treatment. Compared to best supportive care, the vaccine may result in little to no difference in global health status, but the evidence is very uncertain (MD 7.90, 95% CI -0.49 to 16.29; 1 study, 86 participants; very low-certainty evidence; Analysis 2.5). We downgraded the certainty of the evidence two levels for risk of bias (lack of blinding; incomplete outcome data), and one level for imprecision.

Comparison 3. hTERT (vx-001) vaccine versus placebo for maintenance treatment after first-line chemotherapy

One study with participants from 70 places in Europe assessed this comparison (Gridelli 2020). The study included 221 participants, 109 were randomised to the vaccine and 112 to placebo (Gridelli 2020). Ultimately, 190 participants were included in the analyses: 132 men and 58 women.

All participants had metastatic NSCLC that did not progress after first-line platinum-based chemotherapy, and had human leukocyte antigen HLA-A*0201 haplotype and tumoural expression of TElomerase Reverse Transcriptase (TERT).

Fifty-three per cent of participants were older than 65 years and 46.5% were younger than 65 years. They were followed up for 50 months.

Primary outcomes

Overall survival

Data from the study showed that the vaccine may result in little to no difference in overall survival compared with placebo (HR 0.97, 95% CI 0.70 to 1.34; 1 study, 190 participants; Analysis 3.1). Median survival times in the vaccine and control groups were 14.3 versus 11.3 months, respectively.

Progression-free survival

The study did not assess this outcome.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

The authors did not provide detailed data on this outcome. They reported that no participant required treatment discontinuation because of severe grade 3 or 4 adverse events, and mentioned that a participant developed grade 3 fever, which completely resolved with paracetamol within two days.

Secondary outcomes

Survival rates at three and five years

Survival rate at three years: the study did not report survival data at three years. However, the authors reported on data at 40 months of follow-up. Results showed that there might be no differences in survival at 40 months between the vaccine and best supportive care (RR 0.38, 95% CI 0.04 to 3.57; 1 study, 190 participants; Analysis 3.2).

Survival rate at five years: no participants were alive at 50 months of follow-up.

Health-related quality of life (HRQoL)

The study did not assess this outcome.

Comparison 4. Racotumomab versus placebo for switch maintenance treatment after first-line chemotherapy

One study conducted in Cuba assessed this comparison (Alfonso 2014). It included 176 participants: 118 men and 58 women; 87 were randomised to the vaccine and 89 to placebo. The participants had stage IIIB/IV NSCLC and had at least stable disease after first-line chemotherapy. Ninety-nine participants had stage IIIB cancer and 77 had stage IV cancer. Seventy-nine participants were 60 years old or less and 97 were over 60 years. They were followed up for 84 months.

Primary outcomes

Overall survival

Data from the study showed that racotumomab may increase overall survival compared with placebo (HR 0.63, 95% CI 0.46 to 0.87; 1 study, 176 participants; Analysis 4.1). Median survival times in the vaccine and control groups were 8.2 versus 6.8 months, respectively.

Progression-free survival

Data from the study showed that racotumomab may have little or no effect on progression-free survival compared with placebo (HR 0.73, 95% CI 0.53 to 1.00; 1 study, 176 participants; Analysis 4.2). Median progression-free survival times in the vaccine and control groups were 5.3 versus 3.9 months, respectively.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

The study showed that the vaccine may result in little to no difference in the proportion of people with at least one serious adverse event compared with placebo (RR 1.03, 95% CI 0.15 to 7.18; 1 study, 175 participants; Analysis 4.3).

Secondary outcomes

Survival rates at three and five years

Survival rate at three years: the vaccine may increase the survival rate at three years compared with placebo (RR 4.09, 95% CI 1.20 to 14.00; 1 study, 176 participants; Analysis 1.4).

Survival rate at five years: the vaccine may result in little to no difference in the survival rate at five years compared with placebo (RR 2.05, 95% CI 0.38 to 10.88; 1 study, 176 participants; Analysis 4.5).

Health-related quality of life (HRQoL)

The study did not assess this outcome.

Comparison 5. Racotumomab versus docetaxel for switch maintenance treatment after first-line chemotherapy

One study conducted in Cuba assessed this comparison (Hernandez 2021). It included 145 participants: 88 men and 57 women; 93 were randomised to vaccine and 52 to docetaxel. Participants had stage IIIB or IV NSCLC, with an objective response or stable disease after first-line chemotherapy. Forty-six participants had stage IIIB cancer and 94 had stage IV cancer. The participants' mean age was 63 years. They were followed up for 45 months.

Primary outcomes

Overall survival

The study assessed survival but did not report the hazard rate for overall survival. Median survival times in the vaccine and control groups were 9.8 and 8.6 months, respectively.

Progression-free survival

The study assessed survival but did not report the hazard rate for progression-free survival. Median progression-free survival times in the vaccine and control groups were 4.4 and 4.0 months, respectively.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

The study showed that racotumomab may result in little to no difference in the proportion of people with at least one serious adverse event compared with docetaxel (RR 0.89, 95% CI 0.44 to 1.83; 1 study, 145 participants; Analysis 5.1).

Secondary outcomes

Survival rates at three and five years

The study did not assess these outcomes.

Health-related quality of life (HRQoL)

The study reported that quality of life assessment had similar results in both groups, but did not provide detailed data.

Comparison 6. Personalised peptide vaccine plus docetaxel versus docetaxel plus placebo after first-line treatment

One study conducted in Japan assessed this comparison (Takayama 2016). It included 50 participants: 41 men and 9 women; 26 were randomised to vaccine plus docetaxel and 24 to docetaxel plus placebo. Participants had advanced NSCLC with epidermal growth factor receptor (EGFR) wild genotype previously treated by chemotherapy. Eleven participants had stage IIIB cancer, 34 had stage IV cancer, and five had recurrent cancers. The mean age was 65 years. They were followed up for 700 days (i.e. 23 months).

Primary outcomes

Overall survival

Data from the study showed that adding the personalised peptide vaccine to docetaxel may result in little to no difference in overall survival compared with docetaxel plus placebo (HR 0.80, 95% CI 0.42 to 1.52; 1 study, 50 participants; Analysis 6.1). Median survival times in the vaccine and control groups were 10.5 versus 7.7 months, respectively.

Progression-free survival

Data from the study showed that adding the personalised peptide vaccine to docetaxel may result in little to no difference in progression-free survival compared with docetaxel plus placebo (HR 0.78, 95% CI 0.43 to 1.42; 1 study, 50 participants; Analysis 6.2). The median progression-free survival times for the vaccine and no-vaccine groups in the study were 1.9 versus 1.7 months, respectively.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

The study did not report the number of participants with at least one serious adverse event. Amongst the 26 participants treated with the vaccine, study authors reported 38 serious grade 3 to 4 adverse events, and 35 events amongst the 24 participants who did not receive the vaccine.

Secondary outcomes

Survival rates at three and five years

The study did not assess this outcome.

Health-related quality of life (HRQoL)

The study did not assess this outcome.

Comparison 7. OSE2101 vaccine versus chemotherapy in HLA-A2+ advanced NSCLC in second/third-line treatment after failure with immune checkpoint inhibitors

One study carried out in the Czech Republic, France, Germany, Hungary, Italy, Israel, Poland, Spain, and the USA, assessed this comparison (Besse 2023). The study planned to recruit at least 363 participants, but recruitment was stopped prematurely in April 2020 at the recommendation of an independent data monitoring committee, due to the risk that the coronavirus disease 2019 (COVID-19) pandemic posed to data integrity. Eligible participants had received one line of immune checkpoint blocker (ICB) therapy for locally advanced or metastatic epidermal growth factor receptor/anaplastic lymphoma kinase (EGFR/ALK)-negative NSCLC, given sequentially (second-line), or combined with platinum-based chemotherapy (first-line) with disease progression (measurable and non-measurable disease), Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and central confirmation of HLA-A2 positivity in total blood. Participants with baseline brain metastases were eligible if asymptomatic.

Ultimately, the study included 219 participants: 139 randomised to the vaccine and 80 to standard-of-care chemotherapy. There were 155 men and 64 women. The participants' mean age was 65 years. Two hundred and five participants had stage IV cancer, and 14 had stage III cancer. They were followed up for 24 months.

Primary outcomes

Overall survival

The study showed that the vaccine may result in little to no difference in overall survival compared with standard-of-care chemotherapy (HR 0.86, 95% CI 0.62 to 1.19; 1 study, 219 participants; Analysis 7.1). Median survival times in the vaccine and control groups were 8.8 versus 8.3 months, respectively.

Progression-free survival

Data on this outcome have not yet been published.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

Data showed that the vaccine may result in little difference in the proportion of people with at least one serious adverse event compared with chemotherapy (RR 0.95, 95% CI 0.91 to 0.99; 1 study, 219 participants; Analysis 7.2).

Survival rates at three and five years

The study followed the participants for up to two years only.

Health-related quality of life (HRQoL)

Data on this outcome have not yet been published.

Comparison 8. SRL172 (killed *Mycobacterium vaccae*) added to chemotherapy versus chemotherapy alone in first-line treatment

One study conducted in centres in the UK, Austria, and Germany assessed this comparison (O'Brien 2004). It included 419 participants: 300 men and 119 women; 210 were randomised to vaccine plus chemotherapy and 209 to chemotherapy alone. Two hundred and fifty participants had stage IV cancer, 128 had stage IIIB, and 41 had stage IIIA. Fifty-nine participants had previously been treated with surgery and 38 with radiotherapy. The participants' mean age was 61 years. They were followed up for 700 days (i.e. 23 months).

Overall survival

The study did not provide hazard ratios, but reported no difference between the treatment groups in overall survival, with a median survival time of 223 days in the chemotherapy plus SRL172 group, compared to 225 days in the chemotherapy-alone group.

Progression-free survival

The study did not evaluate this outcome.

Serious treatment-related adverse events (CTCAE grades 3 to 5)

Data showed that adding the vaccine likely increases the proportion of participants having at least one serious adverse event compared with chemotherapy alone (RR 2.07, 95% CI 1.76 to 2.43; 1 study, 351 participants; Analysis 8.1).

Secondary outcomes

Survival rates at three and five years

The study followed the participants for up to 23 months only.

Health-related quality of life (HRQoL)

The study showed that adding the vaccine may result in a higher HRQoL for the participants, resulting in a smaller decrease in the "Global health status/QoL" score of the QLQ-C30 (EORTC QLQ) questionnaire, compared with chemotherapy alone (MD 7.60, 95% CI 2.26 to 12.94; 1 study, 351 participants; Analysis 8.2), as measured at the end of the 15-week treatment phase. The authors reported that by the end of the maintenance and survival phase, the differences observed at the end of the treatment phase in favour of the chemotherapy plus SRL172 group had diminished.

DISCUSSION

In this review, we assessed the efficacy and safety of seven different types of vaccines in the treatment of people with advanced non-small cell lung cancer (NSCLC). None of them resulted in large effects in the main outcomes of interest in this review: overall survival, progression-free survival, serious treatment-related adverse events, survival rates at three or five years, and participants' health-related quality of life.

Summary of main results

We included a total of 10 studies in this review. We excluded studies on vaccines withdrawn by their manufacturers for being ineffective in treating advanced NSCLC, as these are unavailable for use in clinical practice: tecemotide, belagenpumatucel-L, and MAGE A3 peptide vaccines.

TG4010, a vector-based vaccine, added to chemotherapy as part of first-line therapy, compared with chemotherapy alone, may increase slightly progression-free survival. It may result in little to no difference in overall survival, the proportion of participants with at least one serious treatment-related adverse event, and survival rates at three and five years.

