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Mujeres con alto riesgo de desarrollar cáncer de pulmón en la Unión Europea: estrategias de prevención primaria y secundaria de cáncer de pulmón

Adrián González Marrón

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MUJERES CON ALTO RIESGO DE DESARROLLAR CÁNCER DE PULMÓN EN LA UNIÓN EUROPEA: ESTRATEGIAS DE PREVENCIÓN PRIMARIA Y SECUNDARIA DE CÁNCER DE PULMÓN

Tesis presentada por

Adrián González Marrón

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Directores:

Dr. Jose M Martínez Sánchez

Dr. Juan Carlos Martín Sánchez

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«Verba volant, scripta manent».
Cayo Tito

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RESUMEN

Fumar es uno de los principales factores de riesgo evitables de morbimortalidad. Debido a la epidemia de tabaco, la prevalencia de mujeres fumadoras ha aumentado durante las últimas décadas. Entre las causas de mortalidad asociadas a fumar que mayor impacto tienen en salud pública se encuentra el cáncer de pulmón. Por la alta tasa de letalidad del cáncer de pulmón, la prevención primaria orientada a la no iniciación y a la deshabituación del tabaco es esencial para disminuir la mortalidad específica por esta causa. Incluso después de un diagnóstico de cáncer de pulmón, el abandono del tabaco está asociado a una mayor supervivencia y a mejores estadios funcionales, entre otros beneficios. En este sentido, la ayuda para dejar de fumar forma parte integral de la estrategia MPOWER de la Organización Mundial de la Salud (OMS), cuyo objetivo es la implementación efectiva de las medidas de control del tabaco incluidas en el Convenio Marco de la OMS para el Control del Tabaco.

Respecto a la prevención secundaria, desde hace aproximadamente dos décadas se están llevando a cabo diferentes ensayos clínicos con el objetivo de evaluar la eficacia de la tomografía computarizada de baja dosis como prueba de cribado de cáncer de pulmón. Por su diseño, los ensayos más importantes fueron el *National Lung Screening Trial* (NLST) en Estados Unidos y el *Nederlands-Leuvens Longkanker Screenings Onderzoek* (NELSON) en la Unión Europea (UE). Los criterios de inclusión que se han empleado en dichos ensayos para seleccionar a la población que presenta alto riesgo de desarrollar cáncer de pulmón se basan en la edad, el consumo acumulado de tabaco y, para exfumadores, los años desde el abandono. En contraposición a estos criterios simplificados se encuentran los modelos de predicción de riesgo, que estiman el riesgo individual de incidencia o mortalidad incorporando más variables, como historia familiar de cáncer o comorbilidades, como enfermedad pulmonar obstructiva crónica o enfisema.

Con relación a todo esto, los objetivos de esta tesis fueron: 1) estimar la proporción de individuos en la UE en edad de participar en cribados poblacionales que presenta alto riesgo de desarrollar cáncer de pulmón; 2) caracterizar el patrón de consumo de tabaco y estimar la proporción de mujeres que presenta alto riesgo de desarrollar cáncer de pulmón en un grupo de

participantes en un programa de cribado poblacional de cáncer de mama; 3) comparar las concentraciones de biomarcadores de exposición al tabaco (cotinina y nitrosaminas específicas del tabaco) en muestras de saliva entre fumadores diarios que presentan alto riesgo de desarrollar cáncer de pulmón y fumadores diarios que no presentan alto riesgo de desarrollar cáncer de pulmón; y 4) estimar la asociación entre la implementación de políticas de control del tabaco en la UE y la proporción de individuos que presentan alto riesgo de desarrollar cáncer de pulmón.

En relación con el primer y segundo objetivo, hemos estimado que hay una importante proporción de mujeres que están en edad de participar en cribados poblacionales de cáncer que presentan alto riesgo de desarrollar cáncer de pulmón según los criterios NLST y NELSON, y que por tanto serían elegibles si finalmente se implementaran programas de cribado de cáncer de pulmón en la UE. Sin embargo, y ante la controversia que todavía genera la implementación de programas de cribado de cáncer de pulmón en la UE, creemos que se podrían anidar programas de deshabituación del tabaco en cribados poblacionales de cáncer por la elevada participación en dichos cribados, especialmente en el de mama, y por tratarse de oportunidades de aprendizaje (*teachable moment*).

En relación con el tercer objetivo, las concentraciones (ajustadas por sexo) de nitrosaminas específicas del tabaco asociadas con el desarrollo de cáncer de pulmón (NNK y NNAL) presentes en muestras de saliva fueron significativamente mayores en fumadores diarios que presentaban alto riesgo de desarrollar cáncer de pulmón según los criterios NLST y NELSON que en fumadores diarios que no presentaban alto riesgo en una muestra representativa de la ciudad de Barcelona. Por este motivo, creemos que las variables relacionadas con la concentración de biomarcadores de consumo de tabaco en saliva podrían ser incorporadas en modelos de predicción por su capacidad de discriminación del riesgo.

Finalmente, en relación con el cuarto objetivo, hemos estimado en un análisis exploratorio que una mayor implementación de políticas de control del tabaco

en la UE está asociada a una menor proporción de individuos que presentan alto riesgo de desarrollar cáncer de pulmón. En este sentido, creemos que los Estados miembros deberían implementar políticas de control del tabaco de manera amplia para reducir la población que presenta alto riesgo de desarrollar cáncer de pulmón.

RESUM

Fumar és un dels principals factors de risc evitables de morbimortalitat. Per l'epidèmia de tabac, la prevalença de dones fumadores ha augmentat durant les últimes dècades. Entre les causes de mortalitat associades a fumar que major impacte tenen en salut pública es troba el càncer de pulmó. Per l'alta taxa de letalitat del càncer de pulmó, la prevenció primària orientada a la no iniciació i a la deshabituació del tabac és essencial per a disminuir la mortalitat específica per aquesta causa. Fins i tot, després d'un diagnòstic de càncer de pulmó, l'abandonament del tabac està associat a una major supervivència i a millors estadis funcionals, entre altres beneficis. En aquest sentit, l'ajuda per a deixar de fumar forma part integral de l'estratègia MPOWER de l'Organització Mundial de la Salut (OMS), l'objectiu de la qual és la implementació efectiva de mesures de control del tabac incloses en el Conveni Marc de l'OMS per al Control del Tabac.

Respecte a la prevenció secundària, des de fa aproximadament dues dècades s'estan duent a terme diferents assajos clínics amb l'objectiu d'avaluar l'eficàcia de la tomografia computada de baixa dosi com a prova de cribratge de càncer de pulmó. Pel seu disseny, els assajos més importants van ser el *National Lung Screening Trial* (NLST) als Estats Units i el *Nederlands-Leuvens Longkanker Screenings Onderzoek* (NELSON) a la Unió Europea (UE). Els criteris d'inclusió que s'han emprat en aquests assajos per a seleccionar a la població que presenta alt risc de desenvolupar càncer de pulmó es basen en l'edat, el consum acumulat de tabac i, per a exfumadors, els anys des de l'abandonament. En contraposició a aquests criteris simplificats es troben els models de predicció de risc, que estimen el risc individual d'incidència o mortalitat incorporant més variables, com per exemple, història familiar de càncer o comorbiditats, com a malaltia pulmonar obstructiva crònica o emfisema.

En relació amb tot això, els objectius d'aquesta tesi van ser: 1) estimar la proporció de individus a la UE en edat de participar en cribratges poblacionals que presenten alt risc de desenvolupar càncer de pulmó; 2) caracteritzar el patró de consum de tabac i estimar la proporció de dones que presenta alt risc de desenvolupar càncer de pulmó en un grup de participants en un programa de cribratge poblacional de càncer de mama; 3) comparar les concentracions de

biomarcadors d'exposició al tabac (cotinina i nitrosamines específiques del tabac) en mostres de saliva entre fumadors diaris que presenten alt risc de desenvolupar càncer de pulmó i fumadors diaris que no presenten alt risc de desenvolupar càncer de pulmó; i 4) estimar la associació entre la implementació de polítiques de control del tabac a la UE i la proporció d'individus que presenten alt risc de desenvolupar càncer de pulmó.

En relació amb el primer i segon objectiu, hem estimat que hi ha una important proporció de dones que estan en edat de participar en cribratges poblacionals que presenten alt risc de desenvolupar càncer de pulmó segons els criteris NLST i NELSON i que per tant serien elegibles si finalment s'implementessin programes de cribratge de càncer de pulmó a la UE. No obstant això, i davant la controvèrsia que encara genera la implementació de programes de cribratge de càncer de pulmó a la UE, creiem que es podrien niar programes de deshabituació del tabac en cribratges poblacionals de càncer per l'elevada participació en aquests cribratges, especialment en el de mama, i per tractar-se d'oportunitats d'aprenentatge (*teachable moment*).

En relació amb el tercer objectiu, les concentracions (ajustades per sexe) de nitrosamines específiques del tabac associats amb el desenvolupament de càncer de pulmó (NNK i NNAL) presents en mostres de saliva van ser significativament majors en fumadors diaris que presentaven alt risc de desenvolupar càncer de pulmó segons els criteris NLST i NELSON que en fumadors diaris que no presentaven alt risc en una mostra representativa de la ciutat de Barcelona. Per aquest motiu, creiem que les variables relacionades amb la concentració de biomarcadors de consum de tabac en saliva podrien ser incorporades en models de predicció per la seva capacitat de discriminació del risc.

Finalment, en relació amb el quart objectiu, hem estimat en una anàlisi exploratòria que una major implementació de polítiques de control del tabac a la UE està associada a una menor proporció d'individus que presenten alt risc de desenvolupar càncer de pulmó. En aquest sentit, creiem que els Estats membres

haurien d'implementar polítiques de control del tabac de manera àmplia per a reduir la població que presenta alt risc de desenvolupar càncer de pulmó.

ABSTRACT

Smoking is one of the main avoidable risk factors of morbidity and mortality. Due to the tobacco epidemic, the prevalence of women who smoke has increased during the last decades. Among the causes of mortality associated with smoking with a greater impact in public health is lung cancer. Due to the high lethality rate of lung cancer, primary prevention oriented to no initiation and smoking cessation is essential to decrease the cause-specific mortality rate. Even after the diagnosis of lung cancer, tobacco cessation is associated with a higher survival and better performance status, among other benefits. In this sense, help to give up smoking is an integral part of the World Health Organization (WHO) MPOWER strategy, whose aim is the effective implementation of tobacco control measures included in the WHO Framework Convention on Tobacco Control.

Regarding secondary prevention, since approximately two decades ago different clinical trials are being carried out with the aim of assessing the efficacy of low-dose computed tomography as test for lung cancer screening. As far as the design is concerned, the most important trials were the National Lung Screening Trial (NLST) in the United States and the *Nederlands-Leuvens Longkanker Screenings Onderzoek* (NELSON) in the European Union (EU). Inclusion criteria applied in these trials to select the population presenting high risk of developing lung cancer are based on age, cumulative tobacco consumption and, for former smokers, years since giving up. Opposing these simplified eligibility criteria, risk prediction models estimate the individual risk of lung cancer incidence or mortality incorporating further variables, such as family history of cancer or comorbidities, such as chronic obstructive pulmonary disease or emphysema.

Regarding all of the above, the objectives of this thesis were: 1) to estimate the proportion of individuals in the EU in the screening age range for population-based screenings at high risk of developing lung cancer; 2) to characterize the smoking pattern and estimate the proportion of women at high risk of developing lung cancer in a group of participants in a population-based breast cancer screening program; 3) to compare the concentrations of biomarkers of smoke exposure (cotinine and tobacco-specific nitrosamines) in saliva samples between daily smokers at high risk of developing lung cancer and daily smokers

not at high risk of developing lung cancer; and 4) to estimate the association between the implementation of tobacco control policies and the proportion of individuals at high risk of developing lung cancer in the EU.

Regarding the first and second objective, we have estimated that there is an important proportion of women within the age range of participating in population-based screenings that are at high risk of developing lung cancer according to NLST and NELSON criteria and, therefore, would be eligible if lung cancer screening programs were eventually implemented. However, and taking into account the controversy that still surrounds the implementation of lung cancer screening programs in the EU, we believe that tobacco cessation programs could be nested in population-based cancer screenings due to the high participation in those screenings, especially in breast cancer screening, and for their condition of teachable moment.

Regarding the third objective, concentrations (adjusted for sex) of tobacco specific nitrosamines associated with the development of lung cancer (NNK and NNAL) in saliva samples were significantly higher in daily smokers at high risk of lung cancer according to NLST and NELSON criteria than in those not at high risk in a representative sample of individuals of the city of Barcelona. For this reason, we believe that variables related to the concentration of biomarkers of tobacco consumption in saliva could be incorporated in risk prediction models due to their capacity of risk discrimination.

Finally, regarding the fourth objective, we have estimated in an exploratory analysis that a higher implementation of tobacco control policies in the EU is associated with a lower proportion of individuals at high risk of lung cancer. In this sense, we believe that Member states should implement comprehensive tobacco control policies to reduce the population at high risk of developing lung cancer.

1. INTRODUCCIÓN

1.1 Epidemia de tabaco y cáncer de pulmón: una perspectiva de género.

Fumar es uno de los principales factores de riesgo de muerte evitables. Se estima que alrededor de un 50% de los fumadores mueren por causas relacionadas con el consumo de tabaco[1]. Además, el impacto en salud del consumo de tabaco se extiende más allá de los consumidores activos, suponiendo la mortalidad relacionada con la exposición al humo ambiental del tabaco cerca de un 1% de la mortalidad global anual[2].

Además de a una elevada mortalidad, el tabaquismo está asociado a una gran carga de morbilidad, lo que conlleva un importante impacto en términos de coste y utilización de servicios sanitarios[3]. Multitud de enfermedades, incluidas enfermedades cardiovasculares, respiratorias y varios tipos de cáncer, entre otras, están relacionadas con el consumo de tabaco. Uno de los tipos de cáncer más fuertemente asociados a fumar es el cáncer de pulmón, estimándose que entre el 80% y el 90% de la incidencia de esta enfermedad en la población es atribuible al consumo de tabaco[4], muy lejos de otros factores de exposición como el radón[5].

Epidemiológicamente, el cáncer de pulmón se caracteriza por una elevada prevalencia y baja supervivencia, características que lo convierten en el cáncer que más muertes causa a nivel global, unos 1,7 millones en el año 2018[6]. En España, donde se produjeron más de 22.000 muertes por cáncer de pulmón en el año 2017[7], la tasa de supervivencia es de aproximadamente del 37,7% al año del diagnóstico, del 14,9% a los tres años y del 10,7% a los cinco años[8]. Esta baja supervivencia es consecuencia, frecuentemente, de una detección tardía en fases avanzadas por la presentación clínica inicial inespecífica que hace que el proceso pase inadvertido hasta que el pronóstico es muy negativo.

El cáncer de pulmón se ha tratado, históricamente, de una enfermedad asociada a los hombres por la mayor prevalencia de consumo de tabaco en comparación con las mujeres y por la exposición ocupacional a otros factores ambientales, como el asbesto. Sin embargo, en los últimos años, la incidencia de cáncer de

pulmón en mujeres ha aumentado notablemente. En España, la tasa de incidencia estandarizada por edad de cáncer de pulmón en mujeres ha pasado de un 7% anual entre 1993 y 1997 a un 11,2% entre 2003 y 2007[9]. Este hecho se puede explicar, principalmente, por dos factores. Por un lado, por la incorporación de la mujer al consumo de tabaco en las últimas décadas, tal y como se describe en el modelo propuesto por López et al.[10] de la epidemia del tabaco en países desarrollados. De acuerdo a dicho modelo, las curvas de prevalencia de consumo de tabaco y de mortalidad atribuible al consumo están diferidas unas dos o tres décadas en mujeres con respecto a las de los hombres. Por otro lado, por el intervalo (*gap*) a nivel poblacional entre la prevalencia de consumo de tabaco y la incidencia de cáncer de pulmón, estimado en alrededor de unos treinta años[11]. Por este aumento en la incidencia de cáncer de pulmón, así como por un descenso en la mortalidad por cáncer de mama por las mejoras en su diagnóstico y tratamiento, se ha proyectado que la mortalidad por cáncer de pulmón en mujeres superará a la de cáncer de mama en varios de los países donde no lo ha hecho ya, incluido España, antes del año 2030[12].

1.2 Prevención primaria y secundaria del cáncer de pulmón: dónde nos encontramos y hacia dónde vamos.

La prevención del cáncer de pulmón se basa en actividades a nivel primario, esencialmente orientadas a la no iniciación y a la deshabituación del tabaco y fundamentadas en la implementación de políticas de control del tabaco. A nivel secundario, las pruebas de cribado, como la radiografía de tórax acompañada o no por citología de esputo, se habían mostrado ineficaces en la reducción de la mortalidad por cáncer de pulmón[13]. Sin embargo, durante los últimos veinte años se han realizado diversos ensayos clínicos con el objetivo de estimar la reducción de la mortalidad por cáncer de pulmón asociada al uso de la tomografía computarizada de baja dosis (TCBD) como prueba de cribado[14]. El más importante, por su diseño, fue el *National Lung Screening Trial* (NLST) en Estados Unidos (EE.UU.), en el que se observó una reducción de la mortalidad por cáncer de pulmón del 20% y por todas las causas del 6,7% en el brazo cribado con TCBD frente al brazo cribado con radiografía de tórax en individuos

cribados anualmente durante tres rondas[15]. Este resultado condujo a la recomendación positiva por parte de diversas organizaciones, como el *US Preventive Services Task Force* (USPSTF)[16], de la implementación de programas de cribado de cáncer de pulmón con TCBD para incorporar individuos que presentan alto riesgo de desarrollar cáncer de pulmón, y que finalmente se acabaran implementando dichos programas en EE.UU. Actualmente, la participación en los programas de cribado de cáncer de pulmón en EE.UU es muy baja[17]. En la Unión Europea (UE) también se han llevado a cabo diversos ensayos para comprobar la eficacia de la TCBD, destacando por el tamaño muestral el estudio *Nederlands Leuvens Longkanker Screenings Onderzoek* (NELSON)[18], en el que se ha observado preliminarmente una reducción de la mortalidad por cáncer de pulmón a los 10 años de seguimiento en el brazo cribado con TCBD frente al brazo no cribado[19]. A pesar de la reducción observada en la mortalidad por cáncer de pulmón, el cribado de cáncer de pulmón no se ha implementado todavía en ningún país de la UE. En este sentido, en la actualidad hay una intensa discusión en la comunidad científica con relación al balance beneficio-riesgo de esta intervención por los efectos negativos descritos en los ensayos, como altas tasas de falsos positivos y sobrediagnóstico, exposición a radiación o efectos psicológicos ante un resultado positivo[20,21].

En todos los ensayos clínicos realizados hasta el momento se han utilizado para definir los criterios de inclusión, y por tanto como variables que delimitan la población que presenta alto riesgo, la edad, el consumo acumulado de cigarrillos a lo largo de la vida y los años desde el abandono en los exfumadores[14], en lo que ha sido denominado por otros autores como criterios de selección simplificados[22]. La selección de individuos que presentan alto riesgo por medio de estos criterios ha sido criticada, fundamentalmente, por la baja sensibilidad de los mismos[23]. En este sentido, se ha observado que una considerable proporción de casos de cáncer de pulmón recogidos en registros en EE.UU. ocurren en individuos que no cumplen los criterios de inclusión en el NLST[24].

Por otro lado, es destacable que en diferentes ensayos se ha observado una mayor reducción de la mortalidad por cáncer de pulmón en mujeres que en

hombres. Como ejemplo, en el estudio NELSON, aunque no se alcanzó significación estadística por el limitado número de mujeres participantes, el ratio de las tasas de mortalidad por cáncer de pulmón a los diez años desde la aleatorización fue del 0,61 (IC95% 0,35-1,04) en mujeres cribadas frente a no cribadas, mientras que en hombres fue de 0,74 (IC95% 0,60-0,91)[19]. Del mismo modo, en el *German Lung Cancer Screening Intervention* (LUSI), la razón de riesgo (*hazard ratio*) en mujeres fue de 0,31 (IC95% 0,10-0,96; p = 0,04) y en hombres de 0,94 (IC95% 0,54-1,61; p = 0,81) en la mortalidad por cáncer de pulmón[25]. Se especula con que el origen de esta divergencia se encuentre en diferencias en rutas celulares hormonales (progesterona y estrógenos), en la del citocromo P450 o en mutaciones en el gen del receptor del factor de crecimiento epidérmico, que pueden aportar un beneficio en la respuesta a la carcinogénesis y a los tratamientos[26].

Por las etapas de cambio por las que se transcurre hasta el abandono del tabaco[27] y las necesidades de seguimiento que implican, la atención primaria se ha descrito como un ámbito esencial para ofrecer la ayuda para la cesación del consumo de tabaco[28]. A su vez, también se ha abogado por que las intervenciones para la cesación formen parte integral de los cribados de cáncer de pulmón[29]. Esta propuesta se fundamenta en que las consecuencias positivas del abandono del tabaco se extienden más allá del momento del diagnóstico de cáncer de pulmón, ya que en el caso de un diagnóstico en fases tempranas el dejar de fumar puede rebajar el riesgo de muerte hasta a la mitad[29], además de añadir beneficios complementarios como reducción del dolor[30] y mejores estadios funcionales[31]. Además, los programas de cribado poblacional de cáncer se han descrito como oportunidad de aprendizaje (*teachable moment*), es decir, un marco en el que se pueden promover hábitos de vida saludables, como el abandono del tabaco, ya que los participantes en dichos cribados tienen una mayor percepción del riesgo y son propensos al cambio en sus hábitos de vida[32].

1.3 Nitrosaminas específicas del tabaco y cotinina: biomarcadores potencialmente incorporables a los modelos de predicción de riesgo de cáncer de pulmón.

De las diferentes sustancias carcinogénicas para los humanos que contiene el tabaco y el humo del tabaco, las únicas que están presentes exclusivamente en los mismos son las nitrosaminas específicas del tabaco (*Tobacco Specific Nitrosamines*, TSNA)[33], consideradas carcinógeno de tipo 1 por la Agencia Internacional para la Investigación del Cáncer[34]. Entre las TSNA que presentan mayor efecto carcinogénico se encuentran la 4-(metilnitrosamino)-1-(3-piridil)-1-butanona (NNK), la 4-(metilnitrosamino)-1-(3-piridil)-1-butanona (NNAL) y la N′-nitrosonornicotina (NNN)[33]. En concreto, la NNK y uno de sus metabolitos, la NNAL, están fuertemente asociadas con la inducción de cáncer de pulmón[35]. Tanto las TSNA como la cotinina, principal metabolito de la nicotina, han sido descritas como biomarcadores de exposición al humo de tabaco activo y pasivo[36].

En los ensayos clínicos que se han llevado a cabo hasta ahora para evaluar la TCBD como herramienta de cribado de cáncer de pulmón se han utilizado como variables para definir los criterios de selección: la edad, el consumo acumulado autodeclarado de tabaco y los años desde la cesación para los exfumadores[14]. En este sentido, además de los sesgos ampliamente descritos asociados al autorreporte[37], la variabilidad individual por diferencias en la marca consumida, las características individuales de consumo (*smoking topography*)[38] y el metabolismo de los carcinógenos, entre otros factores, pueden hacer variar las concentraciones de sustancias carcinogénicas entre sujetos que reportan el mismo consumo, siendo por tanto sus perfiles de riesgo diferentes. Por ello, se ha propuesto la incorporación de los biomarcadores de exposición al tabaco a los modelos de predicción del riesgo del cáncer de pulmón[39].

Frente a los anteriormente comentados criterios de selección simplificados utilizados hasta ahora en ensayos clínicos, fácilmente generalizables, se encuentran los modelos de predicción de riesgo[22]. Estos modelos estiman el

riesgo individual de incidencia o mortalidad por cáncer de pulmón e incorporan más variables, como por ejemplo comorbilidades, exposiciones a otros agentes o historia familiar de cáncer[40]. Estos modelos muestran mejor rendimiento que los criterios simplificados (por ejemplo, menor número de falsos positivos o menor número necesario a cribar)[41], lo que ha llevado a que en la actualidad se estén valorando como una alternativa para delimitar la población que presenta alto riesgo[42].