Epidermal growth factor vaccine as switch maintenance treatment after first-line chemotherapy, compared to best supportive care, may result in little to no difference in overall survival, in the proportion of participants who have at least one serious treatment-related adverse event, and in the survival rate at three years. It may increase the survival rate slightly at five years.

The hTERT (vx-001) vaccine compared to placebo as maintenance treatment after first-line chemotherapy may result in little to no difference in overall survival and survival rates at five years.

Racotumomab as a switch maintenance treatment after first-line chemotherapy, compared to placebo, may increase overall survival. It may make little to no difference in progression-free survival, and in the proportion of participants with at least one serious treatment-related adverse event. It may increase survival rates at three years, but not at five years.

Racotumomab as switch maintenance therapy post-chemotherapy was compared to docetaxel, but researchers did not publish information on hazard rates for overall survival or progression-free survival time. Anyway, differences in median survival times were very short, less than one month. Racotumomab may result in little to no difference in the proportion of people with at least one serious adverse event compared with docetaxel.

Personalised peptide vaccine plus docetaxel compared to docetaxel plus placebo after chemotherapy treatment may result in little to no difference in overall survival and progression-free survival.

The OSE2101 vaccine compared with chemotherapy after chemotherapy or immunotherapy, in HLA-A2+ advanced NSCLC in second/third-line treatment after failure with immune checkpoint inhibitors, may result in little to no difference in overall survival. It may result in a slight decrease in the proportion of people having at least one serious treatment-related adverse event.

The SRL172 vaccine of killed *Mycobacterium vaccae*, added to chemotherapy, compared to chemotherapy alone, may result in no difference in overall survival, and may increase the proportion of participants having at least one serious treatment-related adverse event.

Overall completeness and applicability of evidence

Although we made every effort to conduct an exhaustive search for eligible studies, it is possible that we failed to identify relevant studies, particularly studies not registered in publicly accessible registers, or those published in journals not indexed in CENTRAL, MEDLINE, or Embase.

Of the 10 clinical trials included, only the most recent one – Besse 2023 – focused on what can be regarded as a modern clinical situation. It explored the efficacy and safety of the OSE2101 vaccine in people who had received one line of immune checkpoint blocker (ICB) therapy for locally advanced or metastatic epidermal growth factor receptor/anaplastic lymphoma kinase (EGFR/ALK)-negative NSCLC, given sequentially (second-line), or combined with platinum-based chemotherapy (first-line) for those with disease progression.

It should also be taken into account that the participants included in these clinical trials were selected because, for example, they had a better performance status than is typical for the population considered as a whole, and thus were probably not representative of all people with advanced NSCLC.

Few studies evaluated the impact of vaccines on the health-related quality of life of their participants. This is a problem in itself and also a significant limitation, given that the effect of the assessed vaccines on prolonging the life of people with advanced NSCLC is, in general, small – in the best case, a few months. Therefore, it is essential to know whether an improvement in length of life is coupled with a better quality of life and acceptable side effects of the vaccines.

Today, none of these vaccines have been approved by authorities such as the American Food and Drug Administration or the European Medicines Agency. They are therefore not available on the market.

Certainty of the evidence

All the included studies were parallel-group, randomised controlled trials.

We lacked information from some RCTs to properly assess some domains of risk of bias, even though we sent emails to authors requesting further information on their studies. We lacked detailed information on some studies' randomisation procedures or allocation concealment methods. Regarding blinding of participants, personnel, or evaluators, we believe that the lack of blinding of participants could be a source of performance bias and detection bias for subjective outcomes, such as progression-free survival or quality of life. We did not find any cases of selective reporting of outcomes in the studies prospectively registered in clinical trials registers, or those for which the protocol of the study was available. However, most of the studies gave insufficient information about their statistical methods, which impeded our evaluation of selective reporting bias. As only one or two studies analysed each vaccine type, we could not investigate the risk of publication bias through funnel plot analysis.

For most comparisons, especially for those assessed by a single study, the total number of participants included was small and the analysis for some outcomes was based on a few events. In many cases, this situation resulted in wide confidence intervals of estimations of the efficacy and safety of the vaccines. We thus frequently downgraded the certainty of the evidence for imprecision, reducing the strength of the conclusions about the vaccines addressed in this review. This last problem is difficult to solve, given that the number of people with advanced NSCLC willing to participate in RCTs is limited.

Potential biases in the review process

Although we have done an extensive search of the literature, we cannot rule out the possibility that we have missed some trials, mainly because of the overlap between immunotherapy and vaccines, and the poor indexing of trials in this area. It is also possible that we did not identify trials that did not publish results, either because they did not manage to recruit the participants needed, or because they did not find favourable results for the vaccine they were evaluating.

In this review, we included 10 trials with a total of 2177 participants, which is insufficient to detect possible rare serious adverse effects of the vaccines evaluated.

There were also scant data on some vaccines' effects on participants' quality of life. And in some cases, where there were data, quality of life assessment was not blinded, because participants knew whether they had received the vaccine or not.

Agreements and disagreements with other studies or reviews

We have not found any other systematic review that specifically addressed the effects of vaccines in people with advanced NSCLC (that is, stages IIIB or higher) with separate analyses of the effects of each type of vaccine.

We found two reviews focused on people with advanced NSCLC (Wang 2015; Zhou 2016). Wang and colleagues pooled the results of 11 studies on different types of vaccines and found that vaccines improved overall survival, progression-free survival, and resulted in fewer severe adverse effects in the vaccine groups, compared to the control groups (Wang 2015). Zhou and colleagues included studies on immunotherapies in general: studies on vaccines as well as studies on immune checkpoint inhibitors (Zhou 2016). They combined the results of the eight studies on vaccines in meta-analysis, and found that therapeutic vaccines plus chemotherapy improved survival compared to chemotherapy plus placebo. They found no differences in the incidence of serious adverse events (≥ grade 3) between the two groups.

In addition, we found three reviews that included studies involving people with early-stage NSCLC (Dammeijer 2016; Ding 2014; Zhu 2021), who have better prognoses than people with advanced NSCLC. Pooling the results of studies including participants with lower stages of cancer and a better prognosis would overestimate the real benefits of the vaccines in participants with advanced NSCLC.

All five reviews pooled in meta-analyses the results of studies on different types of vaccines and with heterogeneous types of participants.

We decided against pooling the results of vaccines with very different mechanisms of action. We also decided against pooling results from studies with heterogeneous participant inclusion

criteria. For example, some studies included only people receiving first-line treatment, and others included participants in whom previous first-line treatments had failed. For good reasons, patients and clinicians are more interested in the specific effect of a specific vaccine in a specific type of situation than in the average of the effects of different types of vaccines.

In our review, we decided not to include vaccines that had been withdrawn by their manufacturers for having poor clinical results, and are thus unavailable for medical use: tecemotide, belagenpumatucel-L, and MAGE A3 peptide vaccines. Of the reviews mentioned above, four included studies on the effect of tecemotide in their meta-analyses (Dammeijer 2016; Ding 2014; Wang 2015; Zhou 2016); two reviews included a study on belagenpumatucel-L in their meta-analyses (Dammeijer 2016; Zhou 2016); and one review also included a study on the MAGE-A3 vaccine (Ding 2014).

None of the other reviews mentioned above included health-related quality of life as a prespecified review outcome, as we did in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Therapeutic vaccines for advanced non-small cell lung cancer may make little to no difference to survival, except for racotumomab. Racotumomab showed some improvement in survival time compared to placebo, but the difference in median survival was very short (1.4 months), and the study included only 176 participants.

Severe adverse events of vaccines were rare, but both the number of participants and the events in the studies were small.

Implications for research

Future studies should implement blinded evaluation of the effect of the interventions on the health-related quality of life of participants. They should also aim to include sufficient participants to reach enough statistical power for the outcomes that are most important to people with non-small cell lung cancer.

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* Indicates the major publication for the study

5.3 Publicación 3. Cortés-Jofré M, Madera M, Tirado-Amador L, Asenjo-Lobos C, Bonfill-Cosp X. Treatments for non-small cell lung cancer: a systematic quality assessment of clinical practice guidelines. Clin Transl Oncol. 2023 May 30. doi: 10.1007/s12094-023-03223-4. Epub ahead of print. PMID: 37254015 (97).

5.3.3 Resumen de los Resultados

Veintidós guías cumplieron los criterios de elegibilidad. El acuerdo entre los evaluadores fue muy bueno. Las puntuaciones medias por dominio AGREE II fueron: alcance y propósito 90,7% (que van del 64,8% al 100%), participación de los grupos de interés 76,9% (entre el 27,8% y el 96,3%), rigor del desarrollo 80,9% (osciló entre el 27,1% y el 92,4%), claridad de presentación 89,8% (que van del 50% al 100%), aplicabilidad 46,5% (rango del 12,5% al 87,5%) e independencia editorial 91,7% (que van del 27,8% al 100%). Entre todas las GPC [16-37] evaluadas, seis GPC [17, 18, 20, 21, 34, 37] (27,3%) fueron “recomendadas” por los revisores para uso en clínica: 12 GPC [19, 22–27, 30, 31, 33, 35, 36] (54,5%) fueron “recomendadas con modificaciones”; y cuatro GPC [16, 28, 29, 32] (18,2%) fueron "no recomendadas". La mediana de la tasa global fue de 5 (mínimo 3, máximo 6) puntos (97).

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RESEARCH ARTICLE

Treatments for non-small cell lung cancer: a systematic quality assessment of clinical practice guidelines

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Abstract

Aim To evaluate the methodological quality of clinical practice guidelines (CPGs) on treatments for non-small cell lung cancer (NSCLC).

Methods We searched MEDLINE, CPG developer websites, lung cancer societies, and oncology organizations to identify CPGs providing recommendations on treatments for NSCLC. The methodological quality for each CPG was determined independently by three appraisers using the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument.

Results Twenty-two CPGs met the eligibility criteria. The median scores per AGREE II domain were: scope and purpose 90.7% (64.8–100%), stakeholder involvement 76.9% (27.8–96.3%); rigor of development 80.9% (27.1–92.4%); clarity of presentation 89.8% (50–100%); applicability 46.5% (12.5–87.5%); and editorial independence 91.7% (27.8–100%). Most of the CPGs (54.5%) were rated as "recommended with modifications" for clinical use.

Conclusions Overall, the methodological quality of CPGs proving recommendations on the management of NSCLC is moderate, but there is still room for improvement in their development and implementation.

Keywords Guidelines · Clinical guidelines · Non-small cells lung cancer · Lung cancer

Introduction

Lung cancer is one of the most common cancers worldwide and is considered a public health issue. According to the 2020 World Cancer Report, it had an incidence of 2.1 million new cases in 2018, and around 1.8 million deaths were reported for the same period [1]. It has been reported males have an incidence about 2 times higher than women and its incidence increases considerably with age [2]. One of the main risk factors for lung cancer is smoking, which could increase 20 times the chance of suffering lung cancer compared to non-smokers [3]. This risk could even increase when smoking is combined with other potential risk factors associated with lung cancers such as low physical activity, air pollution, vitamin A deficiency, child wasting, iron deficiency, exposition to asbestos and arsenic, unhealthy diet (high in sodium and low in vegetables and fruits), family history of lung cancer, and human immunodeficiency virus infection [4, 5]. Moreover, radon exposure is the leading risk factor for lung cancer among never-smokers and the second one in smokers [6].

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Non-small cell lung cancer (NSCLC) stands as the most prevalent lung tumor, accounting for around 85% of all lung neoplasms [7]. There are three subtypes of NSCLC: adenocarcinoma (40%), squamous cell carcinoma (25% to 30%), and giant cell carcinoma (10% to 15%) [8]. Although its 5-year survival rate has improved in recent decades, it remains a concern and can change depending on the stage of the disease. To illustrate, for people with localized NSCLC, the 5-year survival rate is 63%; for individuals with regional NSCLC, in which cancer has spread outside the lung to nearby lymph nodes, the 5-year survival rate is 35%; while it is just 7% for people with metastatic NSCLC. Moreover, its risk of relapse is high around 30% to 55% [9].

Due to the symptomatic manifestations of NSCLC are usually presented in advanced stages, the diagnosis is commonly established late when the disease has spread to other organs and its prognosis is poor [8]; consequently, the therapeutic interventions at this stage are limited. Overall, the management of NSCLC is stage-specific. To illustrate, people with stage I or II are usually treated with a surgical approach, while inoperable NSCLC are treated with radiotherapy or chemotherapy[10].

It is important to highlight that the most effective treatments are usually included in clinical practice guidelines (CPGs), which are systematically developed statements intended to help physicians and patients make decisions about appropriate medical care in specific circumstances[11]. Among the advantages of using CPGs are the improvement of clinical outcomes, adherence of clinicians and patients, promotion of a cost-effective and evidence-based practice[12]. Thus, using high-quality CPGs is a key approach to improving the survival rate and quality of life of people suffering from NSCLC.

Among the core aspects that strongly are recommended during the CPGs' development is that it must be based on a systematic review process, assessing the quality of the evidence, and translating the evidence into recommendations [11]. However, not all CGPs are developed with this evidence-based approach, which can lead to biased harmful recommendations [13]. Although the development, implementation, and systematic evaluation of CPGs have improved in recent years, they still have serious limitations in their methods, scope, and content.

In this sense, it is imperative to evaluate periodically the CPGs' development process, focusing on the standard methodology, reporting, quality, and the content of the CPGs to ensure that their recommendations are valid and reliable, and therefore, a useful and invaluable tool for decision-making [14]. Therefore, this study aimed to evaluate the methodological quality of CPGs proving recommendations on treatments for NSCLC.

Methods

Study design

A systematic assessment of the methodological quality of CPGs was conducted. The aim and all methods of this study were described in advance in a protocol.

Search strategy

We searched MEDLINE (via PubMed), CPGs developer websites, cancer scientific organizations, and lung cancer societies to identify CPGs proving recommendations on NSCLC. The Mesh term "Carcinoma, Non-Small-Cell Lung" was used in combination with terms related to CPGs such as "guidance", "practice guideline" and "recommendation". There was no restriction on languages. The last search was performed on 6th October 2022. The search strategy used, and the websites consulted are presented in detail in the Appendix A.

Eligibility criteria

We included CPGs providing recommendations for the management of primary or metastatic NSCLC in people aged 18 or over; CPGs had to have an explicit methodology chapter describing how their recommendations were formulated; publication in the last 10 years in English or Spanish, and the most updated version of the CPG. We excluded adaptations of CPGs and CPG retracted or archived by their developer.

Selection of CPGs

Initially, all records identified were retained and handled on the Covidence website. After removing duplicates, two authors independently revised titles/abstracts to identify potential CPGs, then the full texts were gathered to decide on the final inclusion of eligible CPGs. Discrepancies were resolved by discussion, with the participation of a third author, whether was needed.

Instrument to assess of methodological quality of CPGs

We used the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument [15], which contains 23 items using a seven-point Likert scale and considered six domains: (a) Scope and purpose: this focuses on the aim, the target population and clinical questions addressed in the CPG; (b) Stakeholder involvement; this focuses on the extent to which the CPG was developed by the appropriate

stakeholders and represents the views of its intended users; (c) Rigor of development; this focuses on the methods used to formulate the recommendations and how evidence was gathered and summarized; (d) Clarity and presentation; this evaluates the way how recommendations are presented, if they are easily recognizable, unambiguous and clear, and whether there are various alternatives to the management of the disease; (e) Applicability; dealing with implementation issues, such as the assessment of organizational facilitators and barriers, the development of educational sources, economic implications, and monitoring or audit criteria; (f) Editorial independence; assessing whether the views or interests of the funding sources have influenced the recommendations, and if the conflicts of interest statement reports all information about the CPG developer team. In addition, the AGREE II instrument also contains two overall quality items for each CPG: an overall score of 1 to 7, and whether the assessor would recommend using the CPG, rating it as "recommended", "recommended with modifications" or "not recommended". The methodological quality assessment was independently conducted by three reviewers.

Data extraction and analysis

We extracted data on general characteristics from each CPG such as title, publication year, authoring organization, country, language, level of development, funding source, whether or not it is an update, methods used to formulate recommendations, level of evidence, and grading of the recommendations. This process was conducted independently by two authors. Discrepancies were resulted by discussion with the participation of a third author if necessary. We performed a descriptive analysis of these characteristics using tables and a synthesis narrative. Statistical analyses were performed with SPSS® version 27.0 software (SPSS Inc, Chicago, IL). Initially, we calculated the intraclass correlation coefficient (ICC) with its 95% confidence interval (95% CI) as an indicator of agreement between reviewers. Then, we calculated the domain scores by adding up all the scores of the individual items within a domain and calculated the percentage of the maximum possible score for that domain. Standardized scores (range, 0% to 100%) for each domain were calculated as follows: [(obtained score – minimum possible score)/(maximum possible score – minimum possible score)] × 100%. We assumed a threshold of 60% as an indicator of adequate quality. Median and minimum–maximum values were calculated for each domain score for each CPG. Moreover, to determine if the methodological quality of CPGs has improved in recent years, we compare the AGREE II scores between recent CPGs (published in last 5 years) and not recent CPGs (published before 2018) using the Mann–Whitney U test with a significance level of 0.05.

Results

CPGs identified

After removing duplicates, 498 titles/abstracts were reviewed, then 46 full-text documents were reviewed and 22 [16–37] of them met the eligibility criteria (Fig. 1). All documents considered relevant, and their reasons for exclusion are presented in the Appendix B.

General characteristics of the included CPGs

All included CPGs [16–37] were published between 2012 and 2022, 19 [16–21, 23, 24, 26–29, 31–37] of them were published in English, and three [22, 25, 30] in the Spanish language. All CPGs [16–37] provided recommendations for the management of NSCLC, whereas some of them also provided recommendations about diagnosis and follow-up [17–19, 22, 32, 33]. Sixteen [16–20, 23, 25–28, 31–33, 35–37] CPGs were an update of previous versions. There were eight CPGs [17–19, 27, 34–37] from the United States, five CPGs [16, 21, 23, 24, 26] were from Canada, three CPGs [22, 25, 28] from Spain, two CPGs [32, 33] from Europe, while the others were one from each one of the following countries: Mexico [30], Japan [31], Scotland [20], and Italy [29]. Nineteen CPGs [17–19, 21–35, 37] were developed by a professional organization, while three CPGs [16, 20, 36] were developed by a government agency. Five CPGs [21, 23, 29, 31, 34] used the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) approach to develop their recommendations, whereas most of the CPGs [16–20, 22, 25, 27, 28, 30, 32, 33, 35–37] used a systematic review of the literature and critical appraisal of evidence (Table 1).

The methodological quality of CPGs

The overall agreement between appraisers was substantial (ICC: 0.72; 95% IC = 0.68–0.8). The median scores per AGREE II domain were: scope and purpose 90.7% (ranging from 64.8% to 100%), stakeholder involvement 76.9% (ranging from 27.8% to 96.3%); rigor of development 80.9% (ranged from 27.1% to 92.4%); clarity of presentation 89.8% (ranging from 50% to 100%); applicability 46.5% (ranging from 12.5% to 87.5%); and editorial independence 91.7% (ranging from 27.8% to 100%). Among all CPGs [16–37] evaluated, six CPGs [17, 18, 20, 21, 34, 37] (27.3%) were "recommended" by the reviewers for cline use; 12 CPGs [19, 22–27, 30, 31, 33, 35, 36] (54.5%) were "recommended with modifications"; and four CPGs [16, 28, 29, 32] (18.2%) were "not recommended". The median of the overall rate was 5

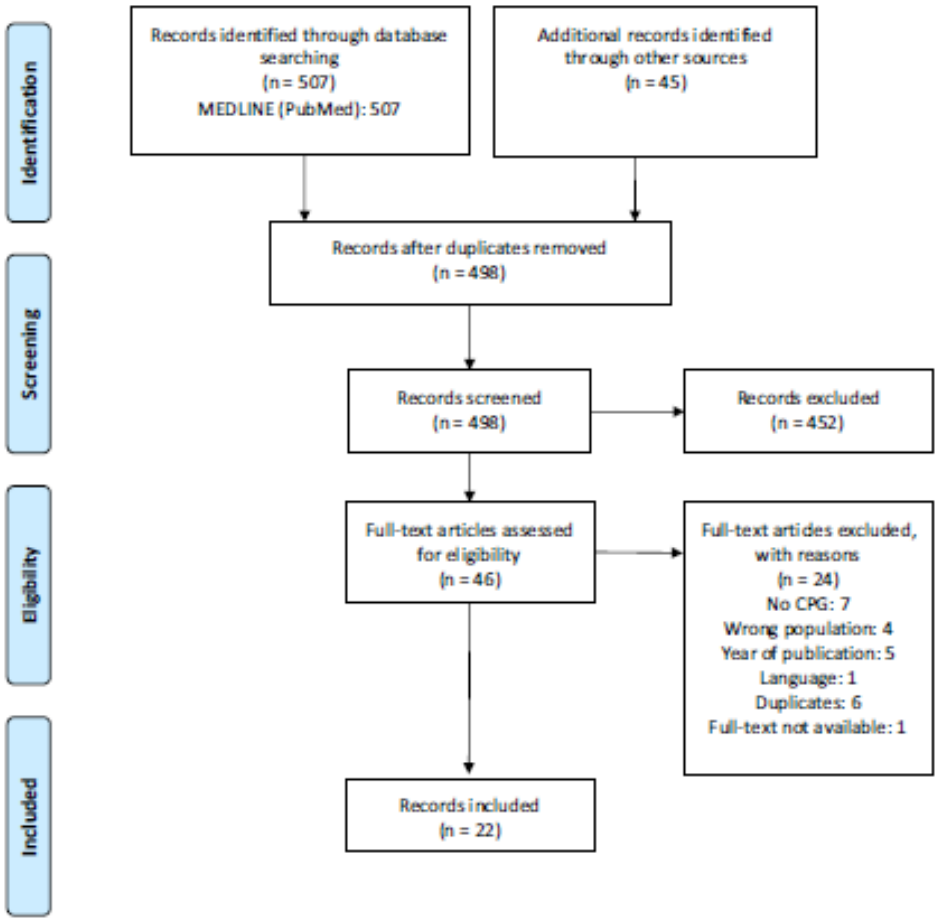

Fig. 1 The selection process of CPGs

(minimum 3, maximum 6) points. The standardized scores across CPGs by domain in detail and the overall recommendation for clinical use of the included CPGs are presented in Table 2.

Table 3 shows the comparison of the AGREE II scores by publication period. Overall, our analysis found no statistically significant differences between the methodological quality of recent CPGs (published in 2018–2022) and not recent CPGs (published in 2012–2017) using the overall AGREE II scores or by domains.

Discussion

CPGs are essential to provide evidence-based health services, thus identifying high-quality CPGs in a specific clinical area will contribute to their implementation and clinician´s adherence. Therefore, this study looked to appraise the methodological quality of CPGs on NSCLC, to help clinicians and patients about the most suitable treatments. Likewise, based on our knowledge, this study could be considered the first one assessing CPGs on treatments for NSCLC, using the AGREE II instrument.