1.4 Políticas de control del tabaco y Escala de Control del Tabaco.

Para poner freno a la epidemia del tabaco, la Organización Mundial de la Salud (OMS) promovió la creación y desarrollo del Convenio Marco para el Control del Tabaco (CMCT) con el objetivo de controlar las causas de dicha epidemia[43]. En la actualidad, 181 Partes se encuentran representadas en dicho Convenio. Tomando como referencia el CMCT, la OMS promovió la estrategia MPOWER, cuyo objetivo es la implementación efectiva a nivel nacional de las medidas de control del tabaco incluidas en el CMCT, es decir: vigilar (*Monitor*) el consumo de tabaco y las políticas de prevención; proteger (*Protect*) a la población del humo de tabaco; ofrecer (*Offer*) ayuda para el abandono del tabaco; advertir (*Warn*) de los peligros del tabaco; hacer cumplir (*Enforce*) las prohibiciones sobre publicidad, promoción y patrocinio del tabaco; y aumentar (*Raise*) los impuestos al tabaco[44].

En línea con las medidas de control de la estrategia MPOWER de la OMS, el Banco Mundial también propuso en 2003 seis estrategias costo-efectivas de control del tabaco: incrementar los impuestos al tabaco, ofrecer acceso a tratamientos de deshabituación, ofrecer información pública, prohibir la publicidad del tabaco, advertir explícitamente en cajetillas sobre los efectos en salud y prohibir fumar en espacios públicos y de trabajo[45]. En la UE, la Escala de Control del Tabaco (*Tobacco Control Scale*, TCS)[46] cuantifica el nivel de implementación de dichas políticas a nivel nacional. Esta escala, publicada por primera vez en 2006, tiene un rango de 0 (peor) a 100 (mejor) puntos. Los 100 puntos se distribuyen de la siguiente manera: 30 a políticas fiscales; 22 a la prohibición de fumar en espacios

sin humo; 15 al gasto en campañas de información pública; 13 a la prohibición de publicidad y promoción del tabaco; 10 al empaquetado y etiquetado de los productos del tabaco; y 10 al tratamiento en el abandono del tabaco[46].

La evidencia apunta a que una mayor implementación de políticas de control del tabaco tiene un impacto positivo sobre diferentes indicadores y resultados en salud. Como ejemplo, se ha observado una menor prevalencia de consumo de tabaco y mayores tasas de cesación del consumo de tabaco[47] y una menor proporción de partos pretérmino y bajo peso al nacer[48], entre otros.

2. HIPÓTESIS Y OBJETIVOS DE LA TESIS

HIPÓTESIS

1. Por el aumento en las últimas décadas del número de mujeres fumadoras, la proporción de mujeres que actualmente presenta alto riesgo de desarrollar cáncer de pulmón en la UE es elevada.
2. Las concentraciones de biomarcadores de exposición al tabaco son mayores en los individuos que presentan alto riesgo de desarrollar cáncer de pulmón que en aquellos individuos que no presentan alto riesgo.
3. Una implementación más intensa de políticas de control del tabaco está asociada a una menor proporción de individuos que presenta alto riesgo de desarrollar cáncer de pulmón.

OBJETIVOS

1. Estimar la proporción de individuos en edad de participar en cribados poblacionales en la UE que presenta alto riesgo de desarrollar cáncer de pulmón.
2. Caracterizar el patrón de consumo de tabaco y estimar la proporción de mujeres que presenta alto riesgo de desarrollar cáncer de pulmón en un grupo de participantes en un cribado poblacional de cáncer de mama.
3. Comparar las concentraciones de biomarcadores de exposición al tabaco (cotinina y nitrosaminas específicas del tabaco) en muestras de saliva entre fumadores diarios que presentan alto riesgo de desarrollar cáncer de pulmón y fumadores diarios que no presentan alto riesgo de desarrollar cáncer de pulmón.
4. Estimar la posible asociación entre la implementación de políticas de control del tabaco en la UE y la proporción de individuos que presentan alto riesgo de desarrollar cáncer de pulmón.

3. OBJETIVOS Y RESULTADOS DE LOS ARTÍCULOS DE LA TESIS

La presente tesis doctoral consta de tres artículos científicos aceptados en revistas indexadas, dos de ellos publicados y uno de ellos en prensa; de un manuscrito que se encuentra actualmente en revisión en una revista indexada; y de una editorial publicada en una revista indexada. Se adjunta en la sección de Anexos el cuestionario diseñado *ad hoc* para el Artículo 2 (Anexo II) y la correspondencia con editores y revisores hasta la aceptación de los artículos y la editorial (Anexos I al V, exceptuando el Anexo II).

A continuación, se expone una reseña sobre los artículos y el manuscrito, así como los objetivos y los resultados más relevantes de cada uno de ellos, y un resumen de la editorial:

1. Estimation of the adult population at high risk of developing lung cancer in the European Union. González-Marrón A, Martín-Sánchez JC, Matilla-Santander N, Cartanyà-Hueso À, Lidón-Moyano C, Vidal C, García M, Martínez-Sánchez JM. Cancer Epidemiol. 2018 Dec;57:140-147. doi: 10.1016/j.canep.2018.10.007.
Cancer Epidemiology está incluida en los Journal Citation Reports con un factor de impacto en 2018 de 2,619. Ocupa la posición 57/185 (Q2) en la categoría Public, Environmental and Occupational Health.

Objetivo: Determinar la prevalencia en 2014 de la población adulta (≥15 años) que presenta alto riesgo de desarrollar cáncer de pulmón en la UE de acuerdo a los criterios NLST y NELSON.

Resultados: Uno de cada diez fumadores (11,6% de hombres y 9,6% de mujeres) de acuerdo a los criterios NLST y uno de cada cuatro fumadores (24,6% de hombres y 22,4% de mujeres) de acuerdo a los criterios NELSON están actualmente a alto riesgo de cáncer de pulmón en la UE. De acuerdo a ambos criterios, la prevalencia de exfumadores a alto riesgo de cáncer de pulmón es del 10%.

2. Estimación del riesgo de cáncer de pulmón en mujeres que participan en un programa de cribado poblacional de cáncer de mama. González-Marrón A, Martín-Sánchez JC, Garcia-Alemany F, Martínez-Martín E, Matilla-Santander N, Cartanyà-Hueso A, Vidal C, García M, Martínez-Sánchez JM. Arch Bronconeumol. En prensa.

Archivos de Bronconeumología está incluida en el Journal Citation Reports con un factor de impacto en 2018 de 4,214. Ocupa la posición 15/63 (Q1) en la categoría Respiratory System.

Objetivo: Estimar la proporción de mujeres que presenta alto riesgo de desarrollar cáncer de pulmón en un grupo de participantes en un cribado poblacional de cáncer de mama.

Resultados: Alrededor de un 20% y un 40% de fumadoras según los criterios NLST y NELSON, respectivamente, y alrededor de un 20% de exfumadoras según ambos criterios, presenta un alto riesgo de desarrollar cáncer de pulmón. Se observa una tendencia positiva y estadísticamente significativa entre la proporción de mujeres que presenta alto riesgo y la dependencia a la nicotina medida por el test de Fagerström breve.

3. Use of biomarkers of tobacco exposure in the assessment of lung cancer risk among daily smokers. González-Marrón A, Martín-Sánchez JC, Pérez-Ortuño R, Fu M, Ballbè M, Cartanyà- Hueso A, Matilla-Santander N, Pascual JA, Fernández E, Mucci L, Martínez-Sánchez JM. Manuscrito en revisión en una revista incluida en los Journal Citation Reports.

Objetivos: Comparar las concentraciones de TSNA y cotinina en muestras de saliva entre fumadores diarios que presentan alto riesgo de cáncer de pulmón y que no presentan alto riesgo de cáncer de pulmón.

Resultados: En fumadores diarios, las concentraciones ajustadas por sexo de TSNA específicas de cáncer de pulmón (NNAL y NNK) fueron significativamente mayores en aquellos con un alto riesgo de cáncer de pulmón, según los criterios

NLST y NELSON. En fumadores diarios en la edad de cribado de cáncer de pulmón, se observaron patrones similares. No encontramos diferencias estadísticamente significativas en las concentraciones de biomarcadores entre hombres y mujeres a alto riesgo de cáncer de pulmón.

4. Relation between tobacco control policies and population at high risk of lung cancer in the European Union. González-Marrón A, Martín-Sánchez JC, Miró Q, Matilla-Santander N, Cartanyà-Hueso A, Mucci L, Martínez-Sánchez JM. Environ Res. 2019 Jul 19;179(Pt A):108594. doi: 10.1016/j.envres.2019.108594
Environmental Research está incluida en el Journal Citation Reports con un factor de impacto en 2018 de 5,026. Ocupa la posición 14/185 (Q1) en la categoría Public, Environmental and Occupational Health.

Objetivos: Evaluar la relación entre el nivel de implementación de políticas de control del tabaco y la población a alto riesgo de cáncer de pulmón en la Unión Europea (UE).

Resultados: Las puntuaciones en la TCS 2010 estaban significativa y negativamente correlacionadas a nivel ecológico con la proporción actual de alguna vez fumadores y exfumadores a alto riesgo de acuerdo a los criterios NELSON (-0,41; IC95% -0,68, -0,04 y -0,49; IC95% -0,73, -0,13, respectivamente). A nivel individual, observamos asociaciones inversas estadísticamente significativas entre el cuartil del país de origen en la puntuación de la TCS 2010 para los cuartiles más altos y la probabilidad de alto riesgo de cáncer de pulmón según ambos criterios. Se observaron correlaciones y asociaciones negativas no estadísticamente significativas con otras TCS.

5. Tobacco control - protecting future generations' lungs. González-Marrón A, Martín-Sánchez JC, Martínez-Sánchez JM. Expert Rev Respir Med. 2019 Jul;13(7):593-595. doi: 10.1080/17476348.2019.1608184.
Expert Review of Respiratory Medicine está incluida en el Journal Citation Reports con un factor de impacto en 2018 de 2,622. Ocupa la posición 33/63 (Q3) en la categoría Respiratory System.

Resumen: Las consecuencias del consumo de tabaco suponen una elevada carga de morbilidad y mortalidad en todo el mundo. Aunque todo individuo expuesto al tabaco está a riesgo de desarrollar diferentes enfermedades, los niños y adolescentes se encuentran entre los grupos más vulnerables y las decisiones legislativas pueden tener un importante impacto en su salud, no solo presente, sino también futura. En esta editorial discutimos cuatro puntos principales (nuevos productos del tabaco y la estrategia de "Reducción de daños en tabaco", la regulación de fumar en lugares privados y espacios públicos, la publicidad y advertencias de los efectos nocivos del tabaco en nuevos medios de comunicación e impuestos al tabaco) que, en nuestra opinión, deberían ser tratados en una estrategia amplia de control del tabaco para proteger los pulmones de futuras generaciones.

Cabe destacar que, durante la realización de la tesis y como parte de su formación predoctoral, el doctorando ha participado activamente, entre otros, en otros tres trabajos científicos que se adjuntan como anexos (Anexos del VI al IX).

4. ARTÍCULOS DE LA TESIS DOCTORAL

4.1. ARTÍCULO PUBLICADO EN CANCER EPIDEMIOLOGY: ESTIMATION OF THE ADULT POPULATION AT HIGH RISK OF DEVELOPING LUNG CANCER IN THE EUROPEAN UNION

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Estimation of the adult population at high risk of developing lung cancer in the European Union

Adrián González-Marrón[a], Juan Carlos Martín-Sánchez[a], Nuria Matilla-Santander[a], Àurea Cartanyà-Hueso[a], Cristina Lidón-Moyano[a], Carmen Vidal[b,c], Montse García[b,c], Jose M. Martínez-Sánchez[a,b,c,*]

[a] Group of Evaluation of Health Determinants and Health Policies, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Spain
[b] Screening Cancer Unit, Cancer Prevention and Control Program, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain
[c] Cancer Prevention and Control Group, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

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ABSTRACT

Background Lung cancer mortality accounts for over 266,000 deaths in the European Union (EU) every year, most of them attributed to smoking. The aim of this study was to estimate the prevalence of the adult population at high risk of developing lung cancer in the EU in 2014.

Methods This is a cross-sectional study. We used data from the Special Eurobarometer 429 (n = 27,801). The fieldwork was conducted between November-December 2014. High risk of lung cancer was defined using the criteria of the National Lung Screening Trial (NLST) and the Dutch-Belgian Lung Cancer Screening Trial (NELSON).

Results One out of ten smokers (11.6% of men and 9.6% of women) according to NLST criteria and one out of four smokers (24.6% of men and 22.4% of women) according to NELSON criteria are currently at high risk of lung cancer in the EU. According to both criteria, the prevalence of former smokers at high risk of lung cancer is under 10%.

Conclusion Around 17 million citizens in the EU according to NLST criteria and 34 million according to NELSON criteria (around 4% and 8% of the adult population, respectively) are at high risk of developing lung cancer. Since the implementation of lung cancer screening programs still remains controversial, primary prevention activities should be encouraged.

1. Introduction

The impact of smoking on health is well known. Smoking is the major preventable risk factor of burden of disease, disability, and death [1], responsible for 7.1 million deaths worldwide per year [2]. Around 700,000 of these deaths, mainly related to a range of cancers and respiratory disorders, occur in the European Union (EU) [3].

Among the different types of cancer associated with smoking (e.g., lung, stomach, liver, urinary bladder), lung cancer, which is one of the deadliest [4], is caused eight out of ten times by smoking [5], a proportion very distant from that related to exposure to radon [6]. In absolute figures, over 266,000 people die from lung cancer in the EU each year [7], many of them prematurely. Besides, in women, the lung cancer mortality rate has been predicted to exceed the breast cancer mortality rate in Europe in 2017 [8], and for specific cohorts in some countries this situation is likely to occur in the near future [9].

The high mortality showed by lung cancer is usually the consequence of a late diagnosis, frequently at stages III-IV, when prognosis is poorer. Overall, the estimated 5-year survival rate from diagnosis is very low (around 17%) [10] and this proportion has practically remained invariable for years. For this reason, in recent years, the implementation of lung cancer screening programs has been assessed in terms of cost-effectiveness [11] and net benefit in all-cause and lung cancer-specific mortality reduction [12]. Among lung cancer screening tests, X-ray with or without sputum cytology have not been recommended since they have been proved not to decrease lung cancer mortality. However, an annual low-dose computed tomography (CT) has been recommended for high risk groups by a number of organizations since low-dose CT can reduce lung cancer mortality and all-cause mortality [13].

* Corresponding author at: Group of Evaluation of Health Determinants and Health Policies, Department of Basic Sciences, Universitat Internacional de Catalunya, Carrer de Josep Trueta s/n, 08195, Sant Cugat del Vallès, Barcelona Spain.
E-mail address: jmmartinez@uic.es (J.M. Martínez-Sánchez).

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Table 1
Smoking pattern and prevalence of population at high risk of lung cancer according to NLST and NELSON criteria in the European Union in 2014 by sex and age, including the age groups undergoing cervical, breast and colorectal cancer screening programs.

			Age				Screening program age-group	
		Overall	15–19	20–39	40–64	> = 65	25–64[a]	50–69[b]
Men	Current smokers	8307 (31.6%)	368 (21.9%)	3450 (38.9%)	3777 (34.6%)	712 (14.6%)	6450 (36.7%)	2391 (29.4%)
	Starting age	17.1 (4.3)	15.0 (1.9)	16.6 (3.1)	17.5 (4.7)	18.1 (6.4)	17.2 (4.2)	17.6 (5.2)
	Cigarrettes / day	15.4 (9.4)	10.6 (6.6)	14.4 (10.2)	16.9 (8.6)	14.8 (8.6)	16.1 (9.7)	17.1 (9.1)
	Lifetime smoking (Pack-years)	20.3 (17.9)	1.7 (2.5)	9.9 (8.2)	28.7 (17.0)	38.5 (23.2)	21.5 (16.4)	34.5 (19.5)
	NLST HRLC							
	Now	963 (11.6%)			658 (17.4%)	305 (42.8%)	658 (10.2%)	836 (35.0%)
	Increase in 5 years	639 (7.7%)			602 (15.9%)	38 (5.3%)	602 (9.3%)	639 (26.7%)
	Increase in 10 years	757 (9.1%)			757 (20.0%)		757 (11.7%)	209 (8.7%)
	NELSON HRLC							
	Now	2045 (24.6%)			1609 (42.6%)	436 (61.2%)	1609 (24.9%)	1870 (78.2%)
	Increase in 5 years	733 (8.8%)			733 (19.4%)		733 (11.4%)	21 (0.9%)
	Increase in 10 years	719 (8.7%)			719 (19.0%)		719 (11.2%)	8 (0.3%)
	Former smokers	6402 (24.3%)	73 (4.4%)	1237 (14.0%)	2945 (27.0%)	2147 (44.2%)	3989 (22.7%)	2787 (34.3%)
	Starting age	17.4 (4.8)	16.1 (8.3)	16.5 (2.9)	17.4 (4.5)	17.9 (5.7)	17.2 (4.2)	17.5 (5.1)
	Cigarrettes / day	17.7 (13.4)	5.6 (6.0)	12.6 (8.3)	18.8 (12.9)	19.6 (15.5)	17.2 (12.1)	20.5 (14.6)
	Lifetime smoking (Pack-years)	17.6 (22.7)	0.5 (0.8)	5.1 (5.9)	17.2 (17.7)	26.9 (29.9)	14.1 (16.3)	22.1 (24.8)
	Quitting years	19.1 (14.9)	0.9 (1.1)	7.2 (5.3)	18.1 (11.5)	27.3 (16.9)	15.4 (11.2)	21.3 (12.9)
	NLST HRLC							
	Now	409 (6.4%)			208 (7.1%)	183 (8.5%)	208 (5.2%)	328 (11.8%)
	Increase in 5 years	281 (4.4%)			191 (6.5%)	102 (4.8%)	191 (4.8%)	293 (10.5%)
	Increase in 10 years	42 (0.7%)			29 (1.0%)		29 (0.7%)	
	NELSON HRLC							
	Now	549 (8.6%)			331 (11.2%)	188 (8.7%)	331 (8.3%)	457 (16.4%)
	Increase in 5 years	54 (0.8%)			34 (1.2%)		34 (0.9%)	
Women	Current smokers	6427 (22.9%)	274 (18.3%)	2537 (29.0%)	3056 (27.3%)	560 (8.4%)	4966 (28.0%)	1834 (20.9%)
	Starting age	18.0 (5.1)	14.8 (2.1)	16.9 (3.6)	18.4 (5.1)	21.9 (8.3)	17.9 (4.7)	19.4 (6.1)
	Cigarrettes / day	12.7 (7.4)	8.4 (5.4)	11.7 (6.9)	13.9 (7.7)	12.5 (6.8)	13.2 (7.5)	14.2 (7.8)
	Lifetime smoking (Pack-years)	16.6 (14.9)	1.5 (1.9)	7.9 (6.8)	22.5 (14.5)	30.8 (18.2)	17.4 (13.7)	27.6 (16.4)
	NLST HRLC							
	Now	617 (9.6%)			431 (14.1%)	185 (33.1%)	431 (8.7%)	553 (30.2%)
	Increase in 5 years	350 (5.4%)			316 (10.3%)	34 (6.1%)	316 (6.4%)	350 (19.1%)
	Increase in 10 years	546 (8.5%)			546 (17.9%)		546 (11.0%)	191 (10.4%)
	NELSON HRLC							
	Now	1442 (22.4%)			1110 (36.3%)	331 (59.2%)	1110 (22.4%)	1319 (71.9%)
	Increase in 5 years	587 (9.1%)			586 (19.2%)	1 (0.2%)	586 (11.8%)	37 (2.0%)
	Increase in 10 years	543 (8.5%)			543 (17.8%)		543 (10.9%)	14 (0.8%)
	Former smokers	4686 (16.7%)	77 (5.1%)	1377 (15.8%)	2101 (18.7%)	1131 (17.0%)	3262 (18.4%)	1761 (20.1%)
	Starting age	18.2 (5.1)	15.3 (1.5)	16.7 (2.9)	18.2 (4.8)	20.3 (6.8)	17.7 (4.3)	18.7 (5.3)
	Cigarrettes / day	11.9 (8.5)	5.8 (5.6)	10.4 (6.9)	13.0 (9.0)	12.1 (9.2)	12.2 (8.3)	13.3 (9.3)
	Lifetime smoking (Pack-years)	9.9 (12.1)	0.5 (0.8)	3.9 (4.5)	11.3 (12.3)	15.8 (16.1)	8.8 (10.8)	14.1 (14.5)
	Quitting years	16.2 (13.2)	1.0 (0.9)	7.6 (5.6)	17.3 (10.9)	26.5 (16.1)	13.8 (10.2)	19.9 (12.6)
	NLST HRLC							
	Now	168 (3.6%)			81 (3.9%)	80 (7.1%)	81 (2.5%)	145 (8.3%)
	Increase in 5 years	61 (1.3%)			53 (2.5%)	15 (1.3%)	53 (1.6%)	68 (3.9%)
	Increase in 10 years	16 (0.3%)			19 (0.9%)		19 (0.6%)	
	NELSON HRLC							
	Now	294 (6.3%)			171 (8.2%)	124 (10.9%)	171 (5.3%)	253 (14.4%)
	Increase in 5 years	17 (0.4%)			27 (1.3%)		27 (0.8%)	

HRLC: high risk of lung cancer.
[a] Cervical (for women) screening program age group.
[b] Breast (for women) and colorectal screening program age group.

This positive assessment on the implementation of low-dose CT screening mainly arises from the National Lung Screening Trial (NLST), a US multicentric randomized trial where a decrease of 20% in the mortality attributable to lung cancer, as well as an all-cause mortality reduction of 6.7%, were observed in the group undergoing low-dose CT compared with the group undergoing chest X-ray [14]. In Europe, different randomized trials have been carried out to assess the effectiveness of the low-dose CT, such as the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) [15], which compared low-dose CT versus no intervention in a protocol of one, two, four and six and a half years and of which interim results showed high specificity and sensitivity [16], although definitive results are still awaited. Nevertheless, thus far, low-dose CT has neither been implemented as a high risk (i.e., selective) screening program in the EU nor recommended by the Council of the EU, contrary to breast, cervical and colorectal cancer, for which official recommendations were already published in 2003 [17]. Besides, there is ongoing debate in the scientific community around the potential benefits and harms related to low-dose CT screening programs [18,19].

To assess the potential impact of the implementation of low-dose CT lung cancer screening programs in the EU in terms of beneficiary population, a preliminary estimation of the population at high risk of developing lung cancer should be provided. The aim of this study was to determine the prevalence in 2014 of the adult population (≥15years) at high risk of developing lung cancer in the EU according to NLST and NELSON criteria.

2. Methods

This is a cross-sectional study. We used the data from the Special Eurobarometer 429 "Attitudes of Europeans towards tobacco and electronic cigarettes", a special survey conducted by the European Commission on a representative sample (n = 27,801) of the adult population (≥15years) in the EU. The fieldwork was conducted between November-December 2014 and the results were published in May 2015. Sampling was carried out in a multi-stage, random basis and interviews were conducted face to face in the native tongues of the participants. We weighted data to obtain more representative results for each country, using the weights provided by Eurobarometer. Further information on the methodology of the Special Eurobarometer 429 could be found elsewhere [20].

We calculated the prevalence of current and former smokers, means and standard deviations (SD) for the smoking pattern (i.e., starting age of smoking, years after quitting smoking for former smokers and cigarettes smoked per day) and the lifetime smoking history measured in pack-years (mean and SD), defined as the number of packs smoked daily by the number of years smoking, overall and stratified by sex and for each age group (15–19, 20–39, 40–64 and over 65 years). We also calculated the prevalence of current and former smokers, means and SD in the target age groups of breast, colorectal and cervical cancer screening programs, the only screening programs recommended to date by the Council of the EU [17]. For breast cancer, the nearly unanimous agreement on the target group among member states was followed (i.e., from 50 to 69) [21]. For cervical and colorectal cancer, since there is heterogeneity between target groups among countries in the EU [21], we chose the age range from 25 to 64 years and from 50 to 69 years, respectively.