Overall, the quality of CPGs providing recommendations on therapeutic interventions for NSCLC is moderate with most CPGs [19, 22–27, 30, 31, 33, 35, 36] being rated as "recommended with modifications" for clinical use. It suggests that there is room for improving the methodological quality of CPGs on NSCLC if their weaknesses are addressed. Among the deficiencies that need to be addressed are: a) the lack of information on sources and barriers to CPGs' implementation; (b) the incorporation of patients and other stakeholders in the CPG development process, (c) the deficiency of patients' views and their preferences; and (c) the inadequate critical appraisal of supporting evidence, especially of its limitations and strengths. These findings are similar to previous reports evaluating of methodological quality of CPGs in oncology[38–41] and other medical disciplines [42–48], which have concluded the quality of CPGs is substantially variable, suggesting a huge chance for improvement. Similarly, there are two previous studies[49, 50] evaluating CPGs on lung cancer suggesting that CPGs in this field must be improved, one[49] of them focused on the quality of CPGs proving recommendations on complementary and integrative medicine therapy such as social and spiritual support,

Table 1 General characteristics of the included CPGs

CPG	Year	Organization	Country/ Region	Language	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Non-small cell lung cancer: stage III [16]	2012	AHS	Canada	English	GA	NR	Yes	SR and CAE	NR	NR
Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines [17]	2013	ACCP	USA	English	Professional organization	Professional society	Yes	SR and CAE	NR	1A, 1B, 1C, 2A, 2B, 2C
Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines [18]	2013	ACCP	USA	English	Professional organization	Professional society	Yes	SR and CAE	NR	1A, 1B, 1C, 2A, 2B, 2C

Table 1 (continued)

CPG	Year	Organization	Country/ Region	Language	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rded: American College of Chest Physicians evidence-based clinical practice guidelines [19]	2013	ACCP	USA	English	Professional organization	Professional society	Yes	SR and CAE	NR	1A, 1B, 1C, 2A, 2B, 2C
Management of lung cancer [20]	2014	SIGN	Scotland	English	GA	Government	Yes	SR and CAE	1++/1+/1-/2++/2+/2-/3/4	A/B/C/D/ GPP
The use of systemic treatment in the maintenance of patients with non-small cell lung Cancer [21]	2015	CCO	Canada	English	Professional organization	Government	No	GRADE	High/Moderate/Low/ Very low	NR
The SEPAR recommendations for the diagnosis and treatment of non-small cell lung cancer [22]	2016	SEPAR	Spain	Spanish	Professional organization	Professional society	No	SR and CAE	NR	1A, 1B, 1C, 2A, 2B, 2C
Systemic treatment for patients with advanced non-small cell lung cancer [23]	2016	CCO	Canada	English	Professional organization	Government	Yes	GRADE	High/Moderate/Low/ Very low	NR

Table 1 (continued)

CPG	Year	Organization	Country/ Region	Language	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer [24]	2016	CCO	Canada	English	Professional organization	Government	No	AGREE II	NR	NR
ICOPractice: treatment for non-small cell lung cancer [25]	2016	ICO	Spain	Spanish	Professional organization	Professional society	Yes	SR and CAE	I, II, III, IV, V	A/B/C/D
Treatment of patients with stage III (N2 or N3) non-small cell lung cancer [26]	2017	CCO	Canada	English	Professional organization	Government	Yes	AGREE II	NR	NR
Palliative thoracic radiation therapy for non-small cell lung cancer: 2018 Update of an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline [27]	2018	ASTRO	USA	English	Professional organization	NR	Yes	SR and CAE	High/Moderate/Low	Strong/Conditional
SEOM clinical guidelines for the treatment of non-small cell lung cancer (2018) [28]	2019	SEOM	Spain	English	Professional organization	NR	Yes	SR and CAE	I, II, III, IV, V	A/B/C/D/

Table 1 (continued)

CPG	Year	Organization	Country/ Region	Language	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Treatment of metastatic non-small cell lung cancer: 2018 guidelines of the Italian Association of Medical Oncology (AIOM) [29]	2019	AIOM	Italy	English	Professional organization	Professional society	No	GRADE and SIGN	High/Moderate/Low/ Very low	A/B/C/D/ OR Strong for to Strong against
National Clinical Practice Guidelines for the management of non-small cell lung cancer in early, locally advanced and metastatic stages [30]	2019	SMO CENETEC	Mexico	Spanish	GA and professional organization	NR	No	SR and CAE	$1^{++}/1^{+}/1^{-}/2^{++}/2^{+}/2^{-}/3/4$	A/B/C/D/
The Japanese Lung Cancer Society Guideline for non-small cell lung cancer, stage IV [31]	2019	JLCS	Japan	English	Professional organization	Professional society	Yes	GRADE	High/Moderate/Low/ Very low	Strong/Weak
Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [32]	2020	ESMO	Europe	English	Professional organization	NR	Yes	SR and CAE	I, II, III, IV, V	A/B/C/D/

Table 1 (continued)

CPG	Year	Organization	Country/ Region	Language	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Early and locally advanced non-small cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy [33]	2021	ESMO	Europe	English	Professional organization	NR	Yes	SR and CAE	I, II, III, IV, V	A/B/C/D/
Management of Stage III Non-Small-Cell: ASCO Guideline [34]	2022	ASCO	USA	English	Professional organization	Professional society	No	GRADE	high, moderate, low, and very low	Strong/moderate/weak
Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I-IIIA Completely Resected Non-Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update [35]	2022	ASCO	USA	English	Professional organization	NR	Yes	SR and CAE	NR	NR
Non-Small-Cell Lung Cancer [36]	2022	NCCN	USA	English	GA	Government	Yes	SR and CAE	1, 2A, 2B, 3	NR

Table 1 (continued)

CPG	Year	Organization	Country/ Region	Language	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline [37]	2022	ASCO	USA	English	Professional organization	Professional society	Yes	SR and CAE	High/Intermediate /Low	Strong/moderate/weak

ACCP American College of Chest Physicians; *AGREE II* Appraisal of Guidelines for Research and Evaluation II instrument; *AHS* Alberta Health Services, *AIOM* The Italian Association of Medical Oncology, *ASCO* American Society of Clinical Oncology, *ASTRO* American society for radiation oncology, *CAE* critical appraisal of evidence, *CCO* Cancer Care Ontario, *CENETEC* National Center for Technological Excellence in Health, *ESMO* European Society for Medical Oncology, *GA* Government agency, *GRADE* The grading of recommendations assessment, development and evaluation; *ICO* Catalan institute of oncology, *JLCS* Japan Lung Cancer Society, *NCCN* National comprehensive cancer network; *NR* not reported, *SEOM* the Spanish Society of medical oncology, *SEPAR* The Spanish Society of Pneumology and Thoracic Surgery, *SIGN* Scottish Intercollegiate Guidelines Network, *SMO* The Mexican Society of Oncology, *SR* systematic review of literature, *USA* United States of America

self-care strategies, yoga, massage therapy, exercise, acupuncture, and nutrition/dietary supplements; whereas the other[50] assessed the reporting quality of CPGs on lung cancer using the International Reporting Items for Practice Guidelines in Health Care (RIGHT) instrument. It is useful to highlight that our findings might not be comparable to these studies because they had other aims; to illustrate, they did not focus on NSCLC treatments, exclusively; moreover, one[50] of them used an instrument that captures different spheres of a CPG, thus, it is not comparable to AGREE II tool[51].

Regarding the domain scoring, we would like to highlight that the majority (5 out of 6) of AGREE II domains scored over the threshold of adequate quality (60%); only the "applicability" domain scored under this cut-off point, so it was the domain with the lowest scores, while the "editorial independence" and "scope and purpose" domains had the highest scores. These findings could be considered similar to some previous assessments of CPGs on cancers [38, 39, 49, 52] and other medical specialties[43, 44, 46, 47, 53–57], which support that "applicability" and "scope and purpose" domains are the ones with the lowest and highest scores, respectively. Conversely, some reports suggest that domains such as "rigor of development" [58] and "editorial independence" [59] stand among those with the lowest scores. Thus, it suggests that domain scores can vary depending on fields or topics addressed in the CPGs. Overall, our findings suggest that nowadays the CPCs including recommendations on NSCLC therapies usually do not provide explicit instructions about financial sources, costs, barriers, facilitators, additional materials, and other key factors to ensure the implementation of their recommendations, whereas they fully described their aims, the target population, potential users, developers' conflict of interest, funding sources, and clinical questions to be addressed into the CPG. Therefore, greater efforts are essential to improve their applicability issues. Likewise, to improve clinicians' adherence to these CPGs and decrease the variability of decisions in clinical practice, it is needed to disseminate appropriately the quality of available CPGs in this area.

The main implications of this study are linked to improving CPGs' development in this field, especially their applicability, which can contribute with provide better evidence-based practice and improve clinical outcomes of people suffering from NSCLC. Likewise, the variation in the methodological quality of the included CPGs highlights the need to identify high-quality CPGs before implementing their recommendations. To illustrate, it is widely known that implementing recommendations from low-quality CPGs can lead to negative effects on patients. Therefore, it is important to make available high-quality CPGs on NSCLC that could be a practical and genuine instrument for clinical decision-making.

Table 2 Standardized scores across CPGs by AGREE II domain

CPG	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	Overall rate	Overall recommendation
	%	%	%	%	%	%		
Non-small cell lung cancer: stage III [16]	90.7	77.8	66.7	79.6	27.8	88.9	4	Not recommended
Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer. 3rd ed: american college of chest physicians evidence-based clinical practice guidelines [17]	85.2	72.2	82.6	92.6	62.5	88.9	5	Recommended
Treatment of stage IV non-small cell lung cancer: diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines [18]	92.6	75.9	83.3	94.4	70.8	94.4	6	Recommended
Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines [19]	83.3	81.5	79.2	85.2	62.5	94.4	5	Recommended with modifications
Management of lung cancer [20]	100	81.5	91.7	98.1	76.4	100	6	Recommended
The use of systemic treatment in the maintenance of patients with non-small cell lung cancer [21]	98.1	90.7	92.4	100	70.8	91.7	6	Recommended
The SEPAR recommendations for the diagnosis and treatment of non-small cell lung cancer [22]	87.0	68.5	75.0	87.0	27.8	94.4	5	Recommended with modifications
Systemic treatment for patients with advanced non-small cell lung cancer [23]	98.1	77.8	85.4	90.7	30.6	88.9	5	Recommended with modifications
Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer [24]	98.1	74.1	78.5	88.9	47.2	97.2	5	Recommended with modifications
ICOPractice: treatment for non-small cell lung cancer [25]	83.3	83.3	78.5	75.9	48.6	91.7	5	Recommended with modifications
Treatment of patients with stage III (N2 or N3) non-small cell lung cancer [26]	96.3	75.9	81.3	92.6	30.6	97.2	5	Recommended with modifications
Palliative thoracic radiation therapy for non-small cell lung cancer: 2018 Update of an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline [27]	81.5	61.1	79.9	88.9	38.9	88.9	5	Recommended with modifications
SEOM clinical guidelines for the treatment of non-small cell lung cancer (2018) [28]	64.8	27.8	27.1	50.0	12.5	52.8	3	Not recommended
Treatment of metastatic non-small cell lung cancer: 2018 guidelines of the Italian Association of Medical Oncology (AIOM) [29]	64.8	57.4	54.9	64.8	25.0	86.1	4	Not recommended

Table 2 (continued)