We also calculated the current prevalence of citizens at high risk of developing lung cancer overall and for each sex, age group and smoking status. Individuals were considered to be at high risk when NLST and/or NELSON criteria were met. These criteria were defined as i) current and former smokers from 55 to 74 years of age with a lifetime smoking of at least 30 pack-years, having quit the former smokers within the last 15 years, according to NLST criteria [14], and ii) current and former smokers from 50 to 75 years of age with a lifetime smoking of at least 25 years smoking more than 15 cigarettes per day, or of at least 30 years smoking more than 10 cigarettes per day, having quit the former smokers within the last 10 years according to NELSON criteria [15]. Besides, we estimated the proportion of citizens within each category that may reach the high-risk situation during the next five and ten years if the present smoking pattern was invariable throughout those periods.

For current smokers, we calculated the pack-years from the mean starting age until the day of the survey. For former smokers, we had to estimate the pack-years due to the Eurobarometer not providing specific information on quitting dates. We assumed that cohorts of former smokers who started smoking in the same year had quit following a uniform distribution.

We also stratified the results at the national level for all the 28 EU member states. Finally, we calculated the Spearman correlation coefficients between the proportion of men and women currently smoking and the proportion of individuals in the whole population and ever-smoker population within each member state at high risk of lung cancer according to NLST and NELSON criteria.

3. Results

Table 1 and Fig. 1 show that, according to NLST and NELSON criteria, around one out of ten (11.6% of men and 9.6% of women) and nearly one out of four (24.6% of men and 22.4% of women) current smokers in the EU are at present at high risk of developing lung cancer, respectively. Regarding ever-smokers (i.e., current smokers plus former smokers), around 8% (9.2% of men and 7.0% of women) according to NLST criteria and around 16% (17.5% of men and 15.6% of women) according to NELSON criteria are currently at high risk. Among men who formerly smoked, 6.4% are at high risk of lung cancer according to NLST criteria and 8.6% according to NELSON criteria. In women, these percentages are 3.6% and 6.3%, respectively. The highest prevalences of individuals at high risk are found for the group of over 65 years, which also corresponds to the age group with a highest mean cumulative value of pack-years smoked in life. In this group, around 60% of individuals who currently smoke are currently at high risk of developing lung cancer according to NELSON criteria (Table 1).

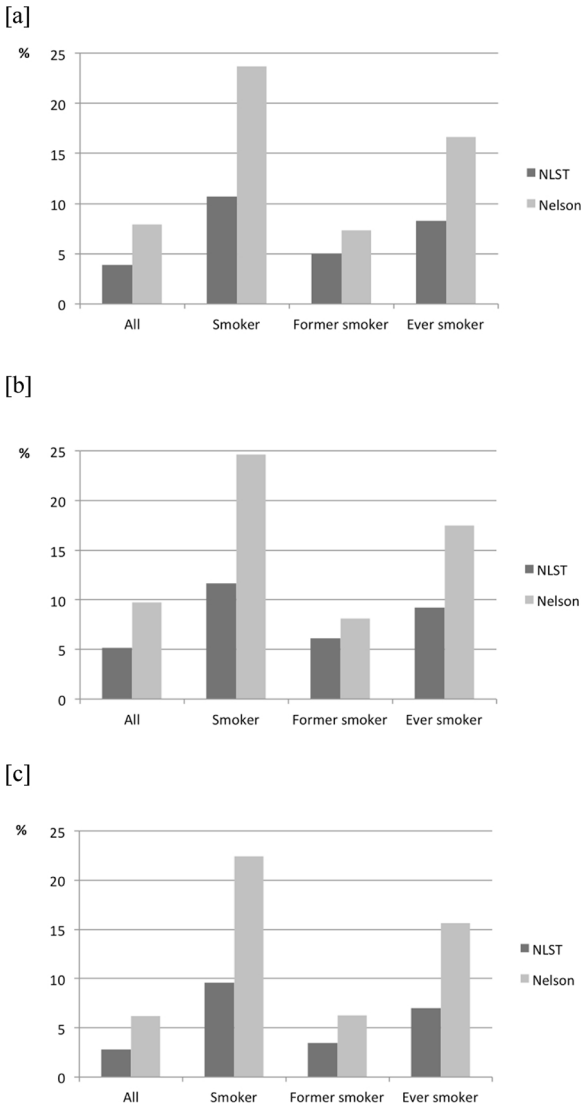

Fig. 1. Overall proportion [a] and sex-specific proportions (men [b], women [c]) of individuals at high risk according to NLST and NELSON criteria categorized by smoking status in the European Union in 2014.

If the smoking pattern does not change in current smokers, an additional variable increase in the prevalence of individuals at high risk could be expected in the following five and ten years (around 17% in men and around 15% in women). Lower increases should be expected in the prevalence of former smokers at high risk in five and ten years time (Table 1), attributable to the compliance of the age criteria during that period.

For the age group in which screening programs for cervical cancer are performed in the EU (25–64 years), and according to NELSON criteria, an estimated 22.4% of women who smoke are at high risk of developing lung cancer. For the age group in which breast and colorectal cancer screening programs are performed (estimated as 50–69 years), over 70% of men and women who currently smoke are at high

Table 2
Prevalence of current and former smokers and population at high risk of lung cancer according to NLST (up) and NELSON (down) criteria by sex and country in the European Union in 2014.

	Men					Women				
	Current smokers	Former smokers	High risk of lung cancer (NLST & NELSON)			Current smokers	Former smokers	High risk of lung cancer (NLST & NELSON)		
			Current smokers	Former smokers	Total[a]			Current smokers	Former smokers	Total[a]
France	1020(32.9%)	930 (30.0%)	88 (8.6%)	57 (6.1%)	145 (4.7%)	934 (27.5%)	563 (16.6%)	75 (8.0%)	19 (3.4%)	94 (2.8%)
			200 (19.6%)	61 (6.6%)	261 (8.4%)			168 (18.0%)	25 (4.4%)	193 (5.7%)
Belgium	168 (29.1%)	145 (25.1%)	16 (9.5%)	6 (4.1%)	22 (3.8%)	144 (23.6%)	88 (14.4%)	16 (11.1%)	6 (6.8%)	22 (3.6%)
			37 (22.1%)	11 (7.6%)	48 (8.3%)			34 (23.7%)	6 (6.8%)	40 (6.6%)
Netherlands	237 (27.0%)	262 (29.8%)	20 (8.4%)	15 (5.7%)	35 (4.0%)	174 (19.2%)	294 (32.5%)	25 (14.4%)	14 (4.8%)	39 (4.3%)
			52 (21.9%)	18 (6.9%)	70 (8.0%)			49 (28.2%)	23 (7.8%)	72 (8.0%)
Germany	1407(32.7%)	1183(27.5%)	184(13.1%)	66 (5.6%)	250 (5.8%)	965 (21.3%)	914 (20.1%)	89 (9.2%)	39 (4.3%)	128 (2.8%)
			423(30.1%)	98 (8.3%)	521(12.1%)			254 (26.3%)	65 (7.1%)	319 (7.0%)
Italy	864 (26.8%)	614 (19.0%)	130 (15.0%)	39 (6.4%)	169 (5.2%)	657 (18.7%)	381 (10.9%)	77 (11.7%)	9 (2.4%)	86 (2.5%)
			266 (30.8%)	60 (9.8%)	326(10.1%)			169 (25.7%)	26 (6.8%)	195 (5.6%)
Luxembourg	7 (27.0%)	7 (25.3%)	1 (13.5%)	1 (14.4%)	2 (7.3%)	6 (21.2%)	5 (18.0%)	1 (16.9%)	0 (0.0%)	1 (3.6%)
			1 (13.5%)	0 (0.0%)	1 (3.7%)			1 (16.9%)	0 (0.0%)	1 (3.6%)
Denmark	74 (25.2%)	91 (30.6%)	13 (17.5%)	3 (3.3%)	16 (5.4%)	72 (23.5%)	92 (30.2%)	9 (12.5%)	3 (3.3%)	12 (4.0%)
			19 (25.5%)	6 (6.6%)	25 (8.5%)			20 (27.9%)	6 (6.5%)	26 (8.5%)
Ireland	56 (25.0%)	46 (20.1%)	6 (10.6%)	3 (6.6%)	9 (4.0%)	61 (25.7%)	43 (18.2%)	5 (8.3%)	1 (2.3%)	6 (2.5%)
			11 (19.5%)	3 (6.6%)	14 (6.2%)			12 (19.8%)	2 (4.7%)	14 (5.9%)
Great Britain	840 (25.3%)	786 (23.7%)	84 (10.0%)	57 (7.3%)	141 (4.3%)	801 (23.0%)	755 (21.7%)	93 (11.6%)	22 (2.9%)	115 (3.3%)
			150 (17.9%)	74 (9.4%)	224 (6.8%)			178 (22.2%)	46 (6.1%)	224 (6.4%)
Greece	249 (44.7%)	127 (22.8%)	41 (16.5%)	11 (8.7%)	52 (9.3%)	197 (33.5%)	67 (11.5%)	22 (11.2%)	1 (1.5%)	23 (3.9%)
			68 (27.3%)	10 (7.9%)	78 (14.0%)			47 (23.9%)	2 (3.0%)	49 (8.4%)
Spain	933 (37.1%)	647 (25.7%)	85 (9.1%)	32 (5.0%)	117 (4.7%)	665 (25.2%)	403 (15.3%)	43 (6.5%)	21 (5.2%)	64 (2.4%)
			210 (22.5%)	45 (7.0%)	255(10.1%)			103 (15.5%)	34 (8.4%)	137 (5.2%)
Portugal	169 (33.0%)	110 (21.3%)	17 (10.0%)	8 (7.3%)	25 (4.9%)	92 (16.2%)	36 (6.4%)	5 (5.4%)	0 (0.0%)	5 (1.0%)
			41 (24.2%)	11 (10.0%)	52 (10.1%)			12 (13.0%)	1 (2.8%)	13 (2.3%)
Finland	69 (24.2%)	87 (30.4%)	7 (10.2%)	4 (4.6%)	11 (3.9%)	59 (19.5%)	49 (16.3%)	6 (10.3%)	1 (2.0%)	7 (2.3%)
			19 (27.6%)	7 (8.1%)	26 (9.1%)			15 (25.6%)	2 (4.1%)	17 (5.7%)
Sweden	59 (11.5%)	161 (31.3%)	6 (10.2%)	5 (3.1%)	11 (2.1%)	65 (12.7%)	172 (33.6%)	7 (10.8%)	5 (2.9%)	12 (2.4%)
			16 (27.1%)	9 (5.6%)	25 (4.9%)			20 (30.7%)	12 (7.0%)	32 (6.3%)
Austria	153 (34.0%)	97 (21.6%)	23 (15.1%)	8 (8.3%)	31 (6.9%)	119 (24.7%)	74 (15.4%)	14 (11.8%)	3 (4.1%)	17 (3.5%)
			37 (24.2%)	9 (9.3%)	46 (10.2%)			29 (24.4%)	5 (6.8%)	34 (7.1%)
Cyprus Rep.	19 (43.0%)	10 (22.0%)	3 (15.9%)	1 (10.3%)	4 (9.1%)	9 (18.9%)	3 (6.6%)	1 (11.5%)	0 (0.0%)	1 (2.2%)
			6 (31.7%)	1 (10.3%)	7 (15.9%)			2 (23.0%)	0 (0.0%)	2 (4.3%)
Czech Rep.	188 (32.9%)	115 (20.1%)	29 (15.4%)	9 (7.8%)	38 (6.6%)	127 (21.1%)	90 (14.9%)	13 (10.2%)	0 (0.0%)	13 (2.2%)
			47 (25.0%)	13 (11.3%)	60 (10.5%)			28 (22.0%)	2 (2.2%)	30 (5.0%)
Estonia	19 (32.1%)	16 (26.4%)	2 (10.3%)	1 (6.3%)	3 (4.9%)	13 (17.6%)	12 (16.5%)	1 (7.7%)	0 (0.0%)	1 (1.4%)
			5 (25.7%)	1 (6.3%)	6 (10.0%)			2 (15.4%)	0 (0.0%)	2 (2.7%)
Hungary	194 (37.9%)	86 (16.7%)	29 (15.0%)	6 (7.0%)	35 (6.8%)	149 (25.5%)	59 (10.1%)	17 (11.4%)	3 (5.1%)	20 (3.4%)
			48 (24.7%)	8 (9.3%)	56 (10.9%)			45 (30.3%)	4 (6.8%)	49 (8.4%)
Latvia	46 (48.8%)	23 (24.5%)	4 (8.7%)	1 (4.3%)	5 (5.3%)	22 (19.7%)	17 (14.7%)	1 (4.5%)	0 (0.0%)	1 (0.9%)
			10 (21.7%)	2 (8.6%)	12 (12.7%)			3 (13.5%)	0 (0.0%)	3 (2.7%)
Lithuania	66 (41.4%)	38 (23.8%)	6 (9.2%)	1 (2.7%)	7 (4.4%)	34 (17.7%)	20 (10.4%)	1 (3.0%)	0 (0.0%)	1 (0.5%)
			15 (22.9%)	2 (5.3%)	17 (10.7%)			4 (11.9%)	0 (0.0%)	4 (2.1%)
Malta	6 (28.2%)	6 (24.6%)	1 (15.8%)	1 (18.1%)	2 (8.9%)	4 (19.2%)	3 (12.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
			2 (31.6%)	1 (18.1%)	3 (13.3%)			1 (22.6%)	0 (0.0%)	1 (4.3%)
Poland	721 (35.5%)	419 (20.6%)	97 (13.5%)	32 (7.6%)	129 (6.4%)	563 (25.5%)	336 (15.2%)	70 (12.4%)	9 (2.7%)	79 (3.6%)
			211 (29.3%)	40 (9.5%)	251(12.4%)			169 (30.0%)	24 (7.1%)	193 (8.7%)
Slovakia	84 (29.2%)	71 (24.6%)	11 (13.1%)	3 (4.3%)	14 (4.9%)	47 (15.1%)	41 (13.4%)	2 (4.3%)	1 (2.4%)	3 (1.0%)
			21 (25.1%)	3 (4.3%)	25 (8.4%)			6 (12.9%)	1 (2.4%)	7 (2.3%)
Slovenia	39 (34.3%)	26 (22.8%)	4 (10.3%)	3 (11.6%)	7 (6.2%)	28 (23.9%)	17 (14.4%)	2 (7.2%)	1 (5.9%)	3 (2.6%)
			9 (23.2%)	3 (11.6%)	12 (10.6%)			7 (25.0%)	1 (5.9%)	8 (6.8%)
Bulgaria	176 (43.6%)	83 (20.5%)	24 (13.7%)	6 (7.3%)	30 (7.5%)	123 (28.1%)	50 (11.5%)	5 (4.1%)	2 (4.0%)	7 (1.6%)
			49 (27.9%)	11 (13.3%)	60 (15.0%)			22 (18.0%)	4 (8.0%)	26 (5.7%)
Romania	401 (36.3%)	203 (18.4%)	28 (7.0%)	10 (4.9%)	38 (3.4%)	262 (22.2%)	82 (6.9%)	11 (4.2%)	1 (1.2%)	12 (1.0%)
			63 (15.7%)	13 (6.4%)	76 (6.9%)			31 (11.8%)	2 (2.5%)	33 (2.8%)
Croatia	41 (36.6%)	18 (15.5%)	7 (16.9%)	1 (5.7%)	8 (7.1%)	37 (30.0%)	20 (15.9%)	5 (13.4%)	2 (10.2%)	7 (5.6%)
			10 (24.1%)	1 (5.7%)	11 (9.7%)			11 (29.5%)	1 (5.1%)	12 (9.7%)
TOTAL	8307 (31.6%)	6402 (24.3%)	966 (11.6%)	390 (6.1%)	1356(5.2%)	6427(22.9%)	4686(16.7%)	616 (9.6%)	163 (3.5%)	779 (2.8%)
			2046(24.6%)	521 (8.1%)	2567(9.8%)			1442(22.4%)	294 (6.3%)	1736(6.2%)

[a] Proportions calculated with the total population of each member state.

risk of developing lung cancer as per NELSON criteria. The estimations in ten years for current smokers show that an additional 35.4% of men in the age group undergoing colorectal cancer screening may reach the high risk situation according to NLST criteria. In women, in the age group undergoing breast and colorectal cancer screenings, nearly 30% of the current smokers may reach the condition of high risk in ten years according to NLST criteria, and 22.7% of those in the age group undergoing cervical cancer screenings according to NELSON criteria (Table 1).

Table 2 shows disaggregated data for men and women in every EU

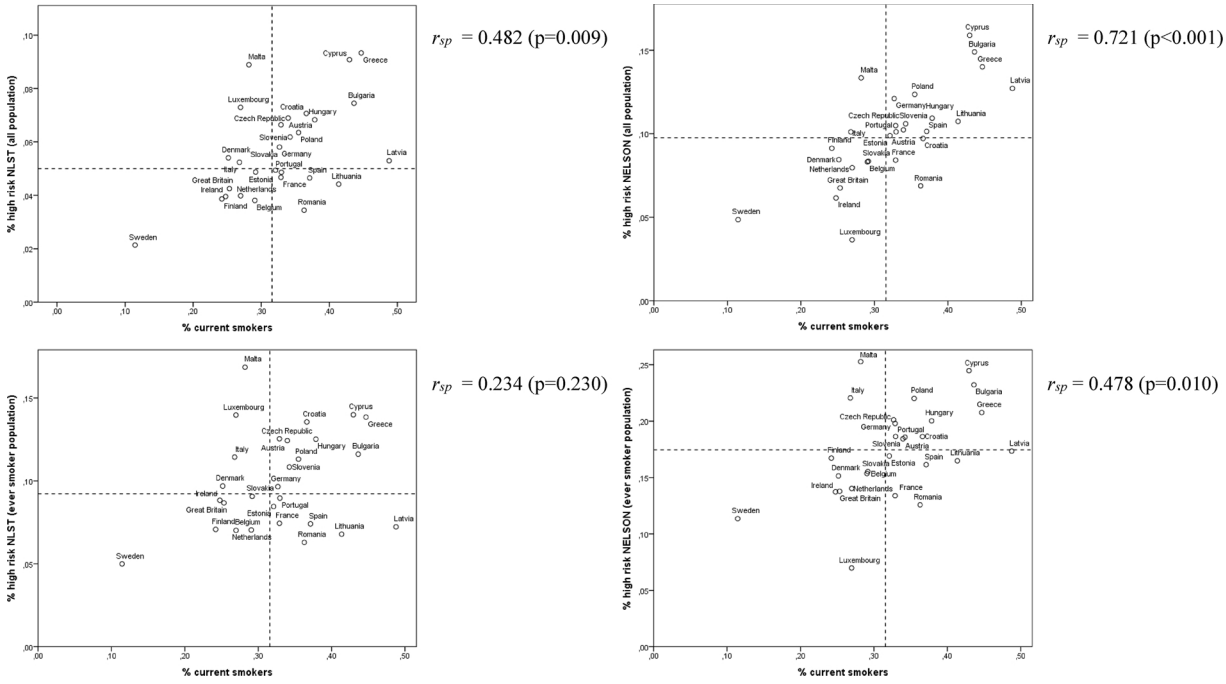

Fig. 2. Scatter plots representing the proportion of men who currently smoke *vs.* the proportion of individuals at high risk according to NLST (left) and NELSON (right) criteria in the whole population (top) and ever-smoker population (bottom) in every EU country in 2014. Dotted lines represent EU median values. r_{sp}: Spearman correlation coefficient.

country on the smoking attitude and current rates of nationals at high risk of developing lung cancer. The highest proportion of women at high risk is found in Croatia (9.7% according to NELSON criteria and 5.6% according to NLST criteria) while in men the highest prevalence corresponds to the Republic of Cyprus (15.9%) according to NELSON criteria and to Greece (9.3%) according to NLST criteria. The only countries in which the proportion of women at high risk is higher than in men are the Netherlands and Sweden.

Moderate to strong, and statistically significant ($p < 0.05$), Spearman correlation coefficients were found between the proportion of current smokers and the proportion of individuals at high risk according to NLST and NELSON criteria at an ecological level, both for men and women alike (Figs. 2 and 3). Only the correlation coefficient between the proportion of men who currently smoke versus the proportion of ever smoker population at high risk according to NLST criteria was found to be non-statistically significant ($r_{sp} = 0.234$; $p = 0.230$).

4. Discussion

As far as we know, this is the first study to provide an estimation of the population at high risk of developing lung cancer in the EU. Our results show that, as per the current EU demographics [22], around 17 million EU citizens according to NLST criteria and around 34 million EU citizens according to NELSON criteria around (4% and 8% of the total adult population, respectively) are at high risk of developing lung cancer. According to all our estimations, the prevalence of individuals at high risk is likely to increase until 2020, as long as the smoking pattern keeps constant.

A similar approach to the one presented in our study was followed for the Spanish adult population elsewhere. The proportion of Spaniards at high risk was estimated to be 4.9% according to NLST criteria (7.9% in men and 2.4% in women) and 6.6% according to NELSON criteria [23]. In the US population [24], around 6.2% of the population over 40 years was found to accomplish NLST eligibility criteria. In our study, the proportions of individuals at high risk in those cohorts are similar only in former smokers (3.9% for the 40–64 age group and 7.1% for the > 65 age group in women and 7.1% for the 40–64 age group in men). For the rest of the age groups, the estimates obtained are much higher in our study. This observation correlates with the lower prevalence of cigarette smoking in the US [25] in comparison to the EU.

Remarkably, our results show that although the prevalences of women and men who smoke are different (22.9% and 31.6%, respectively), the proportions of smokers at high risk are similar, around 11% according to NLST criteria and 24% according to NELSON criteria for both sexes. This could be a consequence of a similar smoking pattern in terms of number of cigarettes smoked per day among men and women who smoke, which could indicate that smoking dependence, represented by lifetime smoking measured in pack-years, is sex-independent. This reductionist analysis must not conceal the particularities observed among member states, which would eventually determine the specific characteristics of each national lung cancer screening program.

National data show notable differences in the prevalence of individuals at high risk among the 28 EU members. We consider that although further research should be done for middle-income countries in terms of sex-specific differences as reported elsewhere [26], the stage at which each country is currently on the tobacco epidemic [27] influences on the prevalence of men and women at high risk. This means that, in general, in countries where women started smoking earlier in the 20th century (e.g., Western Europe), we found that the prevalence of women at high risk is higher and even surpasses or is similar to the proportion of men at high risk (e.g., the Netherlands, Sweden, Denmark). The opposite situation is also observed. In Eastern European countries, where women started smoking later, large differences between the proportion of men at high risk and the proportion of women at high risk are generally found (e.g., Baltic states, Bulgaria).

Specific national-based studies based on modelling should be carried out to assess, in terms of effectiveness and cost-effectiveness, the implementation of lung cancer screening programs due to the aforementioned variability in the prevalence of individuals at high risk among member states and to healthcare system access and funding for each country. Since the feasibility of a cancer screening program highly

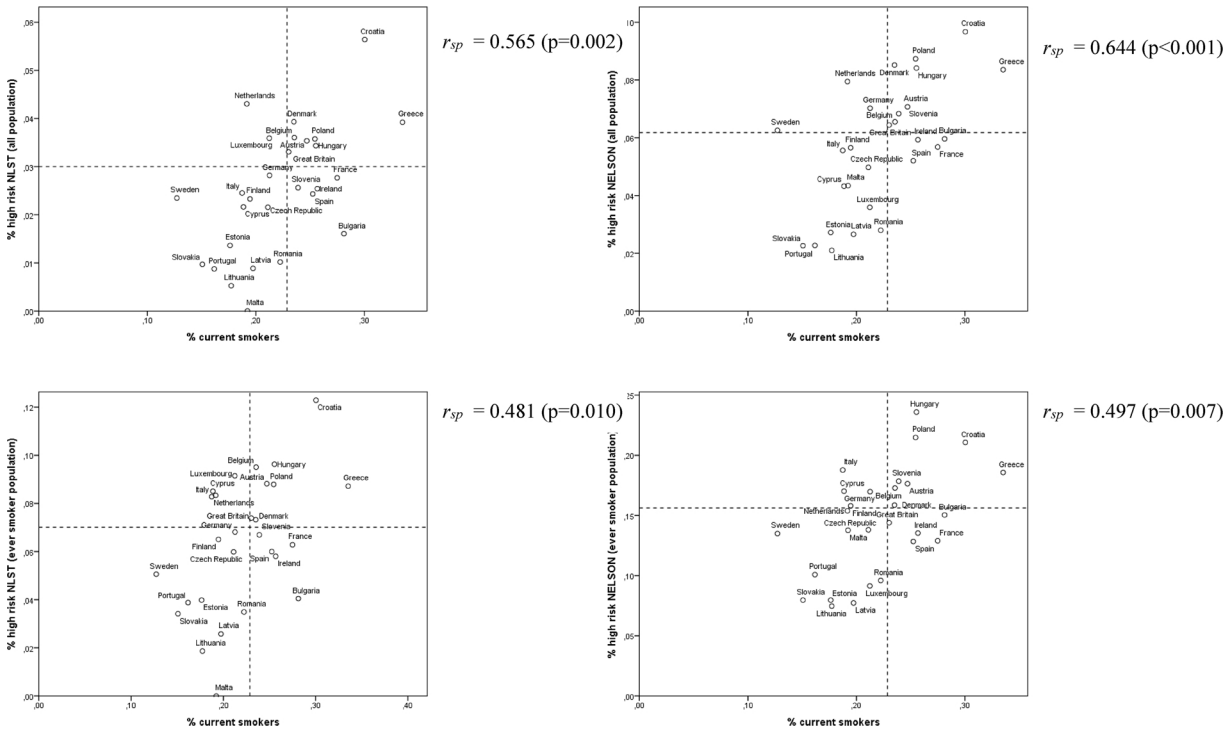

Fig. 3. Scatter plots representing the proportion of women who currently smoke *vs.* the proportion of individuals at high risk according to NLST (left) and NELSON (right) criteria in the whole population (top) and ever-smoker population (bottom) in every EU country in 2014. Dotted lines represent EU median values. r_{sp}: Spearman correlation coefficient.

relies on the optimal selection of individuals at high risk, the use of risk models, introducing individual factors such as occupational exposures (e.g., asbestos), other exposures (e.g., radon), family history or underlying lung diseases (e.g., emphysema, COPD) [28–30], may better delimit the population at high risk [31]. Nevertheless, risk prediction models including the variables age and smoking history only have yielded high values of specificity and sensitivity [32].

The discussion on which role smoking cessation activities and lung cancer screening should play in reducing lung cancer mortality rates is extended in the scientific community also in terms of cost-effectiveness [18,19]. We consider that the gap between prevalence of tobacco smoking and lung cancer, which is around 30 years [33], could be used to implement smoking cessation activities, which have been estimated to be much more cost-effective than screening since the cost of screening an individual is similar to 25 individuals undergoing smoking cessation activities [18]. However, smoking cessation policies have been seldom implemented in the EU [34], mainly due to budget limitations. For this reason, the member states are encouraged to implement policies to promote smoking cessation and reduce initiation. In this sense, there is a strong support among European citizens towards tobacco products regulations [35].

In Europe, the prevalence of smoking in adults is the highest among all the WHO regions [1], being smoking associated with up to 90% of all the lung cancers diagnosed [36]. With an approximately 25% of the individuals participating in cancer screening programs who are current smokers, these settings could be useful to implement smoking cessation activities as per the “teachable moment” approach [37]. Remarkably, screening programs pose a good opportunity to implement nested primary prevention activities, such as giving advice on abandoning unhealthy habits (e.g., tobacco smoking), due to interventions being highly effective in terms of adherence to the recommendations given [38,39].

The main limitations of our study rely on the use of the Special Eurobarometer 429 as the source of our data. Firstly, the aim of our research exceeds those of the Eurobarometer, and the *ad-hoc* estimation of the years after quitting smoking for former smokers and projections for 5 and 10 years may add some bias to our conclusions. In this sense, the Special Eurobarometer 429 does not provide information on quitting dates for former smokers. Hence, we estimated quitting dates via a uniform distribution, meaning the occurrence of the event giving up smoking was equiprobable for every year since the individual started smoking to their present age. However, as stated above, the proportion of individuals at high risk in Spain was estimated to be 7.9% in men and 2.4% in women according to NLST criteria and 9.7% in men and 3.9% in women according to NELSON criteria [23]. These results were obtained from the Spanish National Health Survey 2011–2012, in which the time of quitting smoking is provided. Since our estimations of men and women at high risk in Spain are 4.7% and 2.4% according to NLST criteria and 10.1% and 5.2%, likewise, according to NELSON criteria we consider that our method is valid, although a slight misestimation may be added. Nevertheless, we presume that part of the discrepancies observed should be imputed to considerable differences between national and EU surveys when assessing smoking patterns [40] and not entirely to our analysis. Besides, since specific data on individual historical tobacco consumption is not provided in the Eurobarometer, the present consumption of cigarettes for each cohort was used to calculate the lifetime smoking history in pack-years. On the other hand, the proportions of current smokers who would potentially reach the high-risk situation in five and ten years time were computed assuming constant the declared current consumption in the sample throughout those periods. Although this situation is unlikely to occur, this approach underscores the necessity of action in terms of smoking cessation, since if no action is taken, those smokers will effectively reach the high-risk status. In this sense, recent reviews assessing quit rates accomplished by different interventions showed that the increase in quit rates between the intervention group and the control group ranged from 24% to 338% [41]. However, the real impact of these interventions should be further analyzed since it would highly depend on the profile of those quitting smoking, including their age, history of tobacco consumption in pack-years, or other individual features which determine the overall risk.

Secondly, updated surveys on the attitudes of Europeans towards tobacco and electronic cigarettes have been published [42]. However, the smoking pattern in the EU was concluded not to have substantially changed from 2014 [42] so only minor differences could be expected. Also of note, since we have followed NLST and NELSON criteria, only the variables age, smoking status and pack-years have been included in the assessment. This approach may not be as accurate in delimiting the proportion of individuals at high risk as risk models are. However, as stated above, the use in risk models of the variables age and smoking history only have yielded high values of specificity and sensitivity [32] since these variables compose most of the risk of lung cancer. Finally, disaggregated data may lack of statistical power for certain countries due to small sample sizes. On the other hand, the main strength of our study is the use of both NLST and NELSON criteria. We have obtained two different sets of estimates which have allowed us to compare two scenarios determined by the restriction of the inclusion criteria, being NLST criteria more restrictive than NELSON criteria since the age range to be considered at high risk is wider in the latter (19 *vs.* 25 years) and the smoking history measured in pack-years lower (30 *vs.* 20 or 17 pack-years).

5. Conclusions

We have found that around 17 million citizens in the EU according to NLST criteria and 34 million according to NELSON criteria are at high risk of lung cancer, and that these figures are going to increase if the current smoking pattern is kept. Lung cancer screening with low-dose CT is still a matter of debate and the balance between upsides and downsides is being discussed. Hence, we consider that primary prevention activities should still be pivotal in lung cancer prevention, even if lung cancer screening programs are eventually implemented.

Authorship contribution

JMMS, AGM and JCMS substantially contributed to the conception and design of the study. JCMS developed the dataset and conducted the analyses. AGM drafted the manuscript with the supervision of JMMS. All the authors interpreted the data and intellectually contributed to the review. All the authors approve the final version.

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Declarations of interest

None

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4.2. ARTÍCULO EN PRENSA EN ARCHIVOS DE BRONCONEUMOLOGÍA: ESTIMACIÓN DEL RIESGO DE CÁNCER DE PULMÓN EN MUJERES QUE PARTICIPAN EN UN PROGRAMA DE CRIBADO POBLACIONAL DE CÁNCER DE MAMA

ESTIMACIÓN DEL RIESGO DE CÁNCER DE PULMÓN EN MUJERES QUE PARTICIPAN EN UN PROGRAMA DE CRIBADO POBLACIONAL DE CÁNCER DE MAMA

ESTIMATION OF THE RISK OF LUNG CANCER IN WOMEN PARTICIPATING IN A POPULATION-BASED BREAST CANCER SCREENING PROGRAM

Adrián González-Marrón[a], Juan Carlos Martín-Sánchez[a], Ferrán Garcia-Alemany[b], Encarna Martínez-Martín[b], Nuria Matilla-Santander[a], Àurea Cartanyà-Hueso, Carmen Vidal[b,], Montse García[b,], Jose M Martínez-Sánchez[a*]

[a] Group of Evaluation of Health Determinants and Health Policies, Universitat Internacional de Catalunya, SantCugat del Vallès, Spain

[b] Screening Cancer Unit, Cancer Prevention and Control Program, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain

***Corresponding author**
Jose M. Martínez Sánchez, BSc, MPH, PhD
Group of Evaluation of Health Determinants and Health Policies
Department of Basic Sciences
Universitat Internacional de Catalunya
Carrer de Josep Trueta s/n
08195 Sant Cugat del Vallès (Barcelona)
TLF: 93 504 20 18
E-mail: jmmartinez@uic.es

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ESTIMACIÓN DEL RIESGO DE CÁNCER DE PULMÓN EN MUJERES QUE PARTICIPAN EN UN PROGRAMA DE CRIBADO POBLACIONAL DE CÁNCER DE MAMA

ESTIMATION OF THE RISK OF LUNG CANCER IN WOMEN PARTICIPATING IN A POPULATION-BASED BREAST CANCER SCREENING PROGRAM

RESUMEN

INTRODUCCIÓN

La mortalidad por cáncer de pulmón está aumentando en mujeres. Se ha proyectado que en España pueda superar a la mortalidad por cáncer de mama, la principal causa de mortalidad por cáncer en mujeres, en pocos años. El objetivo de este estudio es estimar la proporción de mujeres que presentan alto riesgo de desarrollar cáncer de pulmón en un grupo de participantes en un cribado poblacional de cáncer de mama.

MÉTODOS

Estudio transversal de una muestra de mujeres que participaron en un cribado poblacional de cáncer de mama en el año 2016 en Hospitalet de Llobregat (n=1.601). El riesgo elevado de cáncer de pulmón se definió según los criterios del *National Lung Screening Trial* (NLST) y del *Dutch-Belgian randomised lung cancer screening trial* (NELSON).

RESULTADOS

Alrededor de un 20% y un 40% de fumadoras según los criterios NLST y NELSON, respectivamente, y alrededor de un 20% de exfumadoras según ambos criterios, presentan un alto riesgo de desarrollar cáncer de pulmón. Se observa una tendencia positiva y estadísticamente significativa entre la proporción de mujeres que presentan alto riesgo y la dependencia a la nicotina medida por el Test de Fagerström breve.

CONCLUSIÓN

Una alta proporción de participantes en este cribado de cáncer de mama presenta un riesgo elevado de desarrollar cáncer de pulmón y sería elegible para participar en un programa de cribado de cáncer de pulmón. Los cribados poblacionales de cáncer de mama pueden ser útiles para implementar estrategias de prevención primaria de cáncer de pulmón.

Palabras clave: cáncer de pulmón; fumar; prevención secundaria; prevención primaria; tabaco.

ABSTRACT

INTRODUCTION

Lung cancer mortality is increasing in women. It has been projected that in Spain lung cancer mortality may surpass breast cancer mortality, the main cause of cancer mortality among women, in few years. The aim of this study is to estimate the proportion of women at high risk of developing lung cancer in a group of participants in a population-based breast cancer screening program.

METHODS

Cross-sectional study in a sample of women who participated in a population-based breast cancer screening program in 2016 in Hospitalet de Llobregat (n=1,601). High risk of lung cancer was defined according to the criteria of the National Lung Screening Trial (NLST) and the Dutch-Belgian randomized lung cancer screening trial (NELSON).

RESULTS

Around 20% and 40% of smokers according to NLST and NELSON criteria, respectively, and around 20% of former smokers according to both criteria, are at high risk of developing lung cancer. A positive and statistically significant trend is observed between the proportion of women at high risk and nicotine dependence measured with the brief Fagerström Test.

CONCLUSIONS

A high proportion of participants in this breast cancer screening program have a high risk of developing lung cancer and would be eligible to participate in a lung cancer screening program. Population-based breast cancer screening programs may be useful to implement lung cancer primary prevention activities.

Keywords: lung cancer; smoking; secondary prevention; primary prevention; tobacco.

INTRODUCCIÓN

Fumar tabaco es el segundo factor de riesgo de muerte en el mundo, solo por detrás de la exposición a contaminación [1], considerándose un factor de inequidad en salud que afecta a grupos socioeconómicamente más desfavorecidos [2]. Se estima que alrededor de un 50% de la población fumadora muere por este hábito [3]. Además de a una elevada mortalidad, el tabaquismo está asociado a una elevada morbilidad y supone un gran impacto en términos de coste y utilización de servicios sanitarios [4].

Fumar está asociado a diferentes patologías, incluidos varios tipos de cáncer (vejiga o pulmón, por ejemplo) [4]. Uno de los de mayor letalidad es el cáncer de pulmón [5], con una tasa de supervivencia en España del 37,7% al año del diagnóstico, del 14,9% a los tres años y del 10,7% a los cinco años [6]. Esta baja supervivencia es frecuentemente consecuencia de una detección tardía, en estadios III-IV [7]. Entre las mujeres, la mortalidad por cáncer de pulmón está en aumento y se ha pronosticado que superará a la de cáncer de mama en los próximos años en diversos países de ingresos medios o altos [8], incluido España [9], consecuencia en este caso de una tendencia creciente en la tasa de incidencia de cáncer de pulmón en mujeres, desde un 7% entre 1993 y 1997 hasta un 11,2% entre 2003 y 2007[10].

Por la idiosincrasia del cáncer de pulmón, las actividades de prevención primaria (deshabituación tabáquica y prevención del tabaquismo) son esenciales para disminuir la incidencia y, por tanto, las tasas de mortalidad. Además, las consecuencias positivas del abandono del tabaco se extienden más allá del momento del diagnóstico de cáncer de pulmón, ya que incluso después de un diagnóstico en fases tempranas el dejar de fumar puede rebajar el riesgo de muerte hasta a la mitad [11], además de añadir

beneficios complementarios como reducción del dolor [12] y mejores estados funcionales [13]. En este sentido, los cribados poblacionales se han descrito como *teachable moment* para implementar actividades de prevención primaria, es decir, un marco en el que se pueden promover hábitos de vida saludables [14]. El cribado de cáncer de mama tiene, además, una participación en general elevada [15] hecho que puede permitir incorporar a un mayor número de mujeres a dichas actividades de prevención.

Por otro lado, en los últimos años se han realizado diversos estudios con el objetivo de analizar la reducción de la mortalidad por cáncer de pulmón y por todas las causas que supone la utilización de la tomografía computarizada de baja dosis (TCBD) [16,17,18] como técnica de cribado (prevención secundaria), con el fin último de evaluar su potencial implementación en los sistemas sanitarios como cribado selectivo en fumadores y exfumadores adultos con un historial de consumo acumulado medio-alto. Por su diseño, el más importante fue el *National Lung Screening Trial* (NLST) en Estados Unidos, en el que se observó una reducción de la mortalidad por cáncer de pulmón del 20% y por todas las causas del 6,7% frente al cribado con radiografía de tórax [16]. Estos resultados condujeron a la recomendación positiva por parte de diversas organizaciones, como el *US Preventive Services Task Force* [19], de la TCBD, y que finalmente se implementara para grupos de alto riesgo en EEUU [20]. En la Unión Europea (UE), donde el cribado de cáncer de pulmón no se ha implementado todavía, también se han llevado a cabo diversos estudios, destacando por el tamaño muestral el estudio NELSON [18], en el que se ha observado preliminarmente una reducción de la mortalidad por cáncer de pulmón a los diez años de seguimiento del 26% (p-valor = 0,003) en hombres y del 39% (p-valor = 0,0543) en mujeres [21]. En ambos ensayos se utilizaron como criterios de inclusión las variables edad y consumo

acumulado de cigarrillos en paquetes-año en lo que ha sido denominado por otros autores como criterios de selección simplificados, opuestamente a los modelos de predicción de riesgo que tienen en cuenta más variables (por ejemplo, comorbilidades y exposiciones a otros agentes) [22]. En términos de coste-efectividad, se ha estimado que por cada cribado de cáncer de pulmón se podrían realizar veinte intervenciones de deshabituación [23].

Por estos motivos, y dado el incremento observado en la mortalidad por cáncer de pulmón en mujeres, el objetivo de este estudio es estimar la proporción de participantes en un programa de cribado poblacional de cáncer de mama que presenta alto riesgo de desarrollar cáncer de pulmón según los criterios de inclusión en los estudios NLST y NELSON.

MÉTODOS

Diseño

Estudio transversal en una muestra (n=1.601) de mujeres participantes en un cribado poblacional de cáncer de mama. El estudio se llevó a cabo entre los meses de mayo y julio de 2016 en el Instituto Catalán de Oncología (ICO), Hospitalet de Llobregat. Dos técnicos realizaron individualmente las pruebas mamográficas de las que consta el cribado poblacional de cáncer de mama. Una vez finalizadas, se solicitó el consentimiento de participar en un estudio sobre patrón de consumo y dependencia del tabaco. En caso afirmativo, se procedió a realizar un breve cuestionario cara a cara formado por dieciséis preguntas sobre patrón de consumo, excluyentes algunas de estas preguntas según el comportamiento actual frente al tabaco (no fumadoras, exfumadoras y fumadoras). Además, se incluyó una pregunta sobre el nivel de estudios y otra de recontacto (total de dieciocho preguntas).

Análisis estadístico

Se realizó un análisis descriptivo para definir el patrón de consumo de las mujeres fumadoras y exfumadoras a partir de la información autodeclarada en el cuestionario. Para las fumadoras, se calcularon media e IC95% de la edad de inicio en el consumo de tabaco, de los cigarrillos fumados al día y el tiempo de consumo. A continuación, se estimó el consumo acumulado a lo largo de la vida medido en paquetes-año a partir del número de cigarrillos fumados al día dividido por veinte (cigarrillos por paquete) multiplicado por los años fumando y se calculó media e IC95%. Además de lo anterior, para las exfumadoras se calcularon media e IC95% del tiempo en años desde el abandono.

Se estimó la proporción sobre el total de mujeres fumadoras y exfumadoras de aquéllas que presentan actualmente un alto riesgo de desarrollar cáncer de pulmón según los criterios NLST y NELSON, definidos como i) edad entre 55 y 74 años, con un consumo acumulado de al menos 30 paquetes-año y, en el caso de las exfumadoras, haberlo dejado hace menos de 15 años según los criterios NLST [16] y ii) edad entre 50 y 75 años, con un consumo acumulado de al menos 25 años fumando más de 15 cigarrillos al día o al menos 30 años fumando más de 10 cigarrillos al día y, en el caso de las exfumadoras, haberlo dejado hace menos de 10 años según los criterios NELSON [18]. Para calcular el consumo histórico acumulado, se consideró el último consumo reportado como constante desde la fecha de inicio en el tabaco. Además, se estimaron las proporciones de mujeres fumadoras y exfumadoras que presentan alto riesgo estratificando por las variables edad (50-54 años, 55-59 años, 60-64 años y 65-69 años) y ronda de cribado en la que participa (primera o segunda, tercera o cuarta, quinta o sexta, séptima u octava y novena o décima) a partir de

información anonimizada recogida en el registro; dependencia a la nicotina clasificada por el Test de Fagerström breve [24] como baja (0-2 puntos), media (3-4 puntos) y alta (5-6 puntos); y estado de cambio [25] (precontemplación, contemplación y preparación). El programa estadístico utilizado fue SPSS v.21.

RESULTADOS

La media de edad de las participantes era de 61 años (desviación típica = 4,9). El 18,7% se declararon fumadoras y el 19,9% exfumadoras. Cerca de un 73% no tenían estudios o eran primarios. El porcentaje de participación en el programa de cribado en los meses de realización del estudio fue de 75,5%, 78,4% y 70,9% para mayo, junio y julio respectivamente, mientras que la tasa de respuesta de la encuesta sobre el total de participantes en el cribado fue del 95,5%, 90,1% y 77,0% para los mismos meses.

En la Tabla 1 se muestra el patrón de consumo de tabaco en mujeres fumadoras y exfumadoras y la proporción de mujeres que presenta alto riesgo de desarrollar cáncer de pulmón. Según los criterios NLST, un 23,4% (IC95% 18,6-28,2) de las fumadoras y un 18,2% (IC95% 14,2-22,5) de las exfumadoras presentan un alto riesgo de desarrollar cáncer de pulmón. Por otro lado, según los criterios NELSON, el 42,8% (IC95% 37,2-48,4) de las fumadoras y el 20,8% (IC95% 16,3-25,2) de las exfumadoras presentan un alto riesgo de desarrollar cáncer de pulmón. Asumiendo estas proporciones, y teniendo en cuenta que aproximadamente 52.000 mujeres participan en el cribado poblacional de cáncer de mama en el centro donde se realizó el estudio, alrededor de 4.150 participantes según los criterios NLST y de 6.300 participantes según los criterios NELSON serían elegibles en caso de que se implementara el cribado de cáncer de pulmón.

En la Tabla 2 se muestran las proporciones de fumadoras y exfumadoras que presentan alto riesgo estratificadas por las variables edad, ronda de participación, test de Fagerström breve y estado de cambio. Las proporciones de fumadoras que presentan alto riesgo son similares entre los diferentes grupos de edad, observándose la mayor prevalencia en el grupo de entre 55 y 59 años según los criterios NLST y de entre 50 y 54 años según los criterios NELSON. Se observa una tendencia creciente, estadísticamente significativa, en la proporción de mujeres que presentan elevado riesgo a medida que aumenta la dependencia a la nicotina según el Test de Fagerström breve. Además, de acuerdo a los criterios NELSON, se observa una tendencia decreciente, no estadísticamente significativa, en la proporción de mujeres que presentan elevado riesgo a medida que el estado de cambio avanza hacia el estado de preparación (Tabla 2).

DISCUSIÓN

Alrededor de dos de cada diez y cuatro de cada diez fumadoras que participan en este cribado poblacional de cáncer mama presentan un alto riesgo de desarrollar cáncer de pulmón según los criterios NLST y NELSON, respectivamente. Además, dos de cada diez exfumadoras presentan un elevado riesgo según estos mismos criterios. Según nuestras estimaciones, de las 80.000 mujeres invitadas al cribado de cáncer de mama en nuestro centro, cerca de 9.300 según los criterios NLST y más de 13.000 según los criterios NELSON formarían parte de un hipotético cribado de cáncer de pulmón.

Los resultados según los criterios NLST son similares a los descritos en un estudio realizado en España a partir de datos de la Encuesta Nacional de Salud de España (ENSE) de 2011-2012, que estimó el porcentaje de mujeres con un riesgo elevado de

cáncer de pulmón entre las mujeres que habían participado en un cribado de cáncer de mama en los últimos tres años [26].

A nivel de la Unión Europea (UE), se ha estimado que alrededor de un 30% de las fumadoras y un 8% de las exfumadoras según los criterios NLST y un 70% de las fumadoras y un 14% de las exfumadoras según los criterios NELSON que se encontraban en edad de participar en cribados de cáncer de mama presentaban un alto riesgo de desarrollar cáncer de pulmón [27]. Las menores proporciones de fumadoras y las mayores proporciones de exfumadoras que presentan alto riesgo observadas en nuestro estudio comparadas con las de la UE son compatibles con las diferencias entre ambas en el consumo medio acumulado de tabaco durante la vida. El consumo medio estimado en fumadoras de la UE fue de 27,6 paquetes-año, mientras en nuestra muestra es de 22,7 paquetes-año. En las exfumadoras, se estimó un consumo acumulado de 14,1 paquetes-año en el caso de la UE, mientras que en nuestra muestra es de 20,4 paquetes-año. Estas diferencias podrían deberse al menor nivel educativo medio de nuestra muestra en comparación con la media de la UE [28], y la relación inversa ya descrita entre nivel educativo y consumo de tabaco [29].