CPG	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	Overall rate	Overall recommendation
	%	%	%	%	%	%		
National Clinical Practice Guidelines for the management of non-small cell lung cancer in early, locally advanced and metastatic stages [30]	92.6	96.3	80.6	90.7	45.8	27.8	5	Recommended with modifications
The Japanese lung cancer society guideline for non-small cell lung cancer, stage IV [31]	88.9	70.4	81.3	92.6	23.6	97.2	5	Recommended with modifications
Metastatic non-small cell lung cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up [32]	68.5	48.1	59.0	85.2	27.8	83.3	5	Not recommended
Early and locally advanced non-small cell lung cancer: an update of the ESMO Clinical practice guidelines focusing on diagnosis, staging, systemic and local therapy [33]	90.7	61.1	64.6	94.4	37.5	88.9	5	Recommended with modifications
Management of stage III Non–small cell: ASCO Guideline [34]	98.1	85.2	86.8	81.5	75.0	88.9	6	Recommended
Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small cell lung cancer: ASCO guideline rapid recommendation update [35]	100	79.6	86.1	90.7	70.8	97.2	5	Recommended with modifications
Non-small cell lung cancer [36]	85.2	81.5	81.3	83.3	68.1	97.2	5	Recommended with modifications
Therapy for stage IV non-small cell lung cancer without driver alterations: ASCO living guideline [37]	100	94.4	88.2	94.4	87.5	100	6	Recommended
Median	90.7	76.9	80.9	89.8	46.5	91.7	5	
Minimum–maximum	64.8–100	27.8–96.3	27.1–92.4	50–100	12.5–87.5	27.8–100	3–6	

Table 3 Comparison of the AGREE II scores by publication period

AGREE II domains	Not recent CPGs ($n=11$)		Recent CPGs ($n=11$)		p value*
	Median (%)	IQR (%)	Median (%)	IQR (%)	
Scope and purpose	92.6	13.0	88.9	29.6	0.365
Stakeholder involvement	77.8	7.4	70.4	27.8	0.438
Rigour of development	81.2	6.9	80.5	27.1	0.438
Clarity of presentation	90.7	9.3	88.9	11.1	0.365
Applicability	48.6	40.3	38.9	45.8	0.562
Editorial independence	94.4	8.3	88.9	13.9	0.243
Overall median	5.3	0.7	5.3	1.0	0.652

Mann–Whitney *U* test; *IQR* The interquartile range

Among the limitations of this study are the language barriers since we only included CPGs published in English and Spanish, which limits the external validity of our results to CPGs published in other languages. Likewise, another limitation could be our incapacity to identify non-indexed CPGs. However, it has been reported that CPGs that are not indexed have poorer quality compared to those indexed [60]. This study also has some strengths, such as the assessment of all CPGs was independently performed by three appraisers with a substantial agreement using a validated and reliable instrument. Moreover, a comprehensive search was carried out to identify all relevant CPGs, so it is not likely that relevant CPGs are missing. Thus, all these processes provide trustworthiness to our findings.

Conclusion

Overall, the methodological quality of CPGs proving recommendations on the management of NSCLC is moderate. Most CPGs were rated as "recommended with modifications" for clinical use, and the "applicability" domain scored lowest; thus, great efforts are needed to improve the development and implementation of CPGs in this field, which could contribute to the decision-making process and lead better clinical outcomes in people suffering from NSCLC.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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6.- DISCUSION

La presente tesis aborda de manera integral el cáncer de pulmón, una patología de gran relevancia en la investigación médica. La estructura de la discusión en tres trabajos independientes permite una exploración detallada de diferentes aspectos clave relacionados con la prevención y tratamiento del cáncer de pulmón. Específicamente, se han evaluado de manera exhaustiva intervenciones preventivas y terapéuticas novedosas, contribuyendo al conocimiento científico del cáncer de pulmón y con potencial de influir en políticas de salud y práctica clínica, mejorando así los resultados para los pacientes.

Discusión Específica

6.1 EVIDENCIA SOBRE INTERVENCIONES PREVENTIVAS EN EL CÁNCER DE PULMON

La revisión sistemática sobre fármacos para la prevención del cáncer de pulmón en personas sanas representa un aspecto innovador y relevante, dado que la prevención desempeña un papel fundamental en la reducción de la incidencia de esta enfermedad (99,100). El enfoque quimiopreventivo (101), que incluye la identificación de suplementos vitamínicos y ciertos antioxidantes dirigidos a la neutralización de las especies reactivas de oxígeno, tiene el potencial de impedir el desarrollo del cáncer de pulmón y reducir el riesgo en poblaciones sanas, lo que podría generar un impacto significativo en la salud pública (102-104).

Nuestros resultados concluyen que la vitamina A incrementa el riesgo de cáncer de pulmón en fumadores y en personas expuestas al asbesto. La vitamina C no presenta un efecto significativo en

hombres, pero sí aumenta el riesgo en mujeres. La combinación de vitamina D y calcio muestra poco o ningún efecto en mujeres posmenopáusicas. La vitamina E no exhibe diferencias significativas en la incidencia y mortalidad, aunque se asocia con un aumento del riesgo de accidentes cerebrovasculares hemorrágicos. El calcio tampoco muestra diferencias significativas en la incidencia entre mujeres posmenopáusicas. En cuanto al selenio, no se observan diferencias significativas en la incidencia y mortalidad en hombres. Por último, las combinaciones de vitaminas y minerales no evidencian diferencias significativas en la incidencia de cáncer de pulmón (96).

La calidad de los estudios permite afirmar que estas son conclusiones sólidas en el caso de las vitaminas A, C, E y la combinación de vitaminas A, C, E + selenio + zinc, con alta certeza de evidencia. En tanto las vitaminas D + calcio, así como el calcio y el selenio, resultaron con certeza de evidencia baja (96).

El uso de suplementos vitamínicos y minerales para la prevención del cáncer se ha debatido durante mucho tiempo y ha sido ampliamente estudiado, con resultados variables y generalmente decepcionantes (104 -106). Nuestros hallazgos confirman que la mayoría de estos suplementos no ofrecen beneficios significativos en la prevención del cáncer de pulmón y pueden, en algunos casos, aumentar los riesgos. Estos resultados son consistentes con estudios previos, los que han encontrado poca o ninguna evidencia de beneficios protectores y, en algunos casos, riesgos aumentados (107-108). La revisión Cochrane sobre fármacos para la prevención del cáncer de pulmón en personas sanas coincide con lo reportado en la actualización de la revisión Cochrane "Selenio para la prevención del cáncer", donde los autores concluyen que los ensayos clínicos incluidos en sus análisis no han

mostrado efectos beneficiosos con la administración de suplementos de selenio en la reducción del riesgo de cáncer, con evidencia de alta certeza (109). De igual manera, las conclusiones de la revisión sistemática del Grupo de Trabajo de Servicios Preventivos de EEUU, respaldan esta afirmación en relación con la suplementación con vitaminas y minerales en adultos sanos para prevenir enfermedades cardiovasculares y cáncer (110).

Por otra parte, nuestros hallazgos difieren de la RS de Sun K 2021. Su objetivo fue verificar los roles de la vitamina D y el calcio en la incidencia y el pronóstico del cáncer de pulmón. Sus resultados informan que la incidencia y mortalidad del cáncer de pulmón disminuyen significativamente debido al alto nivel del metabolito biológicamente activo 25-hidroxivitamina D [25(OH) D] circulante. Aunque la ingesta separada de vitamina D no mostró un efecto protector sobre el cáncer de pulmón, el suplemento combinado de vitamina D y calcio redujo significativamente la incidencia de cáncer de pulmón. Concluyen que un alto nivel de 25(OH) D en suero podría desempeñar un papel preventivo en el cáncer de pulmón. Además, la vitamina D podría complementarse junto con el calcio contra el cáncer de pulmón (111).

Otros estudios en el ámbito de la nutrición con la ingesta de frutas y vegetales han reportado resultados contradictorios o no concluyentes (36-38).

6.2 EVIDENCIAS SOBRE INTERVENCIONES TERAPEUTICAS EN EL CÁNCER DE PULMON

El primer trabajo sobre este tema (el segundo que forma parte de este compendio de publicaciones), consistió en la revisión sistemática sobre vacunas terapéuticas para el cáncer de pulmón de células no pequeñas (97). Esta es un área de interés debido a su potencial para inducir respuestas inmunológicas específicas. Evaluar la eficacia y seguridad de estas vacunas puede ofrecer nuevas perspectivas sobre cómo mejorar los tratamientos existentes y potencialmente aumentar las tasas de supervivencia.

Se evaluaron siete tipos diferentes de vacunas, y ninguna de ellas mostró efectos significativos en los principales resultados de interés. Con la vacuna TG4010 se observó un ligero aumento en la supervivencia libre de progresión. Las vacunas OSE2101, hTERT (vx-001), EGF, TG4010, SRL172 y la vacuna de péptidos personalizados presentaron poca o ninguna diferencia en la supervivencia global. Solo Racotumomab mostró una ligera mejora en la supervivencia general. La vacuna EGF evidenció únicamente un leve incremento en la tasa de supervivencia a cinco años. En cuanto a la vacuna hTERT (vx-001), no se encontraron diferencias en la tasa de supervivencia a cinco años. Solo con la vacuna SRL172 (Mycobacterium vaccae inactivado), se registró un aumento en los eventos adversos graves (97).

La confianza en la evidencia varió de moderada a muy baja para las diferentes vacunas y desenlaces evaluados, principalmente debido al tamaño reducido de los estudios y a la insuficiencia de investigaciones que permitan asegurar los resultados ya que muchas vacunas fueron evaluadas en un único estudio con un número limitado de participantes y eventos. Por tanto, los resultados deben interpretarse con cautela (97).

En cuanto a los acuerdos y desacuerdos con otros estudios, nuestros hallazgos se alinean con investigaciones previas que muestran resultados contradictorios en cuanto a la eficacia de estas vacunas. La heterogeneidad en los diseños de estudio y las poblaciones de pacientes complica la evaluación de su efectividad general. No se encontró ninguna revisión sistemática que abordara específicamente los efectos de las vacunas en pacientes con NSCLC avanzado (es decir, estadios IIIB o superiores), con análisis diferenciados según el tipo de vacuna. Se identificaron dos revisiones centradas en pacientes con NSCLC avanzado, Wang y Zhou combinaron los resultados con diferentes tipos de vacunas en conjunto y concluyeron que estas mejoran la supervivencia global, la supervivencia libre de progresión y presentan menos efectos adversos graves en los grupos vacunados en comparación con los grupos de control (112, 113).

Existen otras revisiones sobre inmunoterapias en general, incluyendo investigaciones sobre vacunas y estudios sobre inhibidores de puntos de control inmunológico (114). En un metaanálisis se combinaron los resultados de ocho estudios sobre vacunas, revelando que las vacunas terapéuticas, en combinación con quimioterapia, mejoran la supervivencia en comparación con la quimioterapia más placebo. No se encontraron diferencias significativas en la incidencia de eventos adversos graves (grado 3), entre los dos grupos. No obstante, los investigadores advierten que se deben considerar las diferencias de fabricación, las diferencias individuales, la dosis del fármaco y los procedimientos de administración de las vacunas (115). Por otra parte, en una actualización de una RS Cochrane, en la que se evaluó la eficacia y seguridad de la inmunoterapia (excluyendo los inhibidores de puntos de control) en personas con NSCLC localizado en estadios I a III que recibieron radioterapia o cirugía con intención curativa los autores concluyen que no hubo beneficio de supervivencia en las personas que

recibieron inmunoterapia basada en vacunas ni aumento de efectos secundarios (116). Concluyen señalando que no hay evidencia que respalde o refute la administración de inmunoterapia (principalmente basada en vacunas) a personas con NSCLC localizado (estadios I a III) (116).