Nuestros resultados señalan que los mayores incrementos en la proporción de mujeres que alcanzarían la situación de alto riesgo ocurrirían, siempre que el consumo se mantuviera constante, y según los criterios NLST, dentro de los grupos de mujeres de entre 50 y 54 y 55 y 59 años. Esta transición estimada al estado de alto riesgo para las próximas rondas, que fundamentalmente ocurre siguiendo los criterios NLST, pone de manifiesto las diferencias en la restricción de los criterios NLST y NELSON, siendo los segundos mucho más laxos tanto en la variable edad como en el consumo acumulado en paquetes-año, lo que adelanta el estado de alto riesgo según estos criterios.

Por otro lado, en nuestro estudio, ninguna de las exfumadoras va a presentar alto riesgo en los próximos años. Esta situación es compatible con la dicotomización del riesgo que conlleva aplicar los criterios NLST y NELSON, por el hecho de que una vez que las exfumadoras han dejado de fumar solo pueden pasar a la situación de alto riesgo cuando cumplen el criterio de edad, ya que el consumo acumulado no se modifica. En el caso del cribado de cáncer de mama, debido a que todas las mujeres de la muestra son mayores de 50 años, ese criterio ya lo han cumplido en la actualidad todas (criterios NELSON) o casi todas (criterios NLST). En este sentido, consideramos que las exfumadoras que presentan alto riesgo se podrían beneficiar de la participación en un cribado de cáncer de pulmón, especialmente tras los resultados preliminares del estudio NELSON, donde se ha observado un gradiente de género en favor de las mujeres al haberse observado una reducción de la mortalidad por cáncer de pulmón mayor que en hombres, de alrededor de un 26% (p-valor = 0,003) en hombres y de un 39% (p-valor = 0,0543) en mujeres a los diez años de seguimiento[21]. Además, y como se ha expuesto en discusiones sobre la posible implementación de este cribado, el ofrecer esta oportunidad a las personas que han dejado de fumar entraría incluso dentro del campo de la ética médica [30].

También hemos observado que, de acuerdo a la variable dependencia a la nicotina medida según el Test de Fagerström breve, la mayor proporción de mujeres que presentan alto riesgo se encuentra en aquéllas con dependencia alta. Este resultado está en línea con las conclusiones de otro estudio en el que se observó retrospectivamente una alta correlación entre la puntuación en el Test de Fagerström en 171 personas y la exposición previa a nicotina (como indicador de riesgo de cáncer de pulmón) [31]. Este hecho sugiere que también el Test de Fagerström breve podría utilizarse como indicador de alto riesgo cáncer de pulmón.

Nuestro estudio tiene ciertas limitaciones que merecen ser comentadas. Por un lado, la aplicación de los criterios NLST y NELSON, que incorporan únicamente las variables edad y consumo acumulado de tabaco, tiene peor comportamiento a la hora de delimitar la población que presenta alto riesgo que los modelos de predicción de riesgo, que incluyen otros factores individuales, como exposiciones a cancerígenos (radón, amianto), factores genéticos o enfermedades subyacentes, entre otros [32]. En concreto, se ha observado una menor sensibilidad de los criterios NLST y NELSON en comparación con los modelos de predicción [33], principalmente por la no inclusión de las mencionadas variables en dichos criterios y que sí se incluyen en los modelos de predicción y que explican una buena parte del riesgo de cáncer pulmón. En este sentido, nuestra estimación está probablemente infravalorando la proporción de mujeres que presentan riesgo elevado, y por tanto un número relevante de cánceres de pulmón podrían pasar desapercibidos. Esta situación ya se ha observado en determinados registros de cáncer de pulmón en diferentes países, en los que una proporción limitada de pacientes con cáncer de pulmón cumplían los criterios NLST [34]. Por otro lado, para calcular el consumo acumulado de tabaco, se consideró el consumo actual como constante desde el inicio en el consumo, lo que ha podido modificar ligeramente, probablemente sobreestimando, la proporción real de mujeres a riesgo. Además, hay que mencionar el impacto que pueden tener en nuestros resultados los sesgos asociados a diseños donde la información se recoge por medio de cuestionarios, como el sesgo de recuerdo o del voluntario sano, lo que ha podido llevar a infraestimar la proporción de población a riesgo.

En conclusión, alrededor de un 20% y un 40% de las mujeres fumadoras y alrededor de un 20% de las exfumadoras que participan en este estudio presentan alto riesgo de desarrollar cáncer de pulmón, lo que las convertiría en candidatas a participar en un

posible cribado de cáncer de pulmón. A partir de la elevada participación observada, creemos que se debería promover la deshabituación tabáquica dentro del cribado de cáncer de mama aprovechando las condiciones que ofrece como *teachable moment*, aunque finalmente se implementaran programas de cribado de cáncer de pulmón en la UE.

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Tabla 1. Patrón de consumo y proporción de mujeres a alto riesgo de desarrollar cáncer de pulmón según los criterios NLST y NELSON en las mujeres encuestadas (Hospitalet de Llobregat, 2016).

	Fumadoras	**Exfumadoras**
	n = 299	n = 318
Edad de inicio en el consumo de tabaco (años)	20,8 (19,9-21,6)	19,7 (19,0-20,4)
Tiempo desde el abandono (años)	-	16,1 (14,8-17,5)
Cigarrillos/día	11,9 (11,1-12,7)	15,1 (13,7-16,5)
Tiempo de consumo (años)	37,6 (36,8-38,5)	24,1 (22,7-25,5)
Consumo a lo largo de la vida (paquetes/año)	22,7 (21,0-24,3)	20,4 (18,0-22,7)
Riesgo de cáncer de pulmón		
Criterios NLST	23,4% (18,6-28,2)	18,2% (14,2-22,5)
Criterios NELSON	42,8% (37,2-48,4)	20,8% (16,3-25,2)

Media (IC95%) para variables cuantitativas, proporción (IC95%) para variable "riesgo de cáncer de pulmón"

Tabla 2. Proporción (IC95%) de mujeres fumadoras y exfumadoras a alto riesgo según los criterios NLST y NELSON estratificada por las variables edad, ronda de cribado actual, dependencia a la nicotina y estado de cambio (Hospitalet de Llobregat, 2016).

	NLST (%, IC95%)		**NELSON (%, IC95%)**	
	Fumadoras n = 70	Exfumadoras n = 58	Fumadoras n = 128	Exfumadoras n = 66
Total	23,4 (18,6 - 28,2)	18,2 (14,0 - 22,5)	42,8 (37,2 - 48,4)	20,8 (16,3 - 25,2)
Edad (años)				
50-54	NA	NA	45,7 (35,5 - 55,8)	25,4 (15,0 - 35,8)
55-59	36,7 (26,1 - 47,3)	28,9 (19,2 - 38,7)	45,6 (34,6 - 56,6)	19,3 (10,8 -27,8)
60-64	32,3 (22,8 - 41,8)	21,8 (13,7 - 29,8)	38,7 (28,8 - 48,6)	23,8 (15,5 - 32,1)
65-69	34,4 (17,9 - 50,8)	19,1 (9,4 - 28,7)	43,8 (26,6 - 60,9)	14,3 (5,6 - 22,9)
Rondas de cribado (categorizada)				
1 y 2	7,0 (1,5 - 19,1)	14,7 (2,8 - 26,6)	41,9 (27,1 - 56,7)	35,3 (19,2 - 51,4)
3 y 4	15,5 (9,3 - 23,6)	16,9 (8,8 - 24,9)	42,7 (33,5 - 52,0)	22,9 (13,9 - 31,9)
5 y 6	40,0 (30,1 - 50,6)	22,3 (14,9 - 29,7)	50,5 (40,5 - 60,6)	20,7 (13,5 - 27,9)
7 y 8	25,0 (12,8 - 37,3)	15,8 (7,6 - 24,0)	31,3 (18,1 - 44,4)	13,2 (5,6 - 20,8)
9 y 10	0,0 (0,0 - 84,2)	0,0 (0,0 - 84,2)	0,0 (0,0 - 84,2)	0,0 (0,0 - 84,2)
Dependencia[a]				
Baja	9,3 (5,2 - 13,4)	NA	19,1 (13,5 - 24,6)	NA
Media	47,4 (37,3 - 57,4)	NA	86,3 (79,4 - 93,2)	NA
Alta	77,8 (40,0 - 97,2)	NA	100,0 (66,4 - 100,0)	NA
Estado de cambio				
Pre-contemplación	28,4 (20,9 - 35,8)	NA	48,2 (40,0 - 56,5)	NA
Contemplación	18,7 (12,6 - 24,9)	NA	38,1 (30,4 - 45,7)	NA
Preparación	33,3 (0,8 - 90,6)	NA	33,3 (0,8 - 90,6)	NA

[a] Medida por el Test de Fagerström breve. NA: no aplica.

4.3 MANUSCRITO EN REVISIÓN: USE OF BIOMARKERS OF TOBACCO EXPOSURE IN THE ASSESSMENT OF LUNG CANCER RISK AMONG DAILY SMOKERS

Use of biomarkers of tobacco exposure in the assessment of lung cancer risk among daily smokers

Adrián González-Marrón[1], Juan Carlos Martín-Sánchez[1], Raúl Pérez-Ortuño[2], Marcela Fu[3,4,5], Montse Ballbè[3,4,6,7], Àurea Cartanyà- Hueso[1], Nuria Matilla-Santander[1], José Antonio Pascual[2,8], Esteve Fernández[3,4,5,6], Lorelei Mucci[9], Jose M Martínez-Sánchez[1,9]

1. Group of Evaluation of Health Determinants and Health Policies, Department of Basic Sciences, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Barcelona, Spain.

2. Group of Integrative Pharmacology and Systems Neuroscience, Neurosciences Programme, IMIM (Hospital del Mar Medical Research Institute), Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain.

3. Tobacco Control Unit, Cancer Prevention and Control Program, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain.

4. Cancer Prevention and Control Group, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain.

5. Department of Clinical Sciences, School of Medicine and Health Sciences, Universitat de Barcelona, Barcelona, Spain.

6. Catalan Network of Smoke-free Hospitals, L'Hospitalet de Llobregat, Barcelona, Spain.

7. Addictions Unit, Institute of Neurosciences, Hospital Clínic de Barcelona, Barcelona, Spain.

8. Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Parc de Recerca Biomèdica de Barcelona, Barcelona, Spain.

9. Cancer Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Objective

To compare the concentrations of tobacco specific N-nitrosamines (TSNAs) and cotinine in saliva samples between daily smokers at high risk and not at high risk of lung cancer.

Methods

Data were retrieved from the Determinants of cotinine phase 3 project (Barcelona, 2013-2014). We determined and compared the concentrations of TSNAs, including NNAL, NNN and NNK, and cotinine, in saliva samples of 142 daily smokers from the general population according to their risk of lung cancer. High risk of lung cancer was defined as per the inclusion criteria in the National Lung Screening Trial (NLST) and in the Dutch-Belgian lung cancer screening trial (NELSON). Generalized linear models adjusted for sex were fitted to estimate the adjusted percentage increase in the concentrations of biomarkers in daily smokers at high risk versus daily smokers not at high risk of lung cancer.

Results

Adjusted concentrations of lung cancer-specific TSNAs (NNAL and NNK) were significantly higher in daily smokers at high risk of lung cancer according to both NLST and NELSON criteria. Similar patterns were observed in daily smokers within the age ranges of both NLST and NELSON trials. There were not statistically significant differences in the concentrations of biomarkers between males and females at high risk of lung cancer.

Conclusion

The incorporation of biomarkers of smoke exposure, particularly NNK and its metabolite NNAL, into the lung cancer risk assessment may improve lung cancer screening selection criteria.

Introduction

Lung cancer is among the deadliest disorders associated with smoking, with a 5-year survival rate under 20%[1] due to its frequent late diagnosis, being the first cause of cancer death worldwide[2]. Primary prevention activities directed to smoking initiation and cessation are associated with a reduction in the morbidity and mortality burden posed by this condition[3]. At the secondary prevention level, however, the use of low-dose computer tomography (LDCT) for the screening of individuals at high risk of lung cancer is still a matter of debate since the risk-benefit balance must still be fully assessed[4,5]. As a result, lung cancer screening based on LDCT has been implemented only in a limited number of countries thus far (e.g. US). Evidence supporting screening with LDCT mainly arose from the results of the US National Lung Screening Trial (NLST), in which a 20% lung-cancer specific mortality rate reduction and a 6.7% overall mortality rate reduction were observed in the LDCT versus the chest X-ray arm[6]. This finding prompted a positive recommendation from the US Preventive Services Task Force[7] on the use of the LDCT. In Europe, the recently published interim conclusions of the Dutch-Belgian Lung Cancer Screening Trial (NELSON) have also shown a reduction in lung cancer mortality[8], confirming the results of the NLST trial.

Around 80% of the cases of lung cancer in the population are attributable to tobacco consumption[9]. Tobacco smoke contains a plethora of potentially harmful substances[10], including tobacco specific N-nitrosamines (TSNAs), which have been quantified to assess both active and passive smoke exposure, along with cotinine and other subproducts[11]. Many TSNAs, including 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) and its metabolite 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanol

(NNAL), or N'-Nitrosonornicotine (NNN), are identified as carcinogens for humans[12]. Specifically, NNK and NNAL are promoters of lung cancer[13].

The incorporation of biomarkers into the lung cancer risk assessment has been proposed to consider the individual variability in tobacco consumption (smoking topography)[14] and to obtain a more valid estimate of consumption than with self-reporting, thus improving the lung cancer risk assessment[15]. The aim of this study is to compare the concentration of TSNAs and cotinine, biomarkers of tobacco consumption, between daily smokers at high risk of lung cancer and daily smokers not at high risk of lung cancer, as defined by the inclusion criteria in NLST and NELSON trials.

Methods

Data were retrieved from the "Determinants of cotinine phase 3 project" (dCOT3 study), a cohort study of a representative sample of the adult general population of the city of Barcelona (Catalonia, Spain). Further information on this project can be found elsewhere[16]. For this research, we only considered the individuals who reported being current daily smokers in the follow-up study in 2013-2014.

The concentrations of TSNAs and cotinine in saliva samples were determined as detailed elsewhere[11]. Geometric means (GM) of these concentrations were computed due to the asymmetry of data. GM concentrations (and 95% confidence intervals) of TSNAs and of cotinine were calculated for current daily smokers and current daily smokers at the age range of NLST and NELSON lung cancer screening trials at the time of the survey (from 55 to 74 years of age according to NLST criteria and from 50 to 75 years of age according to NELSON criteria) who were and who were not at high risk of lung cancer according to NLST criteria (age criterion and a lifetime smoking

of at least 30 pack-years)[6] and NELSON criteria (age criterion and a lifetime smoking of at least 25 years smoking more than 15 cigarettes per day, or of at least 30 years smoking more than 10 cigarettes per day)[17]. Pack-years were defined as the number of packs smoked daily multiplied by the number of years smoking. Results were also stratified by sex.

We compared the concentrations of each TSNA and cotinine between those individuals at high risk and not at high risk of lung cancer using non-parametric Mann-Whitney tests. We also fitted Generalized Linear Models adjusted for sex to estimate the percent change in the GM concentration of biomarkers between individuals at high risk and those not at high risk of lung cancer. Spearman correlation coefficients (r_{sp}) were also calculated between pack-years and the concentration of each biomarker.

Results

There were 142 current daily smokers in our sample. Median age was 48.5 (interquartile range: 59-37). An estimated 8.5% (n=12) and 14.8% (n=21) of current daily smokers in our study were at high risk of lung cancer according to NLST and NELSON criteria, respectively. There were statistically significant positive correlations between pack-years and the concentration of all the biomarkers studied, ranging from 0.32 (CI 95%, 0.13-0.49) for NNN to 0.52 (CI 95%, 0.36-0.65) for cotinine.

Concentrations of TSNAs were significantly higher in individuals at high risk of lung cancer than in those who were not at high risk of lung cancer using both NLST and NELSON criteria (Table 1, part a). The concentration of cotinine was significantly higher according to NELSON criteria only (Table 1, part a). Among daily smokers

within the age range of lung cancer screening, concentrations of NNAL and NNK adjusted for sex were statistically significantly higher in individuals at high risk of lung cancer using both NLST and NELSON criteria (Table 1 part b). There were not statistically significant differences in the concentrations of biomarkers between males and females at high risk of lung cancer (Table 2).

Discussion

Our results show that the concentrations of TSNAs and cotinine are mostly significantly higher in current daily smokers at high risk of lung cancer than in those who are not at high risk. These results are in line with a prospective study, in which the concentrations of biomarkers of smoke exposure in urine were compared between a group of smokers before developing lung cancer and another group of smokers which did not develop lung cancer, and in which cotinine, NNAL and r-1-,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT) were associated with lung cancer risk[15].

Interestingly, NNAL and NNK, specific promoters of lung cancer, are the only products in which we have observed statistically significant differences between participants at high risk and not at high risk in the age of lung cancer screening. In this sense, we believe that these biomarkers, NNAL and NNK, could be incorporated as risk biomarkers in prediction models to improve the lung cancer risk assessment. Further studies should be completed to investigate this hypothesis.

Although we did not find statistically significant differences in the concentrations of biomarkers by sex, we cannot dismiss potential differences that we were not able to identify due to the small sample size. Further research is needed to explore this in depth.

Our study has some limitations that should be addressed. Firstly, we have used NLST and NELSON criteria to identify individuals at high risk of lung cancer. These criteria have been considered elsewhere as simplified eligibility criteria[18], opposing risk prediction models, which have a higher sensibility[19]. In this sense, we may be underestimating the proportion of individuals at high risk of lung cancer. Also, the low number of individuals at high risk of lung cancer limits statistical power, especially when stratifying analysis by sex. Further analysis will require larger sample sizes to clarify the possible differences between males and females. Besides, the consumption of tobacco reported in the survey was considered constant since the smoker started smoking.

In conclusion, we have found higher concentrations of the biomarkers studied, particularly NNK and NNAL, in daily smokers at high risk of lung cancer than in those not at high risk of lung cancer, as defined by NLST and NELSON inclusion criteria. We consider the concentrations of NNK and NNAL may be assessed in lung cancer risk prediction models to improve lung cancer screening selection criteria.

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Table 1. Geometric mean (GM) concentrations (95% CI) of biomarkers (a) in current daily smokers; and (b) in current daily smokers in the age of lung cancer screening according to NLST and NELSON criteria and adjusted % increases in the GM concentrations in those at high risk of lung cancer and those not at high-risk of lung cancer.

(a) All current daily smokers

	Individuals at high risk (NLST criteria) (YES/NO)				Individuals at high risk (NELSON criteria) (YES/NO)			
	yes (n=12)	**not (n=123)**	**p-value***	**% increase in GM (95% CI) ****	**yes (n=21)**	**not (n=111)**	**p-value***	**% increase in GM (95% CI)****
Cotinine (ng/mL)	582.64 (388.69-873.57)	291.54 (229.25-370.77)	0.057	102.53 (27.74-221.11)	584.52 (444.73-768.25)	268.60 (207.11-348.34)	0.004	108.09 (44.67-199.31)
NNN (pg/mL)	32.84 (10.78-100.07)	9.82 (6.74-14.33)	0.044	236.56 (19.83-845.27)	27.78 (13.17-58.60)	8.78 (5.89-13.10)	0.014	216.38 (43.93-595.44)
NNAL (pg/mL)	3.38 (2.26-5.05)	1.26 (1.02-1.57)	0.002	177.13 (93.79-296.31)	3.29 (2.26-4.80)	1.15 (0.93-1.43)	<0.001	175.58 (85.18-310.11)
NNK (pg/mL)	4.73 (2.46-9.10)	2.04 (1.74-2.41)	0.004	133.79 (32.71-311.86)	5.17 (3.53-7.55)	1.83 (1.56-2.15)	<0.001	175.31 (88.16-302.84)

*Mann-Whitney **GLM adjusted for sex. GM = geometric mean. NNN = N'-Nitrosonornicotine. NNAL = 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanol.
NNK = 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone.

(b) Current daily smokers in the age of lung cancer screening

	Individuals at high risk (NLST criteria) (YES/NO)				Individuals at high risk (NELSON criteria) (YES/NO)			
	yes (n=12)	**not (n=23)**	**p-value***	**% increase in GM (95% CI) ****	**yes (n=21)**	**not (n=31)**	**p-value***	**% increase in GM (95% CI) ****
Cotinine (ng/mL)	582.64 (388.69; 873.57)	138.93 (54.56; 353.75)	0.007	306.44 (64.37; 906.67)	584.52 (444.73;768.25)	159.49 (79.21; 321.14)	<0.001	253.57 (88.72; 562.42)
NNN (pg/mL)	32.84 (10.78; 100.07)	10.09 (3.63; 28.03)	0.168	203.39 (-21.41; 1068.76)	27.78 (13.17; 58.60)	11.38 (4.72; 27.42)	0.186	137.15 (-19.36; 597.45)
NNAL (pg/mL)	3.38 (2.26; 5.05)	1.14 (0.63; 2.03)	0.006	191.25 (63.07; 420.18)	3.29 (2.26; 4.80)	1.12 (0.71; 1.76)	0.001	171.85 (59.68; 362. 82)
NNK (pg/mL)	4.73 (2.46; 9.10)	2.04 (1.42; 2.93)	0.031	126.97 (21.76; 323.10)	5.17 (3.53; 7.55)	1.92 (1.43; 2.57)	<0.001	159.95 (66.48; 305.90)

* Mann-Whitney test ** GLM adjusted for sex GM = geometric mean. NNN = N'-Nitrosonornicotine. NNAL = 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanol.
NNK = 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone.

Table 2. Geometric mean concentrations (95%CI) of biomarkers of smoke exposure in male and female daily smokers who are at high risk of lung cancer according to NLST and NELSON criteria.

	Individuals at high risk (NLST criteria) (n=12)			Individuals at high risk (NELSON criteria) (n=21)		
	Males (n=6)	**Females (n=6)**	**p-value***	**Males (n=13)**	**Females (n=8)**	**p-value***
Cotinine (ng/mL)	506.41 (242.86; 1056.09)	670.50 (358.43; 1254.30)	0.589	531.86 (358.76; 788.68)	681.24 (445.45; 1042.08)	0.336
NNN (pg/mL)	25.54 (2.36; 276.50)	42.22 (11.86; 150.21)	0.818	19.15 (6.39; 57.35)	50.86 (19.20; 134.77)	0.860
NNAL (pg/mL)	4.61 (2.41; 8.81)	2.61 (1.44; 4.73)	0.082	3.69 (2.01; 6.80)	2.77 (1.81; 4.23)	0.140
NNK (pg/mL)	5.98 (1.56; 22.92)	3.74 (1.71; 8.21)	0.589	5.58 (3.22; 9.68)	4.55 (2.47; 8.39)	0.305

* Mann-Whitney test

4.4. ARTÍCULO PUBLICADO EN ENVIRONMENTAL RESEARCH: RELATION BETWEEN TOBACCO CONTROL POLICIES AND POPULATION AT HIGH RISK OF LUNG CANCER IN THE EUROPEAN UNION

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Relation between tobacco control policies and population at high risk of lung cancer in the European Union

Adrián González-Marrón[a], Juan Carlos Martín-Sánchez[a], Queralt Miró[a], Nuria Matilla-Santander[a], Àurea Cartanyà-Hueso[a], Lorelei Mucci[b], Jose M. Martínez-Sánchez[a,b,*]

[a] Group of Evaluation of Health Determinants and Health Policies, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Spain
[b] Cancer Epidemiology and Cancer Prevention Program, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

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ABSTRACT

Introduction: Lung cancer accounts for nearly 2 million deaths per year worldwide, the majority of cases due to smoking as the main risk factor associated. The aim of this study was to assess the relation between the level of implementation of tobacco control policies and the population at high risk of lung cancer in the European Union (EU).

Methods: The Special Eurobarometer 458 "Attitudes of Europeans towards tobacco and electronic cigarettes", conducted in 2017, and the Tobacco Control Scale (TCS) 2010, 2013, and 2016 were the sources of our data. High risk of lung cancer was defined by the inclusion criteria in the National Lung Screening Trial (NLST) and the Dutch-Belgian Lung Cancer Screening Trial (NELSON), the largest lung cancer screening trials carried out in the US and the EU. We calculated Spearman's rank correlation coefficients (r_{sp}) and fitted multilevel generalized linear mixed models using the quasi-Poisson family to assess the correlation at the national level and analyze the association at the individual level, respectively, between the scores in the TCS (higher scores means better implementation of tobacco control policies) and the proportion of individuals at high risk of lung cancer in member states of the EU.

Results: The scores in the TCS 2010 were statistically negatively correlated with the current proportion of ever and former smokers at high risk according to NELSON criteria (−0.41; 95%CI −0.68, −0.04 and −0.49; 95%CI −0.73, −0.13, respectively). We observed statistically significant inverse associations between the scores in the TCS 2010 for the highest quartiles and the proportion of individuals at high risk of lung cancer according to both criteria. Non-statistically significant negative correlations and inverse associations were observed with other TCS.

Conclusion: There is a lag between the implementation of tobacco control policies and the reduction of the rates of high risk of lung cancer. Member states should reinforce comprehensive tobacco control policies to reduce the population at high risk of lung cancer in the EU.

1. Introduction

Tobacco smoking carries a high burden of morbidity and mortality worldwide. Among the different conditions associated with smoking, lung cancer is one of the most concerning due to its poor prognosis, with a 5-year survival rate under 20% (De Angelis et al., 2014). Indeed, lung cancer is the primary cause of cancer death around the world (WHO, 2018). A number of organizations have recommended the implementation of selective lung cancer screening programs for adult smokers and former smokers with a high cumulative history of tobacco consumption (Humphrey et al., 2013) (ERS, 2018) given the lung-cancer specific mortality reduction observed in the US National Lung Screening Trial (NLST) (National Lung Screening Trial Research Team et al., 2011) and the Dutch-Belgian Lung Cancer Screening Trial (NELSON) (De Koning et al., 2018), in which low-dose computed tomography (LDCT) was used.

Both trials delimited the population of individuals at high risk of lung cancer by measures of smoking history defined by pack-years (i.e., number of packs smoked per day multiplied by the number of years smoking) and age, in what has been defined elsewhere as "simplified

* Corresponding author at: Group of Evaluation of Health Determinants and Health Policies, Department of Basic Sciences Universitat Internacional de Catalunya, Carrer de Josep Trueta s/n, 08195 Sant Cugat del Vallès, Barcelona, Spain.
E-mail address: jmmartinez@uic.es (J.M. Martínez-Sánchez).

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eligibility criteria" (Kaaks et al., 2017). This strategy opposes risk prediction models, which estimate the probability of developing or dying from lung cancer in a specific time including further variables such as family history of lung cancer, other exposures (e.g., asbestos) or underlying associated conditions (e.g., COPD), mainly (Gray et al., 2016).

Different health benefits have been achieved after the implementation of tobacco control policies (Glantz and Gonzalez, 2012). However, it is unknown if these policies have an effect on the risk of lung cancer in the European Union (EU), and eventually to what extent. Hence, the aim of this study was to explore the association between the implementation of tobacco control policies and the risk of lung cancer in the EU.

2. Methods

The degree of implementation of tobacco control policies was assessed via the Tobacco Control Scale (TCS) scores in 2010, 2013 and 2016. The TCS is a tool firstly published in 2006 in which the implementation of six key policies (taxation on tobacco products, bans/restrictions on smoking in public and work places, improvement of the information provided to the consumer, banning on advertising, adoption of health warnings on boxes of tobacco products and smoking cessation treatment) in 35 European countries is measured in a scale from 0 (minimum) to 100 (maximum). Current allocation of scores is as follows: prices of cigarettes, 30 points; smokefree work and other public places, 22 points; spending on public information campaigns, 15 points; comprehensive bans on advertising and promotion, 13 points; large direct health warning labels, 10 points; and treatment to help smokers stop, 10 points. A higher score in the TCS implies a stronger implementation of tobacco control policies. Due to changes in the methodology used to allocate points from 2010 (Joossens and Raw, 2017), we discarded the TCS of 2006 to allow for comparability of data. Further information on the TCS could be found elsewhere (Joossens and Raw, 2006).

Data on current smoking patterns was retrieved from the Special Eurobarometer 458 "Attitudes of Europeans towards tobacco and electronic cigarettes", a survey conducted in 2017 on a representative sample (n = 27,901) of the adult population (≥15years) in the EU. A multi-stage, random sampling was used and face-to-face interviews were conducted in the national language. Further information on the Special Eurobarometer 458 could be found elsewhere (TNS opinion & social, 2017). High-risk of lung cancer was defined following the NLST and NELSON inclusion criteria, as follows: i) current and former smokers from 55 to 74 years of age with a lifetime smoking history of at least 30 pack-years, having quit the former smokers within the last 15 years, according to NLST criteria (National Lung Screening Trial Research Team et al., 2011), and ii) current and former smokers from 50 to 75 years of age with a lifetime smoking of at least 25 years smoking more than 15 cigarettes per day, or of at least 30 years smoking more than 10 cigarettes per day, having quit the former smokers within the last 10 years according to NELSON criteria (Ru Zhao et al., 2011). Croatia was not included in our analysis due to its entry to the EU in 2013 to allow for comparability.

We calculated Spearman's rank correlation coefficients (r_{sp}) and 95% Confidence Intervals (CI) between the scores in the TCS 2010, 2013 and 2016 and the proportion of current, former and ever smokers at high-risk of developing lung cancer at the national level for the EU members. We also fitted multilevel generalized linear mixed models using the quasi-Poisson family, with country as random effect, to calculate adjusted prevalence ratios (aPR) of being smoker and being at high-risk of lung cancer according to NLST and NELSON criteria. The models were adjusted for sex and age. Quartiles for the TCS scores were calculated to determine the gradient of association, taking as reference the first quartile. Sampling weights were used to produce representative estimates.

Table 1
Tobacco Control Scale (TCS) scores for 2010, 2013 and 2016 and proportion of individuals at high risk of lung cancer according to the National Lung Screening Trial (NLST) and NELSON criteria for member states of the European Union in 2017.

Country	TCS score 2010	TCS score 2013	TCS score 2016	Proportion of individuals at high risk of lung cancer (NLST criteria) (%)	Proportion of individuals at high risk of lung cancer (NELSON criteria) (%)
Austria	32	31	36	4.82	8.62
Belgium	50	47	49	7.34	10.71
Bulgaria	40	46	47	3.59	7.06
Republic of Cyprus	40	33	44	6.27	11.00
Czech Republic	34	34	40	4.64	8.42
Germany	37	32	37	5.12	9.51
Denmark	46	46	45	4.50	8.45
Estonia	43	43	46	4.31	8.36
Spain	46	56	55	3.06	6.40
Finland	52	55	60	4.05	8.19
France	55	57	64	3.39	6.73
Great Britain	77	74	81	6.14	12.29
Greece	32	35	40	3.48	6.92
Hungary	34	48	53	7.86	12.27
Ireland	69	70	68	5.95	9.53
Italy	47	46	51	3.51	5.49
Lithuania	41	35	43	5.20	7.69
Luxembourg	33	37	37	2.39	8.89
Latvia	44	41	44	3.74	5.92
Malta	52	56	51	4.06	11.03
The Netherlands	46	47	53	5.12	6.66
Poland	43	43	50	4.20	7.09
Portugal	43	41	50	7.22	10.73
Romania	45	44	56	2.69	5.65
Sweden	51	48	53	4.21	8.10
Slovenia	44	43	43	3.38	5.27
Slovakia	41	39	41	6.03	9.74

Croatia was not included in the analysis since member only from 2013 to allow for comparability.

3. Results

Table 1 includes country-level data on the TCS scores and on the proportion of individuals at high risk of lung cancer according to NLST and NELSON criteria. In the EU, 53% of the population is never-smoker, 26% is current smoker and 21% is former smoker. An estimated 4.8% and 8.6% of the total population are at high risk of lung cancer according to NLST and NELSON criteria, respectively.

We found an inverse and statistically significant correlation between the scores in the TCS 2010 and the proportion of former ($r_{sp} = -0.49$; 95%CI −0.73, −0.13) and ever smokers ($r_{sp} = -0.41$; 95%CI −0.68, −0.04) at high-risk according to NELSON criteria at ecological level. Non-statistically significant negative estimates for the correlations between the proportions of current and former smokers at high-risk and any TCS according to both criteria were mainly observed (Table 2). Within categories, stronger correlations were mostly observed for the TCS 2010 (Table 2).

We observed statistically significant inverse associations between the score in the TCS 2010 and the current proportion of individuals at high-risk according to NLST and NELSON criteria at the individual level, ranging from aPR = 0.66 (95% CI 0.50, 0.87) for the fourth quartile versus the first quartile in the TCS score and the current proportion of individuals at high-risk according to NLST criteria to aPR = 0.77 (95% CI 0.66, 0.90) for the third quartile versus the first quartile in the TCS score and the proportion of individuals at high-risk according to NELSON criteria (Table 3). An increasing trend is generally observed in the association between the scores of the TCS and the proportion of individuals at high risk (i.e., stronger associations are

Table 2
Spearman's correlation coefficients (r_{sp}) and 95% confidence intervals (95%CI) between the score in the Tobacco Control Scale (TCS) 2010, 2013 and 2016 and the proportion of ever, current and former smokers at high-risk of lung cancer according to NLST and NELSON criteria in the European Union in 2017.

	TCS 10	TCS 13	TCS 16
OVERALL			
% EVER SMOKERS	−0.06 (−0.43, 0.33)	−0.05 (−0.42, 0.34)	−0.14 (−0.49, 0.25)
% CURRENT SMOKERS	**−0.53 (−0.76, −0.18)**	**−0.45 (−0.71, −0.08)**	−0.35 (−0.64, 0.04)
% FORMER SMOKERS	**0.38 (0.00, 0.66)**	0.28 (−0.12, 0.59)	0.10 (−0.29, 0.46)
%NLST	−0.04 (−0.41, 0.35)	−0.06 (−0.43, 0.33)	0.00 (−0.38, 0.38)
%NELSON	−0.06 (−0.43, 0.33)	0.02 (−0.36, 0.40)	−0.03 (−0.41, 0.35)
EVER SMOKERS			
% NLST	−0.35 (−0.64, 0.04)	−0.15 (−0.5, 0.24)	−0.20 (−0.54, 0.20)
% NELSON	**−0.41 (−0.68, −0.04)**	−0.25 (−0.58, 0.14)	−0.22 (−0.56, 0.17)
CURRENT SMOKERS			
% NLST	−0.22 (−0.55, 0.17)	−0.08 (−0.45, 0.31)	−0.15 (−0.50, 0.25)
% NELSON	−0.03 (−0.40, 0.36)	−0.01 (−0.39, 0.37)	0.02 (−0.37, 0.39)
FORMER SMOKERS			
% NLST	−0.30 (−0.61, 0.09)	−0.06 (−0.43, 0.33)	−0.13 (−0.48, 0.26)
% NELSON	**−0.49 (−0.73, −0.13)**	−0.26 (−0.59, 0.13)	−0.32 (−0.63, 0.06)

Statistically significant correlations in bold.

mainly observed in higher quartiles), although statistical significance is lost for the TCS 2013 and 2016 (Table 3).

4. Discussion

To our knowledge, this is the first study to provide evidence on the likely effect of the implementation of tobacco control policies on the proportion of individuals at high risk of lung cancer in the EU. Previous studies have assessed the impact of tobacco control policies in the EU on smoking prevalence (Gallus et al., 2014) (Martínez-Sánchez et al., 2010), preterm births and low birth weight (Díez-Izquierdo et al., 2018), tobacco consumption and quitting (Feliu et al., 2019)(Lidón-Moyano et al., 2017), secondhand smoke exposure in public (Martínez-Sánchez et al., 2010) (Filippidis et al., 2016) and private venues (Martínez-Sánchez et al., 2013), and attitudes towards smoking regulation (Lidón-Moyano et al., 2018) (Martínez-Sánchez et al., 2010). We have observed a possible relation between the level of implementation of tobacco control policies and the proportion of individuals at high risk at the individual level, resulting in our models in a statistically significant reduction of around 30% in the prevalence of being at high risk of lung cancer in 2017 in countries in the highest quartiles of the TCS 2010 score versus the lowest according to NLST and NELSON criteria (i.e., in countries where the TCS 2010 score was higher, the prevalence of individuals at high risk was lower in 2017). For the TCS 2013 and the TCS 2016, although statistical significance is lost, an increasing trend in the association is generally observed from the lowest to the highest quartile, as observed in the TCS 2010. This reinforces the theory of an inverse association between the score in the TCS and high risk of lung cancer, also supported by the results at the national level, where positive correlations between the scores and the proportion of former smokers (statistically significant in 2010) and negative correlations between the scores and the proportion of current smokers (statistically significant in 2010 and 2013) were observed. We suggest that there is a lag between the moment the tobacco control policies come into effect and the impact they have on the smoking reduction, and eventually on the rates of high risk of lung cancer. Being the timeframe shorter between the TCS 2013 and the Special Eurobarometer and the TCS 2016 and the Special Eurobarometer, the effect of the implementation of new policies may not yet be visible. This timeframe between the tobacco control policies come into force and the impact they have on the proportion of individuals at high risk of lung cancer adds to the gap between smoking prevalence and lung cancer mortality, which was estimated elsewhere as around three decades (Martín-Sánchez et al., 2017).

The recent positive outcomes in terms of mortality reduction in the statistically powerful NELSON trial has prompted recommendations by different organizations on the implementation of lung cancer screening in the EU (ERS, 2018). Acknowledging the benefits that this intervention may have on the ever-smoking population, we believe, in view of our results, that stress should still be placed on the primary prevention level, with governments reinforcing the implementation of tobacco control policies, particularly including help to quit for smokers. Besides,

Table 3
Adjusted prevalence ratios (aPR) and 95% confidence intervals (95%CI) of being current smoker and being at high-risk of lung cancer according to NLST and NELSON criteria in 2017 in the EU according to the quartiles of the Tobacco Control Scale (TCS) scores in 2010, 2013 and 2016.

	TCS 2016				TCS 2013				TCS 2010		
	Current smoker aPR (95%CI)	NLST aPR (95%CI)	NELSON aPR (95%CI)		Current smoker aPR (95%CI)	NLST aPR (95%CI)	NELSON aPR (95%CI)		Current smoker aPR (95%CI)	NLST aPR (95%CI)	NELSON aPR (95%CI)
Quartiles*				Quartiles*				Quartiles*			
Q2	1.17 (0.92, 1.5)	0.83 (0.59, 1.17)	0.94 (0.73, 1.21)	Q2	0.91 (0.71, 1.17)	0.90 (0.60, 1.35)	0.94 (0.71, 1.25)	Q2	0.86 (0.70, 1.06)	0.73 (0.51, 1.04)	0.86 (0.67, 1.11)
Q3	0.69 (0.46, 1.04)	0.90 (0.62, 1.32)	0.8 (0.61, 1.05)	Q3	1.15 (0.89, 1.48)	0.87 (0.63, 1.22)	0.83 (0.65, 1.06)	Q3	**0.70 (0.55, 0.90)**	**0.70 (0.58, 0.86)**	**0.77 (0.66, 0.90)**
Q4	1.15 (0.90, 1.47)	0.78 (0.57, 1.07)	0.84 (0.66, 1.08)	Q4	1.15 (0.90, 1.47)	0.80 (0.58, 1.11)	0.81 (0.63, 1.05)	Q4	1.06 (0.84, 1.33)	**0.66 (0.50, 0.87)**	**0.70 (0.53, 0.93)**

Models adjusted for sex (reference category: female) and age. *Q1 taken as reference category.
Statistically significant associations in bold.

tobacco products regulations are strongly supported by citizens in the EU (Lidón-Moyano et al., 2018), while participation in lung cancer screening programs in the US is overwhelmingly low (Pham et al., 2018).

Our study contains some limitations that should be addressed. Firstly, the cross-sectional design of the Special Eurobarometer 458 and the TCS may limit the validity of our conclusions since it is difficult to establish causation between the implementation of the policies and a subsequent decline in smoking and we cannot rule out that other factors may be contributing to the decline we have observed over time. Besides, reverse causality cannot be discarded (i.e., countries with lower proportions of smokers have higher scores in the TCS). Also, our objective exceeds those of the Special Eurobarometer 458, which does not provide quitting dates for former smokers. Hence, we had to estimate quitting dates using a uniform distribution, meaning we considered that the probability of giving up smoking was equiprobable for each year since the moment the individual started smoking until the day of the survey. The lack of quitting dates for former smokers also limited further assessment of the influence of the policies, since having a high proportion of recent quitters may suggest a stronger effect of those policies. Besides, the number of cigarettes smoked per day during lifetime is not provided for each individual in the Special Eurobarometer 458, and only the present consumption is reported in the survey. Thus, we estimated that the present consumption had remained invariable since the smoker started smoking to their present age. In this sense, and if we assume that tobacco control policies have reduced tobacco consumption, we could be underestimating the proportion of individuals at high risk. Also, we believe that the timeframe between the TCS in 2013 and 2016 and the Special Eurobarometer 458 is too short to observe statistically significant results for these years. However, and also considering that the full impact of the implementation of tobacco control policies on the proportion of individuals at high risk of lung cancer may be observable well beyond the largest timeframe studied (8 years), we have observed time trends plausible with this likely impact. We believe that our hypothesis may be confirmed or rejected in a future with further data.

Lung cancer is a deadly condition, and the proportion of individuals at high risk of lung cancer in the EU was found to be around 4% and 8% according to NLST and NELSON criteria, respectively, already for 2014 (González-Marrón et al., 2018). In this study, we have observed a likely relation between the level of implementation of tobacco control policies and the proportion of individuals at high-risk of lung cancer, as defined by NLST and NELSON criteria. We consider that member states should strengthen the six most cost-effective tobacco control polices recommended by the WHO to limit smoking, thus reducing lung cancer risk.

Declarations of interest

None.

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4.5. EDITORIAL PUBLICADA EN EXPERT REVIEW OF RESPIRATORY MEDICINE: TOBACCO CONTROL - PROTECTING FUTURE GENERATIONS' LUNGS

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EDITORIAL

Tobacco control - protecting future generations' lungs

Adrián González-Marrón, Juan Carlos Martín-Sánchez and Jose M. Martínez-Sánchez

Group of Evaluation of Health Determinants and Health Policies, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Spain

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Since the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) [1] was developed, remarkable progress has been achieved around the world to limit smoking and reduce the impact of the tobacco epidemic [2]. Nevertheless, there are still many countries which lack a resolute legislation against tobacco use [3] and smoking still poses a high burden of morbidity and mortality worldwide, being the second single cause of years of life lost. Besides, the industry's relentless efforts to keep novel products in the market in diverse, appealing and profitable forms are hampering the potential positive outcomes in public health by circumventing the frequently incomplete anti-tobacco laws [4]. This approach adds to many other industry interferences that impair tobacco control and, subsequently, the tobacco endgame.

Every individual exposed actively and/or passively to tobacco is at risk of developing a plethora of disorders. Specifically, some respiratory conditions associated with secondhand smoke (SHS) exposure in children include wheeze and bronchitis [5], while also limiting lung development [6]. Smoking at an early age is associated with shortness of breath and increased risk of lung cancer, among other conditions [7]. In this sense, these groups will be quantitatively and qualitatively more impacted during their lifetime by the current implementation of tobacco control policies. That is, present legislative decisions will greatly determine the youth of today's forthcoming health status. We believe there are at least four hot topics that should be addressed when aiming to protect future generations' lungs:

1. New tobacco products and the tobacco harm reduction strategy

Heated tobacco products (HTP) (e.g. IQOS) and electronic nicotine, and non-nicotine delivery systems (e.g. electronic cigarettes) are among the new tobacco products that, along with roll-your-own cigarettes, are shifting the consumption of manufactured cigarettes by youngsters. While the prevalence of combustible (traditional) cigarette smoking is still high in developing countries, denormalization of tobacco in many high and middle-income countries has forced the industry to change its production towards more attractive devices to hook adolescents on nicotine [8]. This is also in line with the new strategy adopted by the tobacco industry and its related stakeholders, the so-called Tobacco Harm Reduction (THR), for which they claim that health benefits could be obtained if a transition to these novel products was accomplished [4]. As a result, the scientific community is now polarized and divided into two trends: those who embrace the THR approach and those who do not. Undoubtedly, this has been the first victory of the tobacco industry, as the saying goes *divide and rule*. On the one hand, this strategy has been broadly described as a way of the tobacco industry to clean their corporate image and bypass modifications in policies with the aim of increasing their sales in a new market niche [9], since industry considers the diverse products containing nicotine a complement to its traditional business [10]. On the other hand, some estimates have shown a gain of years of life lost if a switch from tobacco smoking to other products was accomplished [11]. As of today, there is still limited evidence on the real and long-term effects of the use of these products. However, a large number of entities have already adhered to the THR strategy. One of the most relevant is Public Health England, organization that concluded in a review in 2015 that vaping is around 95% safer than smoking [12], although a number of experts questioned the transparency of this review [13]. Evidence presenting a beneficial use of electronic cigarettes has been found to be more likely affected by conflicts of interest elsewhere [14]. The lack of evidence for a better alternative to combustible tobacco has resulted in the US Food and Drug Administration (FDA) not accepting any Modified Risk Tobacco Product so far. In the meantime, actions under the Youth Tobacco Prevention Plan by the same agency are in action to stop the epidemic of electronic cigarette use in the youth in the US, with a special focus on JUUL products [8]. Also, the WHO urged the countries under the FCTC [1] to regulate HTP as tobacco products, while loopholes in the US legislation (US is not yet a party to the FCTC) are letting the industry to partially evade the law.

Further impartial research is still necessary to understand the risk–benefit balance for these novel products to be prescribed for specific purposes (e.g. quitting smoking), but it is evident that they should not mean a gateway to nicotine for teenagers and stronger legislation should come into force to limit this possibility.

CONTACT Jose M. Martínez-Sánchez jmmartinez@uic.es Group of Evaluation of Health Determinants and Health Policies, Department of Basic Sciences, Universitat Internacional de Catalunya, Carrer de Josep Trueta s/n, 08195, Sant Cugat del Vallès, Barcelona, Spain

2. Regulation of smoking in private places and outdoor spaces: another step towards denormalization of smoking for new generations

While smoking bans in indoor workplaces and public places have been demonstrated to improve health outcomes even shortly after the implementation of the laws [15], few territories have advanced in the same direction and regulated tobacco smoking in private settings thus far (e.g. in Australia, England). The consequence is that children, those more affected by exposure to SHS in private spaces due to physiological (e.g. higher ventilation rates) and behavioral (i.e. spending more time at homes) features, are still unprotected by the law and could be highly exposed to SHS. This situation has been considered as child abuse elsewhere [16] and has guided different court decisions on protecting the children involved [17]. Also, banning smoking in specific outdoor spaces is being discussed due to its possible health benefits [18].

Although we agree with other authors stating that banning smoking in private settings is an ethically complex issue [19], it would be likely to be accepted on a general basis, based on conclusions arising from a variety of research. On the one hand, adults have been usually found to favor the regulation of smoking in cars in the presence of minors [20]. Besides, smokers have performed a voluntary adoption of complete smoke-free homes when legislation limiting consumption in indoor settings (e.g. hospitality venues) in those territories has come into force [21], not producing a displacement into the household. Also for outdoor places, reasons to support the banning include the likely denormalization of tobacco use in the youth [22].

With this information in hand, we consider that policymakers should give a step forward and broaden the prohibition of smoking to certain private settings and outdoors.