De las cinco revisiones citadas anteriormente (112-116), ninguna abordó específicamente los efectos de las vacunas en personas con NSCLC avanzado (es decir, estadios IIIB o superiores) con análisis separados de los efectos para cada tipo de vacuna. Además, en tres de ellas se incluyeron personas con NSCLC en etapa temprana y con mejor pronóstico, lo que podría sobreestimar los beneficios reales de las vacunas en participantes con enfermedad avanzada (114-116). En nuestra RS, decidimos no combinar los resultados de las vacunas con mecanismos de acción muy diferentes. Asimismo, optamos por no agrupar los resultados de estudios con inclusión heterogénea de participantes (97).

En el segundo trabajo en el ámbito de las intervenciones terapéuticas en el cáncer de pulmón, evaluamos la calidad metodológica de las GPC, para el tratamiento del cáncer de pulmón de células no pequeñas utilizando el instrumento AGREE II (98). Este estudio identificó las áreas donde las recomendaciones pueden ser mejoradas o actualizadas como el dominio 3 en el Ítem 9 de AGREE II, que considera el rigor de la elaboración, las fortalezas y limitaciones del conjunto de la evidencia. Es importante monitorear si ellas están claramente descritas y si se ha utilizado el sistema GRADE, para la calificación de la calidad de la evidencia disponible y la elaboración de recomendaciones de atención en salud (92).

En relación con la puntuación según el dominio AGREE II, es importante destacar que la mayoría (5 de 6) de los dominios superaron el umbral de calidad adecuada (60 %) en nuestro estudio. Solo el dominio de "aplicabilidad" obtuvo las puntuaciones más bajas, mientras que "independencia editorial", "alcance y propósito" presentaron las puntuaciones más altas (98). Estos hallazgos pueden considerarse similares a algunas evaluaciones previas de (GPC) sobre cáncer (117 -120) y otras especialidades médicas (121- 124, 125 -129) que informan, que los dominios de "aplicabilidad", así como "alcance y propósito", son aquellos que suelen presentar las puntuaciones más bajas y más altas, respectivamente. Por el contrario, algunos informes sugieren que dominios como el "rigor del desarrollo" (130) y la "independencia editorial" (131) se encuentran entre los que tienen las puntuaciones más bajas. En relación con los acuerdos y desacuerdos con otros estudios, es importante señalar que al comparar hallazgos de diferentes investigaciones, se debe considerar los objetivos y metodologías específicas de cada una. En este caso, si los estudios mencionados no se centraron exclusivamente en tratamientos para el NSCLC o utilizaron instrumentos distintos para la evaluación de GPC, esto puede influir en la comparabilidad de los resultados (98). En este sentido, y basándonos en nuestro conocimiento, este estudio podría considerarse el primero que evalúa GPC sobre tratamientos para el NSCLC utilizando el instrumento AGREE II. La herramienta AGREE II está diseñada para evaluar aspectos específicos que no se abordan en otros instrumentos, lo que limita la capacidad de realizar comparaciones directas. Por lo tanto, es esencial tener en cuenta estas diferencias al interpretar los hallazgos y su relevancia en el contexto del tratamiento del NSCLC (98).

Discusión General

Los hallazgos de esta tesis doctoral son relevantes para las estrategias de Quimioprevención, Inmunoterapia y sus recomendaciones terapéuticas. Los resultados permiten informar, con la evidencia disponible, que el uso de vitaminas y minerales no es útil para prevenir el cáncer de pulmón. Asimismo, las terapias con vacunas tienen un valor terapéutico limitado, y las GPC en general no proporcionan información ni recomendaciones actualizadas sobre Quimioprevención o nuevas estrategias terapéuticas.

En la actualidad, el cáncer de pulmón sigue siendo una de las patologías oncológicas con peor pronóstico, especialmente en las etapas metastásicas avanzadas pues suele diagnosticarse en una etapa avanzada de la enfermedad, momento en el cual las opciones de tratamiento son limitadas. Ante este panorama poco esperanzador, debemos preguntarnos: ¿cuáles son las estrategias para mejorar los desenlaces? Una respuesta inmediata, que ya ha sido abordada, es la necesidad de fortalecer los grupos multidisciplinarios para el diagnóstico y manejo de pacientes con sospecha de cáncer de pulmón. Este enfoque busca optimizar el proceso de diagnóstico y estadificación, garantizando así el inicio oportuno del tratamiento personalizado, lo cual podría asegurar mejoras significativas en la supervivencia y en la calidad de vida (132).

En esta línea es importante destacar, que ya existen programas para la detección precoz del cáncer de pulmón en personas de riesgo, fumadores o exfumadores. El proyecto piloto multicéntrico de España, CASSANDRA, que consiste en el cribado del cáncer de pulmón mediante tomografía computarizada (TC) de baja dosis, tiene una visión centrada en el paciente. Es un programa integral con varios ejes de actuación que vincula tanto la prevención primaria como la secundaria para

optimizar el cribado, integrando la deshabituación tabáquica como un elemento clave, reconociendo que el cáncer de pulmón forma parte de un conjunto de patologías asociadas al tabaquismo (133).

Volviendo a la pregunta, ¿cuáles son las estrategias para mejorar los desenlaces? En general, las estrategias se han centrado principalmente en intervenciones preventivas orientadas a reducir los factores de riesgo, siendo el hábito de fumar su principal exponente (20, 21). Según datos de la Organización Mundial de la Salud (OMS) el tabaquismo causa más de 8 millones de muertes al año en el mundo de los cuales cerca de 1,3 millones son no fumadores que están expuestos al humo ajeno, y alrededor del 80 % de los 1300 millones de consumidores de tabaco que hay en el mundo viven en países de ingresos medianos o bajos (134, 135).

El humo del tabaco exhalado por el fumador y la corriente secundaria emitida desde el cigarrillo y diluidas ambas con el aire ambiente, generan una mezcla que contiene más de 4.700 sustancias químicas, incluidas aminas, carbonilos, hidrocarburos o metales, entre otros (136). Estas sustancias químicas producen un alto grado de estrés oxidativo debido a la cantidad de radicales libre y especies reactivas de oxígeno y nitrógeno originadas en el humo del tabaco (137). Los radicales libres son moléculas inestables que se producen de manera natural durante los procesos metabólicos; sin embargo, también pueden generarse debido a factores externos como la contaminación ambiental, la radiación solar y el estrés (138).

Estas especies reactivas pueden desencadenar una respuesta inflamatoria crónica en el organismo además de estar implicadas en el proceso de carcinogénesis, mediante la activación de vías de proliferación celular e inhibir la apoptosis (139). También se ha demostrado que el daño oxidativo al

ADN conduce a mutaciones que favorecen la inestabilidad genómica provocada por el estrés oxidativo, lo cual puede facilitar tanto la progresión tumoral como la invasión y metástasis de células cancerígenas (140, 141).

Sobre esta base, se ha promovido el uso de agentes antioxidantes, vitaminas y minerales debido a su papel en el proceso de carcinogénesis. El primer trabajo de esta tesis, una revisión sistemática sobre fármacos para la prevención del cáncer de pulmón en personas sanas, evaluó la eficacia de diversas vitaminas y minerales en la prevención de esta enfermedad y concluye que el uso de estos compuestos no resulta útil para prevenir el cáncer de pulmón (96). Una posible explicación radica en la compleja y paradójica relación entre los radicales libres y el cáncer (139). Aunque los radicales libres y el estrés oxidativo pueden inducir la carcinogénesis, las células transformadas, es decir, las células cancerosas, generan más radicales libres que las células normales (142). En este contexto, diversos agentes quimioterapéuticos contra el cáncer pueden ser selectivamente tóxicos para las células tumorales al aumentar el estrés oxidativo, llevando a estas células ya comprometidas más allá de su umbral tolerable (143, 144).

Existen diversos sistemas antioxidantes para la eliminación de las especies reactivas de oxígeno (ROS), no obstante, ellos se pueden alterar debido a los procesos subyacentes a la malignización celular (145). El cáncer puede presentar un comportamiento dual caracterizado por un predominio de actividad prooxidante o antioxidante en la célula tumoral, dependiendo de la etapa de progresión de la enfermedad. Los altos niveles de ROS constituyen, paradójicamente, un fenómeno de daño celular que culmina en la apoptosis de células cancerígenas (145). En consecuencia, los esfuerzos

terapéuticos deberían dirigirse a la promoción o inhibición de componentes oxidantes y antioxidantes, con el objetivo de modular el efecto de las ROS en el microambiente tumoral (145).

El aumento del riesgo asociado a las vitaminas C y E, reflejado en nuestros hallazgos, podría explicarse a partir de los resultados del estudio de Ting Wang (2023), (146). En este estudio se observó que, en pacientes con otros factores de riesgo, las vitaminas C y E estimulaban la angiogénesis tumoral dependiente del factor de transcripción sensible a la oxidación-reducción. Dado que la angiogénesis está regulada por mecanismos transcripcionales que van más allá de los factores de transcripción inducibles por hipoxia (HIF), se determinó que las vitaminas C y E pueden favorecer el crecimiento tumoral al apoyar el desarrollo de nuevos vasos sanguíneos dentro y alrededor de los tumores en condiciones de normoxia. Estos hallazgos subrayan la necesidad de identificar nuevas proteínas y mecanismos que regulen la angiogénesis tumoral (146). Si no se logra controlar la angiogénesis tumoral, se produce la progresión tumoral, un proceso mediante el cual las células normales se transforman en fenotipos neoplásicos. Este proceso es resultado de una serie de mutaciones y cambios genéticos y epigenéticos que afectan a los genes responsables de regular la proliferación celular, la supervivencia y otros cambios asociados con un fenotipo maligno (146).

La Inmunoterapia se presenta como un enfoque terapéutico para el cáncer que estimula el sistema inmunitario, permitiéndole reconocer y atacar las células cancerosas. No obstante, algunos pacientes con cáncer de pulmón avanzado responden favorablemente a la inmunoterapia, mientras que otros no lo hacen. Los resultados obtenidos en el segundo trabajo de esta tesis, revelaron la ausencia o efectos mínimos en la supervivencia global, la supervivencia libre de progresión y la calidad de vida de las vacunas terapéuticas para el cáncer de pulmón de células no pequeñas en estado avanzado (97).

Una posible explicación es que, aunque algunos tumores son eliminados por el sistema inmunitario, en consecuencia, nunca se detectan, otros continúan creciendo a pesar de la vigilancia del sistema inmunológico (147). Se han propuesto mecanismos para explicar esta deficiente respuesta del huésped al cáncer (147). Entre ellos se encuentran: la supresión de la respuesta inmunitaria por parte del propio tumor, mediante mecanismos tales como la disminución de la función de linfocitos T y B, así como de las células presentadoras de antígeno, la reducción en la producción de interleucina 2 (IL-2), la generación de células T "agotadas", y el aumento de receptores solubles de IL-2 que se unen e inactivan a esta citocina (147). Además, se observa la presencia y actividad de células polarizadas TAM-2 (M2), células supresoras derivadas de mieloides y células T reguladoras que promueven una tolerancia inmunitaria específica (147).

Además, en la superficie de las células cancerosas se encuentran las proteínas de puntos de control, el antígeno asociado a los linfocitos T citotóxicos 4 (CTLA-4) y muerte programada 1 (PD-1), que 'frenan' el sistema inmunitario e impiden que este ejerza su función de ataque contra el cáncer (148). Para contrarrestar este efecto, se han desarrollado fármacos inhibidores de puntos de control que permiten al sistema inmunitario liberar las células T para atacar las células cancerosas (148). Es necesario realizar estudios para determinar si la administración conjunta de dos fármacos de inmunoterapia resulta más eficaz que el uso de un solo fármaco en pacientes con cáncer de pulmón avanzado.

El tercer trabajo de esta tesis evaluó la calidad metodológica de las GPC para el tratamiento del NSCLC. Desde 2013, estas guías han incorporado en sus recomendaciones anticuerpos monoclonales dirigidos a mutaciones del ADN e inhibidores de puntos de control, pero no vacunas (98). Las guías más actuales recomiendan realizar pruebas moleculares, dado que se han identificado numerosas alteraciones genéticas que afectan la selección de la terapia. Ya en 2019 se perfilaba la ruta hacia la Inmuno-oncología de precisión, y las recomendaciones de las guías NCCN indicaban que la carga mutacional tumoral (TMB), que refleja la acumulación de mutaciones somáticas y tiene probabilidades de ser útil como biomarcador, debía ser utilizada para seleccionar a los pacientes candidatos a la inmunoterapia (149). Las guías de práctica clínica actuales recomiendan que todos los nuevos pacientes con NSCLC se sometan a un perfil molecular utilizando métodos diagnósticos validados adecuados, para determinar el abordaje terapéutico más apropiado (150).

Las recomendaciones actuales de la ASCO y la NCCN para el NSCLC avanzado, similares a las directrices europeas de la ESMO, sugieren realizar pruebas de biomarcadores iniciales coherentes con el diagnóstico histológico (151–154).

Las guías de práctica clínica señalan que la prueba con muestras del cáncer de pulmón para estas alteraciones es importante para la identificación de terapias dirigidas potencialmente eficaces, así como para evitar terapias que probablemente no proporcionen un beneficio clínico. Además, informan sobre los elementos principales a tener en cuenta para la realización de las pruebas moleculares, que son fundamentales para la utilización e interpretación de los resultados moleculares (153). Los pacientes pueden clasificarse en aquellos con NSCLC que presentan alteraciones impulsoras (152-

154) y aquellos para quienes las pruebas de biomarcadores no indican la presencia de alteraciones impulsoras, o para quienes no fue factible realizar las pruebas (155,156).

En los ámbitos de prevención y detección del cáncer de pulmón, las GPC americanas de CNNC 2024 (153), recomiendan implementar estrategias efectivas en todos los niveles, tanto gubernamentales como en políticas de salud pública, para erradicar el tabaquismo y la exposición al humo del tabaco. Indican que la reducción de la mortalidad por cáncer de pulmón requerirá la implementación generalizada de las pautas de la Agencia para la Investigación y la Calidad de la Atención Médica (AHRQ) (157).

Asimismo, señalan que los agentes de Quimioprevención aún no están establecidos para estos pacientes y sugieren que se les debe incentivar a inscribirse en ensayos clínicos de Quimioprevención. En cuanto a la detección, recomiendan el uso de tomografía computarizada de baja dosis (TC) para pacientes seleccionados con alto riesgo de cáncer de pulmón que fuman o han fumado en el pasado (153).

6.3 LIMITACIONES Y FORTALEZAS

Limitaciones

Una limitación significativa en todos los artículos revisados es la heterogeneidad en los estudios incluidos. Las diferencias en los diseños, las poblaciones de pacientes, las intervenciones y los resultados medidos complican la comparación directa y la síntesis de resultados. Esta variabilidad

puede afectar la capacidad de llegar a conclusiones definitivas y aplicables en la práctica clínica (55, 96, 97).

Por otra parte, la información sobre efectos adversos es a menudo incompleta o no se reporta de manera consistente, lo que dificulta la evaluación de los riesgos asociados con las intervenciones. Esto es particularmente relevante en el contexto de suplementos vitamínicos y minerales, donde los efectos adversos pueden contrarrestar los beneficios potenciales.

En el ámbito de la Inmunoterapia, pocos estudios evaluaron el impacto de las vacunas en los aspectos relacionados con la calidad de vida de sus participantes. Este es un problema en sí mismo y también una limitación significativa (97).

Es de considerar que la evidencia sobre los efectos de las intervenciones en subgrupos, de poblaciones, como fumadores y mujeres posmenopáusicas, es limitada y a menudo inconsistente. Esto impide hacer recomendaciones específicas para estas poblaciones y destaca la necesidad de estudios más focalizados (158, 159).

Una limitación significativa en todos los artículos revisados es la heterogeneidad de los estudios incluidos. Las diferencias en los diseños, las poblaciones de pacientes, las intervenciones y los resultados medidos complican la comparación directa y la síntesis de resultados. Esta variabilidad puede afectar la capacidad para llegar a conclusiones definitivas y aplicables en la práctica clínica. La calidad de la evidencia varía considerablemente entre los estudios; algunos proporcionan datos de

alta certeza, mientras que otros presentan baja certeza, lo que limita, en general, la confianza en los resultados (160,161).

Además, la falta de seguimiento a largo plazo en muchos estudios impide evaluar los efectos sostenidos de las intervenciones. Por otra parte, la información sobre efectos adversos es a menudo incompleta o no se reporta de manera consistente, lo que dificulta la evaluación de los riesgos asociados con las intervenciones. Esto es particularmente relevante en el contexto de suplementos vitamínicos y minerales, donde los efectos adversos pueden contrarrestar los beneficios potenciales (162).

La heterogeneidad en las poblaciones de pacientes y en las intervenciones es evidente en la revisión de vacunas terapéuticas. Las diferencias en los mecanismos de acción, así como su aplicación en los distintos estadios de la enfermedad, incluyendo diferentes esquemas como la terapia de mantenimiento y las terapias de primera, segunda o tercera línea, influyen en los resultados. Además, las características de los pacientes, tales como factores genéticos, alteraciones asociadas a la respuesta inmune, edad, condiciones de comorbilidad, estilo de vida y expectativas del paciente, también desempeñan un papel crucial en la variabilidad de los resultados observados (163).

Fortalezas

La solidez de los resultados presentados en esta tesis se fundamenta en los diseños y métodos seleccionados. Las revisiones sistemáticas se llevaron a cabo en el marco de la Colaboración Cochrane, cumpliendo con rigurosos estándares metodológicos en cada una de las etapas de la investigación. Se realizaron búsquedas exhaustivas de la literatura pertinente, así como la extracción de datos por parte de revisores independientes, seguidas de un análisis cuidadoso e interpretación de los resultados. Además, las publicaciones fueron sometidas a revisión por editores del grupo de revisión Cochrane en cáncer de pulmón y por editores de la Cochrane Central, lo que implicó un extenso y meticuloso proceso de revisión para asegurar la solidez de los resultados (84, 86). Asimismo, el estudio de evaluación de las GPCs fue llevado a cabo por un equipo experimentado. La evaluación de las GPCs se realizó de manera independiente por tres evaluadores, quienes lograron alcanzar un acuerdo sustancial utilizando un instrumento validado y confiable (95). Se realizó una búsqueda exhaustiva para identificar todas las GPCs relevantes, lo que minimiza la probabilidad de omitir guías importantes. Finalmente, el trabajo fue sometido a una revista indexada editada por Springer, lo que garantiza la aplicación de altos estándares de evaluación (98).

6.5 IMPLICACIONES PARA LA PRÁCTICA

Los hallazgos de esta tesis doctoral son relevantes para las estrategias de Quimioprevención, inmunoterapia y sus recomendaciones terapéuticas. Sugieren que los suplementos vitamínicos y minerales no deben ser recomendados de manera rutinaria para la prevención del cáncer de pulmón, especialmente en poblaciones de alto riesgo (96). Por lo tanto, los profesionales de la salud deben desaconsejar el uso de estos suplementos, particularmente en personas expuestas a los factores de riesgo ya mencionados, como el humo del cigarro, asbesto y contaminación ambiental en general. En consecuencia, estos resultados deben ser comunicados tanto a los profesionales de la salud como al

público en general, con el objetivo de aumentar la conciencia sobre las limitaciones de los suplementos vitamínicos y minerales en la prevención del cáncer de pulmón y promover prácticas preventivas basadas en la evidencia (96, 164).

En el ámbito de la inmunoterapia, se ha observado que el efecto de las vacunas en la prolongación de la vida de las personas con NSCLC avanzado es, en general, pequeño, alcanzando en el mejor de los casos unos pocos meses. Por lo tanto, la recomendación actual es no vacunar. Es esencial determinar si una mejora en la duración de la vida se acompaña de una mejora en la calidad de vida y si los efectos secundarios son aceptables. Además, es importante considerar que los participantes en estos ensayos clínicos fueron pacientes seleccionados, quienes generalmente presentaban un mejor estado funcional en comparación con la población general; por lo tanto, probablemente no son representativos de todas las personas con NSCLC avanzado. Una consideración relevante es que, hasta la fecha, ninguna de estas vacunas ha sido aprobada por las autoridades reguladoras como la Administración de Alimentos y Medicamentos (FDA) o la Agencia Europea de Medicamentos (EMA), lo que significa que actualmente no están disponibles en el mercado (97, 153).

Las principales implicaciones del estudio de las GPCs están relacionadas con la mejora de su calidad metodológica y su aplicabilidad. Implementar recomendaciones de GPCs de baja calidad puede tener efectos negativos en los pacientes. Por otro lado, las GPCs, en general, no proporcionan información explícita sobre fuentes de financiación, costos, barreras, facilitadores, materiales adicionales y otros factores clave que son esenciales para garantizar la aplicación efectiva de sus recomendaciones (98).

En consecuencia, es fundamental disponer de GPCs de alta calidad sobre el NSLC que realmente sirvan como herramientas prácticas y genuinas para la toma de decisiones clínicas. Para lograrlo, es necesario que los desarrolladores de guías consideren la utilización del instrumento GRADE para evaluar la calidad de la evidencia disponible y elaborar recomendaciones adecuadas que permitan una interpretación clara y pragmática de recomendaciones fuertes y débiles en los médicos, pacientes y responsables de políticas (165, 92).

Asimismo, es crucial mejorar la adherencia de los médicos a las GPCs para reducir la variabilidad en las decisiones clínicas. Para ello, se debe realizar una difusión adecuada sobre la calidad de las GPC disponibles en este campo (98).

6.6 IMPLICACIONES PARA LA INVESTIGACIÓN

La futura investigación sobre el efecto de vitaminas, minerales y otros antioxidantes en la prevención del cáncer de pulmón en personas sanas probablemente requerirá un mayor estudio de las vías de la carcinogénesis, dado que la evidencia disponible actualmente no respalda su uso. Es fundamental continuar realizando estudios de alta calidad que cuenten con tamaños de muestra amplios y seguimientos prolongados para confirmar estos hallazgos y evaluar de manera más precisa los efectos a largo plazo de los suplementos vitamínicos, minerales y otras intervenciones. Sin embargo, dado el riesgo confirmado en nuestro estudio, la opción de llevar a cabo ensayos clínicos controlados no es éticamente aceptable. En su lugar, sería más apropiado realizar estudios observacionales mediante cohortes prospectivas. En esta línea, resulta interesante investigar el efecto en subgrupos específicos de interés, como aquellos expuestos a factores de riesgo. Además, la inclusión de análisis de costos en estos estudios podría contribuir a guiar las decisiones clínicas y de salud pública (166, 96).