3. Advertising and warning of the effects of tobacco in new media

Tobacco consumption is highly associated with tobacco advertising. As a result, and under the umbrella of article 13 of the FCTC [1], many parties have banned advertising, promotion, and sponsorship of tobacco products in different grades [3]. However, this ban has not fully regulated the new channels through which teenagers receive information nowadays. The tobacco industry has taken advantage of this situation, and different tools such as Twitter [23] and Facebook [24] are observed to be sources where marketing on tobacco products is still carried out, both explicitly and in a veiled way. This adds to evidence showing that watching movies in which the cast smoke is associated with smoking in the youth [25]. With a current rising screen time for teenagers, especially associated with the use of new technologies, the likelihood of being exposed to these outputs is increasing. Due to the global nature of this issue, legislation at the supra-national level should be considered.

4. Taxation

Among the different measures enacted by the WHO and contained in the MPOWER package, raising taxes on tobacco are the most effective to reduce smoking [26]. However, as with other legislative decisions, the tobacco industry has usually responded counterbalancing the potential benefits by applying a range of strategies, including reducing the number of cigarettes per pack, releasing more economical products and even under-shifting, meaning the company assumes totally or partially the cost of the tax increase. While an overall positive impact is expected in the population in which the taxation is performed in terms of reduction of the prevalence of smoking, there are certain subgroups in which amplified outcomes are usually observed. In this sense, a systematic review concluded that when increasing the taxes, teenagers are two to three times more price-responsive than the general population, and that both the prevalence and the quantity of cigarettes smoked decrease [27]. Based on this evidence, increasing taxes and equalizing prices for all tobacco products (traditional and new products) should be a pivotal measure to limit tobacco purchase in adolescents. Other authors supporting the THR approach, however, have advocated for a differential taxing taking into account the supposedly different risks of the nicotine products [28]. In any case, we consider that a debate should be opened to discuss if new nicotine products should be limited only to current smokers who want to quit or reduce their consumption to avoid them being a gateway to nicotine for adolescents as we mentioned before.

To conclude, isolated measures on tobacco control have usually shown limited benefits. Consequently, we believe all of the above issues should be dealt with in comprehensive tobacco control policies.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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5. DISCUSIÓN CONJUNTA

La presente tesis doctoral aporta estimaciones de la potencial población elegible en caso de que se acabaran implementando programas de cribado de cáncer de pulmón en la UE basados en los criterios simplificados de riesgo utilizados en los ensayos NLST y NELSON, estimaciones con las que se podría orientar la provisión de recursos en los diferentes sistemas sanitarios. En este sentido, en el primer artículo de la tesis doctoral publicado en la revista Cancer Epidemiology[49], estimamos que alrededor de 17 millones de ciudadanos de la UE según los criterios NLST y alrededor de 34 millones según los criterios NELSON (4% y 8% de la población adulta, respectivamente) presentaban en 2014 un alto riesgo de desarrollar cáncer de pulmón. En un estudio previo realizado en EE. UU.[24], se estimó que alrededor del 6,2% de la población mayor de 40 años cumplía con los criterios de inclusión del NLST. Esta proporción solo es similar en nuestro estudio a las de las exfumadoras de los grupos de edad de entre 40 y 64 años y de más 65 años, y a la de los exfumadores de entre 40 y 64 años. En el resto de grupos de edad, las estimaciones obtenidas son considerablemente más altas en nuestro estudio. Esta diferencia puede estar explicada, parcialmente, por una menor prevalencia del consumo de tabaco en EE. UU.[50] en comparación con la UE.

En relación con las mujeres, en las que se ha observado un beneficio añadido en la reducción de la mortalidad por cáncer de pulmón en comparación con los hombres en algunos ensayos clínicos[19,25], hemos estimado que un 9,6% y un 22,4% de las fumadoras en la UE cumplen los criterios de inclusión en los ensayos NLST y NELSON, respectivamente. A nivel nacional, hemos observado que la etapa de la epidemia del tabaco[10] en la que se encuentran los Estados miembros tiene una clara influencia en la proporción de mujeres que presenta alto riesgo. En términos generales, en zonas de Europa donde las mujeres comenzaron a fumar antes durante el siglo XX (Europa Occidental y Norte de Europa), la proporción de las mismas a alto riesgo se aproxima, e incluso supera, a la de los hombres, como es el caso de Holanda, Dinamarca y Suecia. Por el contrario, en países donde las mujeres comenzaron a fumar más tarde (en los Países Bálticos, por ejemplo), las diferencias son todavía importantes, en general, entre las proporciones de hombres y mujeres que presentan alto riesgo.

Considerando a las fumadoras que se encuentran en edad de participar en programas de cribado de cáncer de mama y colorrectal (entre 50 y 69 años) en la UE, más de un 70% se encuentran a alto riesgo de desarrollar cáncer de pulmón de acuerdo a los criterios NELSON[51]. A este mismo respecto, en el segundo artículo de la tesis (en prensa en Archivos de Bronconeumología)[52], estimamos que, en un grupo de participantes en un cribado poblacional de cáncer de mama, alrededor de un 20% de fumadoras se encontraban a alto riesgo de desarrollar cáncer de pulmón según los criterios NLST y alrededor de un 40% de fumadoras según los criterios NELSON. Con relación a las exfumadoras, alrededor de un 20% se encontraban a alto riesgo. Los resultados de este estudio, atendiendo a los criterios NLST, están en línea con los de un estudio llevado a cabo a partir de datos de la Encuesta Nacional de Salud de España de 2011-2012, que estimaba la proporción de mujeres que presentaba alto riesgo de desarrollar cáncer de pulmón en participantes en un cribado de cáncer de mama en los últimos tres años[53]. Teniendo en cuenta que el número de invitadas al cribado de cáncer de mama en el centro en el que se llevó a cabo este estudio (Instituto Catalán de Oncología) es de unas 80.000 mujeres, estimamos que cerca de 9.300 y más de 13.000 mujeres según los criterios NLST y NELSON, respectivamente, serían elegibles para participar en un programa de cribado de cáncer de pulmón.

Aunque la atención primaria debe ser la base que sustente los programas de deshabituación por el seguimiento que puede ofrecer el personal sanitario al paciente, todo contacto con el sistema sanitario puede ser útil para promover el cambio de hábitos. En concreto, creemos que sería interesante aprovechar la oportunidad de aprendizaje (*teachable moment*)[32] que suponen los programas de cribado, especialmente el de mama por su alta participación, para anidar en ellos programas de deshabituación del tabaco. En este sentido, nuestras estimaciones de población que presenta alto riesgo podrían emplearse para dirigir los recursos necesarios para la implementación de dichos programas de deshabituación. Del mismo modo, si se acabaran implementando programas de cribado de cáncer de pulmón, otros programas de cribado poblacional de cáncer podrían ser un entorno en el que identificar individuos que presentan alto riesgo de desarrollar cáncer de pulmón.

Por otro lado, se ha propuesto la incorporación de biomarcadores de consumo de tabaco en los modelos de predicción de riesgo de cáncer de pulmón para aumentar la validez y la precisión de la estimación del consumo de tabaco[39]. En este sentido, en el manuscrito en revisión[54], se muestra que hay diferencias estadísticamente significativas en las concentraciones de biomarcadores específicos de cáncer de pulmón (NNK y NNAL) entre los fumadores diarios que se encuentran a alto riesgo y los fumadores diarios que no se encuentran a alto riesgo. Por ello creemos que la incorporación de dichas variables a los modelos podrían mejorar la discriminación del riesgo, ya que para mismas cantidades autorreportadas de consumo de tabaco puede darse variabilidad individual en el consumo[38] que se asocie a diferencias en las concentraciones de biomarcadores y, por tanto, en la carcinogénesis. En el mismo manuscrito se muestra que no hemos encontrado diferencias estadísticamente significativas en las concentraciones de biomarcadores entre hombres y mujeres que puedan explicar las diferencias en la mortalidad observada entre ambos en algunos ensayos clínicos[19,25].

En el artículo publicado en Environmental Research[55] se describe una asociación inversa entre el grado de implementación de las políticas de control del tabaco en Estados miembros de la UE estimado por cuartiles de la TCS y la probabilidad de presentar alto riesgo de cáncer de pulmón a nivel individual en 2017. A nivel nacional, las correlaciones analizadas entre el grado de implementación de las políticas de control de tabaco y los porcentajes de fumadores, exfumadores y alguna vez fumadores que presentan alto riesgo según los criterios NLST y NELSON son mayoritariemente negativas. Es decir, en aquellos países donde el desarrollo de las políticas de control del tabaco es más intenso, medido a través de las puntuaciones de la TCS[46], la proporción de individuos que presentan alto riesgo de cáncer de pulmón es menor. Además, hemos identificado un probable retardo entre la implementación de las políticas de control del tabaco y el efecto de las mismas sobre la reducción de la población que presenta alto riesgo de desarrollar cáncer de pulmón.

Previamente ya se había descrito un impacto positivo de la implementación de las políticas de control del tabaco sobre diferentes indicadores y resultados en salud[47,48,56]. Por todo ello, creemos que el refuerzo de dichas políticas, que han demostrado ser claramente costo-efectivas, aunque algunas de ellas no han sido habitualmente implementadas, como la ayuda al fumador para dejarlo, tendría un impacto positivo, entre otros resultados, en la reducción de población que presenta alto riesgo de desarrollar cáncer de pulmón.

En relación con la implementación de políticas de control del tabaco, en la editorial publicada en Expert Review of Respiratory Medicine[57], se discutieron diferentes aspectos relevantes para proteger a las generaciones futuras de enfermedades respiratorias, como el cáncer de pulmón, relacionadas con el control del tabaco. Entre estos puntos se destaca la necesidad de un mayor control de los nuevos productos de tabaco y de la publicidad en nuevos canales de información, de una regulación que amplíe los espacios al aire libre y privados libres de humo y de una mayor carga impositiva al tabaco.

Finalmente, creemos que el balance beneficio-riesgo de la implementación del cribado de cáncer de pulmón tiene que ser todavía completamente definido. En primer lugar, hay importantes amenazas para la validez externa de los resultados observados hasta ahora en el contexto de los ensayos clínicos. La reducción de la mortalidad se ha demostrado en estudios de muy elevada calidad, donde los recursos materiales y humanos fueron óptimos, tal y como reflejan los investigadores del NLST[15]. Además, las proporciones de falsos positivos y sobrediagnóstico han sido elevadas en diferentes ensayos[21]. Del mismo modo, hay que considerar la exposición a radiación y la posibilidad de inducción de cánceres, sobre todo en individuos a los que se les somete a análisis confirmatorio, a pesar de las mejoras en los equipos que han reducido las dosis de exposición. También es relevante la baja participación que se está registrando en EEUU en los programas de cribado, que limita la eficacia y eficiencia de la intervención[17]. Además, y aunque en esta tesis no se han realizado análisis económicos, se ha estimado que por cada cribado se podrían financiar 25 tratamientos de cesación del tabaco[21].

Valorando conjuntamente las estimaciones de individuos a alto riesgo a nivel comunitario[51], a nivel desagregado por Estado miembro[51] y en un grupo de participantes en un programa concreto de cribado de cáncer de mama[52], así como el probable efecto de la implementación de las políticas de control del tabaco en la UE en la reducción de la proporción de individuos a alto riesgo[55] y la evidencia disponible anteriormente comentada, creemos que la prevención primaria debe seguir siendo el nivel fundamental en el que sustentar la prevención de cáncer de pulmón.

6. LIMITACIONES

Los artículos incluidos en esta tesis tienen ciertas limitaciones que merecen ser comentadas. En primer lugar, tratándose de una limitación transversal en nuestros estudios, hemos aplicado los criterios de selección empleados en los estudios NLST y NELSON para delimitar la población que presenta alto riesgo de desarrollar cáncer de pulmón. Se ha comprobado que los criterios simplificados muestran un peor comportamiento que varios de los diferentes modelos de predicción de riesgo desarrollados[41]. En este sentido, por la menor sensibilidad que muestran los criterios NLST frente a otros modelos[23,58], es posible que estemos infraestimando la proporción de individuos que presentan alto riesgo. Esta limitación es parcialmente superada al complementar nuestras estimaciones con el uso de los criterios NELSON, que ofrecen una estimación más sensible por sus rangos de aplicación. En relación con este punto, en EE.UU., después de la recomendación positiva publicada por la USPSTF para la implementación de programas de cribado de cáncer de pulmón[16], se realizaron estudios de modelización para adaptar los criterios NLST a toda la población de EE.UU. y maximizar el rendimiento del cribado[59], por lo que la aplicación directa de los criterios NLST y NELSON en las poblaciones incluidas en nuestro estudio es posible que no se adapte a los diferentes perfiles de edad y actitud frente al tabaco a nivel nacional.

Por otro lado, los datos se han obtenido principalmente de bases de datos secundarias. Esto ha llevado a tener que asumir ciertas asunciones para responder a algunas de las preguntas de investigación planteadas en esta tesis. Como ejemplo, en el Eurobarómetro Especial 458 solo se recoge el número actual de cigarrillos fumados, por lo que se tuvo que imputar este consumo como constante desde el inicio. Además, en el Eurobarómetro no aparece reflejada la fecha de abandono de los exfumadores, por lo que se tuvo que asumir que los exfumadores habían dejado de fumar siguiendo una distribución uniforme.

Finalmente, por el diseño del estudio que dio lugar al artículo publicado en Environmental Research, no se puede asumir como causal la asociación entre la implementación de las políticas de control del tabaco en la UE y la proporción de individuos a riesgo. Es probable que esta posible asociación se pueda clarificar ampliando el marco temporal entre TCS y los futuros Eurobarómetros Especiales sobre consumo de tabaco.

7. CONCLUSIONES

1. Hay una importante proporción de mujeres en edad de participar en cribados poblacionales de cáncer en la Unión Europea (UE) que presenta alto riesgo de desarrollar cáncer de pulmón.
2. Los biomarcadores de consumo de tabaco específicos de cáncer de pulmón (NNK y NNAL) son significativamente mayores en fumadores diarios que presentan alto riesgo de cáncer de pulmón que en aquellos que no lo presentan.
3. No hemos podido identificar diferencias estadísticamente significativas en las concentraciones de biomarcadores de consumo de tabaco en saliva entre hombres y mujeres a alto riesgo de cáncer de pulmón.
4. En Estados miembros de la UE donde las mujeres se incorporaron antes al consumo de tabaco, la proporción de mujeres que presenta alto riesgo de desarrollar cáncer de pulmón es en general alta, e incluso supera a la proporción de hombres que presenta alto riesgo.
5. La mayor implementación de políticas de control de tabaco está asociada a una menor proporción de población que presenta alto riesgo de desarrollar cáncer de pulmón en la UE, tanto a nivel nacional como a nivel individual.

8. IMPLICACIONES EN SALUD PÚBLICA

1. Se podrían anidar programas de deshabituación del tabaco en programas de cribado poblacional de cáncer, especialmente de cáncer de mama, por la importante proporción de mujeres participantes en dichos cribados que presenta alto riesgo de desarrollar cáncer de pulmón, por la elevada participación registrada y por el carácter de oportunidad de aprendizaje de los cribados poblacionales.
2. Los programas de cribado poblacional de cáncer pueden ser un entorno favorable para identificar individuos que presentan alto riesgo de desarrollar cáncer de pulmón.
3. La incorporación de biomarcadores de consumo de tabaco, como la cotinina y las nitrosaminas específicas del tabaco, y más concretamente las relacionadas con el cáncer de pulmón (NNK y NNAL), a los modelos de predicción de riesgo de cáncer de pulmón podrían mejorar la selección de los individuos que presentan alto riesgo.
4. Se debe seguir apostando por implementar políticas amplias de control del tabaco.

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ANEXOS

ANEXO I. PROCESO EDITORIAL DEL ARTÍCULO «ESTIMATION OF THE ADULT POPULATION AT HIGH RISK OF DEVELOPING LUNG CANCER IN THE EUROPEAN UNION»

Carta de presentación del manuscrito a Cancer Epidemiology

Dear Editor,

Please find enclosed our manuscript entitled "Estimation of the adult population at high risk of developing lung cancer in the European Union" for your consideration.

We believe that in this particular moment, when the implementation of lung cancer screening in the EU is being discussed in the scientific community, the relevant conclusions arising from our manuscript on the proportion of citizens at high risk of lung cancer in every member state would have an important visibility in your journal to add further evidence to guide that decision.

The main text contains just a few words over the word limit. If necessary, we could rephrase some excerpts to adjust the manuscript to 3000 words.

I declare that all the authors, who approve this final manuscript, contributed intellectually and significantly to the work. In their name I also declare that the manuscript is original and it is not submitted anywhere other than your journal. The authors declare there are no conflicts of interest.

If deemed appropriate, we would of course be ready to provide further information about our data and methods.

Thank you very much for your kind attention.

Yours sincerely,
Jose M Martínez-Sánchez
E-mail: jmmartinez@uic.es

Respuesta del Editor y comentarios de los revisores

Ref: CANEP_2018_173
Title: Estimation of the adult population at high risk of developing lung cancer in the European Union
Journal: Cancer Epidemiology

Dear Dr. Martínez-Sánchez,

Thank you for submitting your manuscript to Cancer Epidemiology. We have completed the review of your manuscript. A summary is appended below. While revising the paper please consider the reviewers' comments carefully. We look forward to receiving your detailed response and your revised manuscript.

To submit your revised manuscript:

- Log into
  EVISE® at: http://www.evise.com/evise/faces/pages/navigation/NavController.jspx?JRNL_ACR=CANEP
- Locate your manuscript under the header 'My Submissions that need Revisions' on your 'My Author Tasks' view
- Click on 'Agree to Revise'
- Make the required edits
- Click on 'Complete Submission' to approve

What happens next?
After approving your submission you will receive a notification that the submission is complete. To track the status of your paper throughout the editorial process, log into
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Enrich your article to present your research with maximum impact. This journal supports the following Content Innovations:

I look forward to receiving your revised manuscript as soon as possible.

Kind regards,

Lucy Carpenter
Associate Editor
Cancer Epidemiology

Comments from the editors and reviewers:
-Reviewer 1

This is a well written article estimating the population at high risk of developing LC in the EU, it brings useful information to the discussion on lung cancer screening in a timely manner.

There are a couple of minor points that need to be addressed:

1 in introduction authors claim that among cancers associated with smoking LC is the deadliest. This is not the case, pancreatic cancer is the one with the lowest survival (see Eurocare 5 data in Lancet oncology, De Angelis 2014) and has an attributable fraction to tobacco smoking of about 30%.

2 in methods on page five the sentences where authors explain they estimated numbers of people at risk in the age groups covered by screening programs for other cancers is obscure and needs rewriting for clarity (from "We also calculated the aforementioned" to the end of the paragraph)

3 Limitations of the study in discussion need to have more information on the limits of the data used, and the assumptions taken to provide the estimates.

4 Authors provide projections of at risk populations which are very useful, but assume the the smoking prevalence to stay fixed, which is a debatable choice. Even though the Eurobarometer may say that smoking prevalence is stable overall from 2014, we know that different countries have different prevalence rates and patterns. However, this assumption could be made useful by carrying out a second projection (or more) considering optimal cessation and non-initiation rates to work out the possible future differences in populations at risk according to assumed tobacco consumption.

5. The importance of primary prevention and smoking cessation and non initiation campaigns should be stressed further.

-Reviewer 2

A well-written paper – I only have small comments / points of clarification.

INTRODUCTION: it may be worth clarifying in the first paragraph that the 0.7 m tobacco-related deaths in the EU annually are related to a range of cancers, as well as cardiovascular and respiratory diseases.

RESULTS: figures in the first para refer to current smokers?

DISCUSSION: last para on page 9 could be rephrased for clarity.

TABLE 1: needs 'women' added as row header.

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Respuesta a los revisores

Response to reviewers CANEP_2018_173

The authors would like to thank both reviewers for their feedback, which have improved the initial submission throughout. We enclose a point-by-point response. Besides, the modifications in the text of the manuscript have been highlighted.

Comments from the editors and reviewers:

Reviewer 1

This is a well written article estimating the population at high risk of developing LC in the EU, it brings useful information to the discussion on lung cancer screening in a timely manner.

Thank you for your positive comments on our research.

There are a couple of minor points that need to be addressed:

1 In introduction authors claim that among cancers associated with smoking LC is the deadliest. This is not the case, pancreatic cancer is the one with the lowest survival (see Eurocare 5 data in Lancet oncology, De Angelis 2014) and has an attributable fraction to tobacco smoking of about 30%.

Thank you for your interesting comment. We have relaxed the above-mentioned statement and now it reads as follows:

> "*Among the different types of cancer associated with smoking (e.g., lung, stomach, liver, urinary bladder), lung cancer, which is one of the deadliest [4],..."*

2 In methods on page five the sentences where authors explain they estimated numbers of people at risk in the age groups covered by screening programs for other cancers is obscure and needs rewriting for clarity (from "We also calculated the aforementioned" to the end of the paragraph)

As the reviewer suggested, we have modified the paragraph and now it reads as follows:

> *"We also calculated the prevalence of current and former smokers, means and standard deviations (SD) for the smoking pattern in the target age groups of breast, colorectal and cervical cancer screening programs, the only screening programs recommended to date by the Council of the EU [17]. For breast cancer, the nearly unanimous agreement on the target group among member states was followed (i.e., from 50 to 69 years) [21]. For cervical and colorectal cancer, since there is heterogeneity between target groups among*

countries in the EU [21], we delimited the age range from 25 to 64 years and from 50 to 69 years, respectively."

3 Limitations of the study in discussion need to have more information on the limits of the data used, and the assumptions taken to provide the estimates.

Thank you for your insight. We have expanded the paragraph regarding the limitations of the data source in the Discussion section as follows:

"The main limitations of our study rely on the use of the Special Eurobarometer 429 as the source of our data. Firstly, the aim of our research exceeds those of the Eurobarometer, and the ad-hoc estimation of the years after quitting smoking for former smokers may add some bias to our conclusions. In this sense, the Special Eurobarometer 429 does not provide information on quitting dates for former smokers. Hence, we estimated quitting dates via a uniform distribution, meaning the occurrence of the event giving up smoking was equiprobable for every year since the individual started smoking to their present age."

AND

"Besides, since specific data on individual historical tobacco consumption is not provided in the Eurobarometer, the present consumption of cigarettes for each cohort was used to calculate the lifetime smoking history in pack-years. On the other hand, the proportions of current smokers who would potentially reach the high-risk situation in five and ten years time were computed assuming constant the declared current consumption in the sample throughout those periods. Although this situation is unlikely to occur, this approach underscores the necessity of action in terms of smoking cessation, since if no action is taken, present smokers will effectively reach the high-risk status. In this sense, recent reviews assessing quit rates accomplished by different interventions showed that the increase in quit rates ranged from 24% to 338% between the intervention group and the control group [41]. However, the real impact of these interventions should be further analyzed since it would highly depend on the profile of those quitting smoking, including the variables age, history of tobacco consumption in pack-years, and other individual features which determine the overall risk profile (e.g., body mass index, other sources of exposure such as radon or asbestos, family history of lung cancer)."

4 Authors provide projections of at risk populations which are very useful, but assume the smoking prevalence to stay fixed, which is a debatable choice. Even though the Eurobarometer may say that smoking prevalence is stable overall from 2014, we know that different countries have different prevalence rates and patterns. However, this assumption could be made useful by carrying out a second projection (or more) considering optimal cessation and non-initiation rates to work

out the possible future differences in populations at risk according to assumed tobacco consumption.

Thank you for this interesting comment. As the reviewer mentioned, we have considered including different proportions of individuals potentially reaching the high-risk situation in the future introducing quit rates. In this sense, applying these quit rates would reduce the proportion of individuals who would reach the high-risk situation in five and ten years time. However, the real impact of these interventions should be further analyzed since they would highly depend on the profile of those quitting smoking, including their age, history of tobacco consumption or other individual features, which determine the overall risk profile (e.g., body mass index, other sources of exposure such as radon or asbestos, family history of lung cancer). Unfortunately, we used secondary data in our study (Eurobarometer) and we do not have the information needed to accurately design these new scenarios. We believe that the introduction of other assumptions might destabilize the estimation, which already includes some important ones. Moreover, the design of our study (cross-sectional) has several limitations to model these scenarios, which could be surpassed using a longitudinal study. We have mentioned this limitation as follows:

> *"On the other hand, the proportions of current smokers who would potentially reach the high-risk situation in five and ten years time were computed assuming constant the declared current consumption in the sample throughout those periods. Although this situation is unlikely to occur, this approach underscores the necessity of action in terms of smoking cessation, since if no action is taken, present smokers will effectively reach the high-risk status. In this sense, recent reviews assessing quit rates accomplished by different interventions showed that the increase in quit rates ranged from 24% to 338% between the intervention group and the control group [41]. However, the real impact of these interventions should be further analyzed since it would highly depend on the profile of those quitting smoking, including the variables age, history of tobacco consumption in pack-years, and other individual features which determine the overall risk profile (e.g., body mass index, other sources of exposure such as radon or asbestos, family history of lung cancer)."*

Besides, we have changed the word "projection" for "estimation" throughout the text, since projecting requires further data and fewer assumptions than the used in our analyses.