La evaluación de posibles terapias dirigidas al tratamiento del NSLC, especialmente en estadios avanzados, representa un desafío crucial para orientar la investigación futura. La identificación farmacogenética de mutaciones con la generación de oncogenes que afectan las vías de señalización intracelular, codificando para proteínas del receptor del factor de crecimiento epidérmico (EGFR), así como el descubrimiento, galardonado con el Premio Nobel, del eje de muerte celular programada 1/ligando de muerte programada 1 (PD-1/PD-L1) (167), que surgieron como un objetivo prometedor para la inmunoterapia, con avances significativos en la innovación terapéutica (149). La supresión de la señalización de oncogenes mediante la terapia dirigida y la activación de la respuesta inmune humoral e intercelular por inhibidores de puntos de control inmunitarios (ICI), han transformado el escenario a considerar, para el abordaje del NSCLC (150).

En esta corriente innovadora y debido al beneficio clínico de los inhibidores de la tirosina quinasa (TKI) del EGFR se ha producido un aumento de las aprobaciones a través de aprobación acelerada para nuevos medicamentos dirigidos al NSCLC adicto a oncogenes (150). Para acelerar las aprobaciones de estos nuevos fármacos, cabe señalar que las agencias reguladoras de Estados Unidos y Europa (FDA, y EMA), aceptaron ampliamente los ensayos de un solo brazo o los ensayos de cohortes múltiples como evidencia fundamental para la aprobación regulatoria acelerada (150,152).

Lo anterior marca la importancia para las tendencias del desarrollo de productos terapéuticos oncológicos en el futuro. Se deberían considerar las implicancias en término de la validez de los resultados de los ensayos clínicos de un brazo, con tamaños de muestra limitados o los ensayos de

cohortes múltiples. Por otra parte, se debe considerar que la mayoría de las aprobaciones de medicamentos no contaron con la aprobación simultánea de una prueba diagnóstica. Los estudios posteriores a la comercialización deberían desempeñar un papel fundamental para confirmar tanto la óptima dosificación, como el beneficio clínico y garantizar el rendimiento del dispositivo de diagnóstico complementario en una gama más amplia de tipos de tumores (153, 154).

Respecto de las vacunas terapéuticas contra el cáncer y considerando su limitada eficacia clínica como agentes únicos, la investigación se ha focalizado en el desarrollo de vacunas personalizadas dirigidas a antígenos específicos de cada tumor en los pacientes. Se ha propuesto, que añadir vacunas a la monoterapia con ICI, que es el tratamiento estándar para algunos tipos de cáncer, podría potenciar la eficacia del tratamiento (155).

La combinación de vacunas con otras terapias debería ser explorada para identificar posibles sinergias (97). Se debería fomentar más la búsqueda de nuevos antígenos asociados a tumores (TAA) para atacar la heterogeneidad tumoral y eliminar todos los tipos de células malignas deficientes, incluidas las variantes tumorales multirresistentes con escape inmunitario (51). En este contexto, recientemente se ha informado sobre un ensayo en curso con una vacuna basada en ARN mensajero (ARNm) que codifica seis antígenos tumorales: MAGE A3, CLDN6, KK-LC-1, PRAME, MAGE A4 y MAGE C1. LuCa-MERIT-1 es un ensayo en fase I, abierto y no aleatorizado, diseñado para confirmar la dosis y evaluar la seguridad, tolerabilidad y eficacia preliminar de BNT116, tanto solo como en combinación con Quimioterapia o un inhibidor de puntos de control inmunitario, en pacientes con NSCLC avanzado (168).

Con el conocimiento actual del genoma y avances en el conocimiento de nuevas vías inmunitarias, se reconoce la importancia de la medicina personalizada. En este sentido, la especificidad de la vacunación terapéutica combinada con ICI, podría ofrecer una vía atractiva para el desarrollo de futuras Inmunoterapias contra el cáncer para pacientes con resistencia adquirida a los tratamientos actuales (169).

Finalmente, en términos de recomendaciones terapéuticas, es esencial mejorar la metodología utilizada en el desarrollo de las GPC, así como su plan de difusión. Esto debe hacerse considerando las principales barreras y costos asociados con el proceso de implementación, asegurando que se sigan estándares rigurosos y transparentes, como los propuestos por el instrumento GRADE. La participación activa de pacientes y otros interesados puede aumentar la relevancia y aceptación de las GPC, lo que a su vez mejorará la implementación de las recomendaciones (170, 171).

CONCLUSIONES

Este trabajo de tesis presenta la evidencia disponible sobre la Quimioprevención, la Inmunoterapia con vacunas y las recomendaciones de tratamiento incluidas en las guías de práctica clínica para el cáncer de pulmón. Las principales conclusiones que se derivan de este análisis son las siguientes:

No existe evidencia que respalde que los suplementos de vitaminas A, C, D, E o selenio, ya sea de forma aislada o en diversas combinaciones, prevengan la incidencia ni la mortalidad del cáncer de pulmón en individuos sanos. Sin embargo, se han identificado efectos adversos en fumadores y en personas expuestas al amianto. En particular, la vitamina A se asocia con un aumento en la incidencia y mortalidad por cáncer de pulmón, así como con un incremento en la mortalidad por todas las causas. Por otro lado, la vitamina C incrementa la incidencia de cáncer de pulmón en mujeres, mientras que la vitamina E eleva el riesgo de accidentes cerebrovasculares hemorrágicos.

Podemos afirmar, con un nivel de confianza que varía de moderado a muy bajo, debido al reducido número de estudios y al tamaño limitado de las muestras en los ensayos clínicos incluidos en la revisión, que las vacunas terapéuticas contra el cáncer de pulmón no mejoran la supervivencia general ni la supervivencia libre de progresión, o lo hacen solo en un grado mínimo. En cuanto a los efectos adversos asociados con las vacunas son poco frecuentes, aunque es importante considerar también los posibles efectos a largo plazo.

La mayoría de las GPCs evaluadas sobre cáncer de pulmón presentan una calidad metodológica moderada y pueden ser recomendadas con modificaciones para su uso en el tratamiento del NSCLC. Es necesario desarrollar GPCs de alta calidad que aborden aspectos relacionados con la implementación, tales como la evaluación de facilitadores y barreras organizacionales, el desarrollo de recursos educativos, las implicaciones económicas y los criterios de monitoreo o auditoría. Estos avances son fundamentales para evitar efectos negativos en los pacientes.

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ANEXOS

Anexo 1. *Otras publicaciones relacionadas con el tema de tesis doctoral*

Publicación 1. Cortes-Jofre_M, Rueda_JR, Corsini-Munoz_G, Fonseca-Cortes_C, Caraballoso_M, Bonfill Cosp_X. Drugs for preventing lung cancer in healthy people. Cochrane Database of Systematic Reviews 2012, Issue 10. [DOI: 10.1002/14651858.CD002141.pub2].

Publicación 2. Pelayo Alvarez M, Westeel V, Cortés-Jofré M, Bonfill Cosp X. Chemotherapy versus best supportive care for extensive small cell lung cancer. Cochrane Database of Systematic Reviews 2013, Issue 11. Art.No.CD001990. DOI: 10.1002/14651858.CD001990.pub3.

Publicación 3. Tristán L Mario, Ramírez M Anggie, Cortés Jofre Marcela. Protocolo Informe Rápido regional de evaluación de tecnología sobre la efectividad y seguridad del Erlotinib para pacientes adultos con carcinoma de células no pequeñas de pulmón (CCNPP), con mutación en el receptor del factor de crecimiento epidérmico (EGFR) predictiva de sensibilidad a inhibidores de tirosin kinasa. Proyecto de Cooperación Técnica BID ATN/OC. 214703-RG 016, 2017.

Publication 4. Cortés-Jofré M, Uranga R, Torres Pombert A, Arango Prado MDC, Caballero Aguirrechu I, Pacheco C, Ortiz Reyes RM, Chuecas F, Mas Bermejo PI. Therapeutic vaccines for advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews 2019, Issue 8. Art. No.: CD013377. DOI: 10.1002/14651858.CD013377. [Protocol].

Anexo 2. *Abreviaturas*

NSCLC: Cáncer de pulmón de células no pequeñas

SCLC: cáncer de pulmón de células pequeñas

IARC: Agencia Internacional para la Investigación sobre el Cáncer

LCINS: Cáncer de pulmón en no fumadores

RS: Revisión sistemática

IM: Intervenciones motivacionales

APRN: Agonistas parciales de los receptores de nicotina

AINE: Antiinflamatorios no esteroideos

COX-2: Ciclooxigenasa

TC: Tomografía computarizada

PET-CT: Tomografía por emisión de positrones con tomografía computarizada

EBUS: Ecografía endobronquial

IASLC: Asociación Internacional para el Estudio del Cáncer de Pulmón

ICD: Muerte celular inmunogénica

APC: Células presentadoras de antígenos

MHC: Complejo mayor de histocompatibilidad

TAA: Antígenos asociados a tumores

TGF: Factor de crecimiento tumoral

MBE: Medicina basada en evidencia

GPC: Guías de práctica clínica

Overviews Resúmenes de revisiones

AGREE: Valoración de Directrices para la Investigación y Evaluación

CVRS: Calidad de vida relacionada con la salud

FI: Factor de impacto

Anexo 3. *Presentación poster 81, XXI Colloquium Cochrane, 10 de septiembre, 2024*

Two Cochrane centers collaborate with clinicians to prioritize relevant questions, while students develop evidence summaries ('Support Summaries') that support evidence-based clinical decision-making.

Improving student engagement in the production and transfer of evidence within the Cochrane framework.

Introduction

The collaboration between the UC Evidence Centre (CEUC) and the Universidad Católica de la Santísima Concepción (UCSC), both Cochrane centres associated with Cochrane Chile, focuses on synthesizing evidence to support evidence-based clinical decision-making. The aim is to provide reliable and up-to-date information to healthcare professionals, improving the quality of medical care.

Objectives

- Identify and prioritize clinically relevant questions in collaboration with UCSC medical specialty coordinators.
- With the support of the UC Evidence Center, train medical students in the structured methodology of evidence summaries ("Support Summaries") for systematic reviews.
- Utilize the Open Science Framework (OSF) and 'Estudiantes por la mejor Evidencia' (ExMe) as platforms for sharing summaries, aiming to impact clinical practice.

Methods

The project involved close collaboration with UCSC medical specialty coordinators to identify and prioritize clinically relevant questions. Medical students were trained in Support Summaries methodology and produced summaries of existing systematic reviews for each question. The Open Science Framework (OSF) served as the primary platform for sharing project documents, promoting transparency and collaboration.

Key Results

The Support Summaries produced valuable findings summarizing current evidence, aiding healthcare professionals in making informed decisions.

Students developed skills in generating questions, conducting literature searches, synthesizing evidence, and transferring knowledge.

Rigorous synthesis of existing medical literature ensured the reliability of the results, making them a trusted source of information for healthcare professionals.

The project has been ongoing for more than 3 years, with more than 40 support summaries written. These have now been disseminated on OSF and ExMe (go to QR code) and are being explored for adding them to other databases.

Conclusions and acknowledgments:

The project's findings directly impact clinical practice, guiding treatment choices and informing evidence-based healthcare protocols. They also contribute to evidence-based health policy formulation, thereby improving healthcare systems. Examples of clinical applications include guiding treatment selection for various medical conditions and informing evidence-based healthcare protocols. In conclusion, the project has been instrumental in providing evidence-based information to healthcare professionals, identifying relevant clinical questions, producing Support Summaries of systematic reviews, and publishing findings on the OSF platform. Our aim is to enhance clinical decision-making and promote evidence-based practice to ensure quality healthcare.

We extend our gratitude to the UC Evidence Center, the Universidad Católica de la Santísima Concepción, medical specialty coordinators, and participating students for their collaboration and support, without which this project would not have been possible.

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Supplementary material