5. The importance of primary prevention and smoking cessation and non-initiation campaigns should be stressed further.

We totally agree with the reviewer. As the reviewer suggested, we have highlighted the importance of primary prevention as follows:

> *"However, smoking cessation policies have been seldom implemented in the EU [34], mainly due to budget limitations. For this reason, the member states*

are encouraged to implement policies to promote smoking cessation and reduce initiation. In this sense, there is a strong support among European citizens towards tobacco products regulations [35].

Reviewer 2

- **A well-written paper – I only have small comments / points of clarification.**

Thank you for your kind words on our paper

INTRODUCTION: it may be worth clarifying in the first paragraph that the 0.7 m tobacco-related deaths in the EU annually are related to a range of cancers, as well as cardiovascular and respiratory diseases.

Thank you for pointing this out. We have added this clarification and now the excerpt reads as follows:

"*Around 700,000 of these deaths, mainly related to a range of cancers and cardiorespiratory disorders, occur in the European Union (EU)"*

RESULTS: figures in the first para refer to current smokers?

Figures in the first paragraph refer to current, former, and ever smokers. We have re-written the first section of this paragraph which did not explicitly clarified it concerned current smokers and now it reads as follows:

"*Table 1 and Figure 1 show that, according to NLST and NELSON criteria, around one out of ten (11.6% of men and 9.6% of women) and nearly one out of four (24.6% of men and 22.4% of women) current smokers in the EU are at present at high risk of developing lung cancer, respectively."*

Moreover, the bar charts forming Figure 1 include information on the proportion of individuals at high risk of lung cancer for current smokers, former smokers, ever smokers and the whole population, also stratified by gender.

DISCUSSION: last para on page 9 could be rephrased for clarity.

We have rephrased the last paragraph of the Discussion as reviewer suggested as follows:

"Specific national-based studies based on modelling should be carried out to assess, in terms of effectiveness and cost-effectiveness, the implementation of lung cancer screening programs due to the aforementioned variability in the prevalence of individuals at high risk among member states and to healthcare system access and funding for each country"

TABLE 1: needs ‘women’ added as row header.

Thank you for catching this error. It has now been amended.

Carta de aceptación del artículo en Cancer Epidemiology

Ref: CANEP_2018_173_R1
Title: Estimation of the adult population at high risk of developing lung cancer in the European Union
Journal: Cancer Epidemiology

Dear Dr. Martínez-Sánchez,

I am pleased to inform you that your paper has been accepted for publication. My own comments as well as any reviewer comments are appended to the end of this letter. Now that your manuscript has been accepted for publication it will proceed to copy-editing and production.

Thank you for submitting your work to Cancer Epidemiology. We hope you consider us again for future submissions.

Kind regards,

Lucy Carpenter
Associate Editor
Cancer Epidemiology

Comments from the editors and reviewers:
- Reviewer 1

- The authors have adequately answered my minor reservations. I suggest to accept the manuscript for publication.

- Reviewer 2

- I am satisfied that the authors satisfactorily addressed all the comments and suggestions from reviewers. I think the paper warrants publication.

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ANEXO II. CUESTIONARIO DEL ESTUDIO «ESTIMACIÓN DEL RIESGO DE CÁNCER DE PULMÓN EN MUJERES QUE PARTICIPAN EN UN PROGRAMA DE CRIBADO POBLACIONAL DE CÁNCER DE MAMA»

Universitat Internacional de Catalunya

ICO Institut Català d'Oncologia

Fecha: □□□□□□

Ronda:_____

Entrevistador:_____

Fecha de Nacimiento: _____

Tal y como le he comentado, a continuación le haré unas preguntas sobre el consumo de tabaco y algunos datos sociodemográficos. En unos casos me tendrá que contestar directamente y en otros le leeré las respuestas. Por favor, conteste cuando le haya leído todas las opciones. Le pido, por favor, que me conteste con toda sinceridad y libertad, ya que no hay respuestas correctas ni incorrectas. Si le parece bien, empezamos.

P1. De las siguientes afirmaciones, indique cuál describe mejor su comportamiento actual respecto al tabaco (LEER)

1. Fuma cada día → pasar a la pregunta 2
2. Fuma ocasionalmente → pasar a la pregunta 2
3. Ahora no fuma, pero antes fumaba cada día (al menos un cigarrillo al día) → pasar a la pregunta 11
4. Ahora no fuma, pero antes fumaba ocasionalmente → pasar a la pregunta 11
5. No ha fumado nunca → pasar a la pregunta 17

FUMADORES ACTUALES

P2. ¿A qué edad comenzó usted a fumar regularmente? _____

P3. ¿Qué cantidad de cigarrillos fuma usted regularmente cada día? _____

P4. ¿Cuánto tarda en fumar el primer cigarrillo después de levantarse? (LEER)

1. 5 minutos o menos
2. De 6 a 30 minutos
3. De 31 a 60 minutos
4. Más de 60 minutos

P5. ¿Está considerando seriamente reducir el número de cigarrillos que fuma habitualmente?

1. Sí
2. No
9. NS/NC

P6. ¿Está considerando seriamente la posibilidad de…? (LEER)

1. Dejar de fumar durante el próximo mes
2. Dejar de fumar durante los próximos 6 meses
3. Dejar de fumar, pero no durante los próximos 6 meses
4. No intentará dejar de fumar
9. NS/NC

P7. ¿Ha intentado dejar de fumar alguna vez en su vida?
1. Sí → ¿Cuántas veces? ……..
2. No →**PASAR PREGUNTA 17**
9. NS/NC

P8. ¿y en los los últimos 12 meses?
1. Sí → ¿Cuántas veces? ……..
2. No
9. NS/NC

P9. Para dejar de fumar, ¿recibió alguna vez intervención por algún profesional sanitario (médico/a, enfermero/a, farmacéutico/a, psicólogo/a, etc.)?

1. Sí → ¿Qué tipo de profesional? ……
2. No
9. NS/NC

P10. Cuando ha intentado dejar de dejar de fumar, ¿coincidió con alguno de estos momentos? LEER (RESPUESTA MULTIPLE)

1. Un embaraza.
2. Cuándo me diagnosticaron una enfermedad → ¿Cuál? ……..
3. Una consulta con el médico (de cabecera o especialista)
4. Una prueba hospitalaria (con o sin ingreso)
5. Otro momento en particular → ¿Cuál? ……
6. No fue en ningún momento en particular
9. NS/NC

EXFUMADORES

P11. ¿A qué edad comenzó a fumar regularmente? .....

P12. ¿A qué edad dejó de fumar? .....

P13. ¿Qué cantidad de cigarrillos fumaba usted regularmente cada día? _____

P14. ¿Utilizó algún tratamiento para dejar de fumar tabaco?

1. Si → ¿Qué tratamiento?: _____
2. No

P15. Para dejar de fumar, ¿recibió intervención por algún profesional sanitario (médico/a, enfermero/a, farmacéutico/a, psicólogo/a, etc.)?

1. Sí → ¿Qué tipo de profesional? ……
2. No
9. NS/NC

P16. Cuando decidió dejar de fumar, ¿coincidió con alguno de estos momentos? LEER

1. Un embarazo.
2. Cuándo me diagnosticaron una enfermedad → ¿Cuál? ……
2. Una consulta con el médico (de cabecera o especialista)
3. Una prueba hospitalaria (con o sin ingreso)
4. Otro momento en particular → ¿Cuál? ……
5. No fue en ningún momento en particular
9. NS/NC

TODAS

P17. ¿Cuál es su nivel máximo de estudios finalizados? NO LEER AGRUPAR SEGÚN RESPUESTA

1. Primarios y sin estudios
2. Secundaros
3. Universitarios
9. NS/NC

A continuación le realizaré unas preguntas sobre percepción del riesgo de padecer algún cáncer en comparación con las personas de su edad (50-69 años).

P18. En comparación con el resto de personas de su edad (50-69 años), ¿qué riesgo piensa que tiene Ud. de padecer un cáncer de _____ a lo largo de su vida? Leer cada lugar y preguntar: **(LEER)**

P.19 ¿y en una escala de 0 a 10? (donde 0 es ningún riesgo y 10 el máximo riesgo)

	1. Pienso que tengo más riesgo	2. Pienso que tengo igual riesgo	3. Pienso que tengo menos riesgo	**P19. escala**
0. Cáncer de mama				
1. Cáncer de pulmón				
2. Cáncer de colón				
3. Cáncer de cérvix				
4. Otro cáncer. Especificar: _____				

P20. De qué tipo de cáncer cree que usted que tiene un mayor riesgo de padecer y/o morir en los próximos años.

1. Cáncer de mama.
2. Cáncer de colon
3. Cáncer de pulmón
4. Cáncer de cérvix
5. Otro tipo de cáncer → ¿Cuál? .....
9. NS/NC

RECONTACTO

¿Estaría de acuerdo en que nos volviéramos a poner en contacto con usted para continuar con este estudio sobre tabaquismo?

1. Sí ► *Confirmar el nombre y la dirección y anotad el teléfono y la dirección electrónica en la Hoja de re-contacto*
2. No

ANEXO III. PROCESO EDITORIAL DEL ARTÍCULO «ESTIMACIÓN DEL RIESGO DE CÁNCER DE PULMÓN EN MUJERES QUE PARTICIPAN EN UN PROGRAMA DE CRIBADO POBLACIONAL DE CÁNCER DE MAMA»

Carta de presentación a Archivos de Bronconeumología

Estimada editora:

Adjunto a esta carta se encuentra nuestro manuscrito titulado "Estimación del riesgo de cáncer de pulmón en mujeres que participan en un programa de cribado poblacional de cáncer de mama" para que considere la publicación en su revista como Original.

Creemos que en este momento tan concreto, en el que la posible implementación del cribado de cáncer de pulmón en la Unión Europea se está discutiendo en la comunidad científica, las conclusiones que surgen de nuestro manuscrito pueden añadir más evidencia para guiar esta decisión.

Declaro que todos los autores, que aprueban la versión final de este manuscrito, contribuyeron intelectual y significativamente al trabajo. En su nombre también declaro que el manuscrito es original, que no se encuentra en revisión en ninguna otra revista y que cedemos los derechos de publicación a SEPAR. Los autores declaramos no tener ningún conflicto de interés relacionado directa o indirectamente con los contenidos del manuscrito.

Si lo considera apropiado, estaríamos encantados de proporcionar más información sobre nuestros datos y métodos.

Muchas gracias por su atención,

Reciba un cordial saludo,
Jose M Martínez-Sánchez
E-mail: jmmartinez@uic.es

Comentarios de la editora y los revisores de Archivos de Bronconeumología

Apreciados autores:
Atendiendo a los comentarios de nuestros expertos revisores y a los estándares de nuestra revista, le comunicamos que su manuscrito "Estimación del riesgo de cáncer de pulmón en mujeres que participan en un programa de cribado poblacional de cáncer de mama Estimation of the risk of lung cancer in women participating in a population-based breast cancer screening program"(Ref. ARBR-D-19-00071) no puede ser aceptado en su formato actual, si bien estamos dispuestos a evaluar una versión revisada del mismo, en la que se tengan en cuenta todos los comentarios planteados por los revisores (ver a continuación). A su vez deberán preparar un documento aparte donde se dé respuesta a todos y a cada uno de los comentarios de los revisores, incluyendo los propios comentarios planteados por éstos. Los cambios introducidos en la versión revisada deberán estar debidamente marcados en color para ser visualizados fácilmente por los revisores y el Editor.
Es nuestro deseo recordarle que una versión revisada no garantiza la aceptación inmediata del manuscrito en la revista, ya que podría no alcanzar todavía la suficiente prioridad para su aceptación definitiva en la misma.
Esperamos recibir su versión revisada en los próximos 2 meses. En el caso de que no sea así y no se nos notifique por adelantado entenderemos que desestima el envío de la versión revisada de su manuscrito, y por consiguiente, de su publicación en la revista.
Le agradecemos la confianza depositada en nuestra Revista y esperamos recibir la versión revisada del manuscrito dentro del plazo de tiempo establecido.

Reciba un cordial saludo.

Atentamente,

Esther Barreiro
Editora jefe
Archivos de Bronconeumología
www.archbronconeumol.org

En el caso de tratarse de un Original, en la versión revisada por los autores, será obligatorio incluir un resumen gráfico que se publicará junto con el artículo. Ver las instrucciones de cómo elaborar un resumen gráfico en la página web de la revista

Reviewer #1: Algunas expresiones gramaticales probablemente se podrían mejorar. Por ejemplo la proporción de mujeres a alto riesgo de desarrollar cáncer de pulmón…. debería en mi opinión ser sustituida por la proporción de mujeres que presentan alto riesgo de desarrollar…. Otra: …"como proxy de riesgo cáncer de pulmón"……. O esta:… condiciones que ofrece como teachable moment, incluso

si….

No es completamente exacto asociar el cumplir los criterios de inclusión en los estudios NLST o Nelson con tener alto riesgo de cáncer de pulmón dado que en diversos estudios se ha comprobado que la sensibilidad de tales criterios para predecir CP es baja y además hay una importantes proporción de pacientes que sin cumplir criterios NLST sí que desarrollan CP. Por tanto si se podría afirmar que los pacientes cumplen criterios de inclusión en los estudios NLST o Nelson pero solo esto.

Se debe hacer referencia en la discusión a estas proporciones de pacientes que padecen CP sin cumplir criterios de entrada en NLST o Nelson y los que cumpliendo criterios no padecen CP. Aconsejo revisar al menos estas dos referencias bibliográficas: Sanchez-Salcedo et al. Improving Selection Criteria for Lung Cancer Screening. The Potential Role of Emphysema. American Journal of Respiratory and Critical Care Medicine Volume 191 Number 8 April 15 2015. Y: Pérez-Martínez O, Vidal-García I, Montero-Martínez C, Provencio M, Ruano-Ravina A. Description and Survival of Stage I and II Lung Cancer Patients. Arch Bronconeumol. 2018 Aug;54(8):420-426. doi: 10.1016/j.arbres.2018.02.007

Cuando se afirma: "Se observa una tendencia creciente en la proporción de mujeres a elevado riesgo a medida que aumenta la dependencia al tabaco según el Test de Fagerström breve. Además, atendiendo a los criterios NELSON, se observa una tendencia decreciente en la proporción de mujeres a elevado riesgo a medida que el estado de cambio avanza hacia el estado de preparación" se debe especificar si alcanza o no diferencias estadísticamente significativas

Hemos de ser cautelosos al afirmar: …"a favor de las mujeres al ser la reducción de la mortalidad por cáncer de pulmón mucho mayor que en hombres (alrededor de un 26% para hombres y de hasta un 61% para mujeres en diez años" …. En efecto la reducción del riesgo en los hombres es un 26%, pero en las mujeres cae hasta 0,61, es decir la reducción es del 39% y la P es 0.0543 con lo que en ese momento no se alcanzó diferencia significativa

En mi opinión sería de gran interés llevar a cabo con los datos del presente estudio un cálculo de cual sería el número de mujeres que, siguiendo los criterios de inclusión de NLST y Nelson, podrían ser objeto de estudio en un eventual programa de cribado de CP en el Área geográfica analizada. Se podría incluir en el original reduciendo significativamente la información presentada en el texto sobre lo expuesto en la tabla 3, que en buena medida es hipotético.

Se deberá aportar información sobre la teórica población de mujeres susceptibles de entrar en programas de cribado en su área geográfica de estudio. Esto podría ser útil para una eventual previsión de población y recursos precisos en el marco de proyectos futuros de cribado en España.

Bibliografía:
Presentación de las referencias bibliográficas. Existen algunas discrepancias con las normas que constan en la "Guía para autores": no es preciso poner el número

entre paréntesis que sigue al número de volumen. Por ejemplo cita Nº2: 48(2), la Nº 6: 30 (2), etc…
comprobar, por favor, que se mantiene el acceso a la cita Nº 19. Yo personalmente no he podido acceder. Si no hubiera acceso buscar una cita alternativa

Reviewer #3: Estimación del riesgo de cáncer de pulmón en mujeres que participan en el cribado de cáncer de mama.

Estudio interesante que calcula el riesgo de cáncer de pulmón según los criterios de los ensayos clínicos que existen en la actualidad para llevar a cabo el cribado del cáncer de pulmón (NLST y NELSON)

Recomendaciones:

Introducción línea 22.

Recomendaría incluir en el texto as cifras de supervivencia observadas poblacional observadas en España para hombres y mujeres publicadas en la siguiente publicación:

Clin Transl Oncol. 2018 Feb;20(2):201-211. doi: 10.1007/s12094-017-1710-6. Epub 2017 Jul 17. Cancer survival in adult patients in Spain. Results from nine population-based cancer registries. Chirlaque MD1,2, Salmerón D3,4, Galceran J5, Ameijide A5, Mateos A6, Torrella A7, Jiménez R8, Larrañaga N4,9, Marcos-Gragera R10, Ardanaz E4,11, Sant M12, Minicozzi P12, Navarro C3,4, Sánchez MJ4,13; REDECAN Working Group.

Introducción línea 39, la medidas de prevención primaria no solo disminuyen la mortalidad sino también la incidencia por cáncer de pulmón.

Clin Transl Oncol. 2018 Feb;20(2):201-211. doi: 10.1007/s12094-017-1710-6. Epub 2017 Jul 17. Cancer survival in adult patients in Spain. Results from nine population-based cancer registries. Chirlaque MD1,2, Salmerón D3,4, Galceran J5, Ameijide A5, Mateos A6, Torrella A7, Jiménez R8, Larrañaga N4,9, Marcos-Gragera R10, Ardanaz E4,11, Sant M12, Minicozzi P12, Navarro C3,4, Sánchez MJ4,13; REDECAN Working Group.

En la introducción recomendaría añadir las tendencias del cáncer de pulmón en la mujer en España en los últimos años publicados en la siguiente publicación:
Clin Transl Oncol. 2017 Jul;19(7):799-825. doi: 10.1007/s12094-016-1607-9. Epub 2017 Jan 16. Cancer incidence in Spain, 2015. Galceran J1,2, Ameijide A3,

Carulla M3, Mateos A4, Quirós JR5, Rojas D6, Alemán A7, Torrella A8, Chico M9, Vicente M10, Díaz JM11, Larrañaga N12,13, Marcos-Gragera R14,15, Sánchez MJ13,16,17, Perucha J18, Franch P19, Navarro C13,20,21, Ardanaz E13,22, Bigorra J3, Rodrigo P23, Bonet RP24; REDECAN Working Group.
Comentario general:

En general mejoraría la redacción del texto

Respuesta a los revisores de Archivos de Bronconeumología

Ref. ARBR-D-19-00071

Estimación del riesgo de cáncer de pulmón en mujeres que participan en un programa de cribado poblacional de cáncer de mama

Estimation of the risk of lung cancer in women participating in a population-based breast cancer screening program

Queremos agradecer los útiles comentarios a nuestro trabajo de ambos revisores/as. A continuación respondemos punto por punto a todos ellos.

Reviewer #1:

Algunas expresiones gramaticales probablemente se podrían mejorar. Por ejemplo la proporción de mujeres a alto riesgo de desarrollar cáncer de pulmón…. debería en mi opinión ser sustituida por la proporción de mujeres que presentan alto riesgo de desarrollar…. Otra: ..."como proxy de riesgo cáncer de pulmón"……. O esta:… condiciones que ofrece como teachable moment, incluso si….

Como nos recomienda el/la revisor/a, hemos modificado estas y otras expresiones a lo largo de todo el manuscrito para mejorar el estilo.

No es completamente exacto asociar el cumplir los criterios de inclusión en los estudios NLST o Nelson con tener alto riesgo de cáncer de pulmón dado que en diversos estudios se ha comprobado que la sensibilidad de tales criterios para predecir CP es baja y además hay una importantes proporción de pacientes que sin cumplir criterios NLST sí que desarrollan CP. Por tanto si se podría afirmar que los pacientes cumplen criterios de inclusión en los estudios NLST o Nelson pero solo esto.
Se debe hacer referencia en la discusión a estas proporciones de pacientes que padecen CP sin cumplir criterios de entrada en NLST o Nelson y los que cumpliendo criterios no padecen CP. Aconsejo revisar al menos estas dos referencias bibliográficas:
Sanchez-Salcedo et al. Improving Selection Criteria for Lung Cancer Screening. The Potential Role of Emphysema. American Journal of Respiratory and Critical Care Medicine Volume 191 Number 8 April 15 2015.
Y: Pérez-Martínez O, Vidal-García I, Montero-Martínez C, Provencio M, Ruano-Ravina A. Description and Survival of Stage I and II Lung Cancer Patients. Arch Bronconeumol. 2018 Aug;54(8):420-426. doi: 10.1016/j.arbres.2018.02.007

Muchas gracias por el comentario. Estamos de acuerdo con el/la revisor/a que se trata de una limitación del estudio que merece ser ampliada en la discusión. Por ello, hemos añadido el siguiente extracto en la Discusión del manuscrito:

"Nuestro estudio tiene ciertas limitaciones que merecen ser comentadas. Por un lado, la aplicación de los criterios NLST y NELSON, que incorporan únicamente las variables edad y consumo acumulado de tabaco, tiene peor comportamiento a la hora de delimitar la población que presenta alto riesgo que los modelos de predicción de riesgo, que incluyen otros factores individuales, como exposiciones a cancerígenos (radón, amianto), factores genéticos o enfermedades subyacentes, entre otros [40]. En concreto, se ha observado una menor sensibilidad de los criterios NLST y NELSON en comparación con los modelos de predicción [33], principalmente por la no inclusión de las mencionadas variables que sí se incluyen en los modelos de predicción y que explican una buena parte del riesgo de cáncer pulmón. En este sentido, nuestra estimación esté probablemente infravalorando la proporción de mujeres que participan en el cribado de cáncer de mama y que presentan riesgo elevado, y por tanto un número relevante de cánceres de pulmón podrían pasar desapercibidos. Esta situación ya se ha observado en determinados registros de cáncer de pulmón en diferentes países, en los que una proporción limitada de pacientes con cáncer de pulmón cumplían los criterios NLST [34]."

Cuando se afirma: "Se observa una tendencia creciente en la proporción de mujeres a elevado riesgo a medida que aumenta la dependencia al tabaco según el Test de Fagerström breve. Además, atendiendo a los criterios NELSON, se observa una tendencia decreciente en la proporción de mujeres a elevado riesgo a medida que el estado de cambio avanza hacia el estado de preparación" se debe especificar si alcanza o no diferencias estadísticamente significativas

Como nos recomienda el/la revisor/a, hemos aclarado en el manuscrito este punto del siguiente modo:

"Se observa una tendencia creciente, estadísticamente significativa, en la proporción de mujeres que presentan un riesgo elevado a medida que aumenta la dependencia al tabaco según el Test de Fagerström breve. Además, atendiendo a los criterios NELSON, se observa una tendencia decreciente, no estadísticamente significativa, en la proporción de mujeres a elevado riesgo a medida que el estado de cambio avanza hacia el estado de preparación (Tabla 2)."

Hemos de ser cautelosos al afirmar: ..."a favor de las mujeres al ser la reducción de la mortalidad por cáncer de pulmón mucho mayor que en hombres (alrededor de un 26% para hombres y de hasta un 61% para mujeres en diez años" .... En efecto la reducción del riesgo en los hombres es un 26%, pero en las mujeres cae hasta 0,61, es decir la reducción es del 39% y la P es 0.0543 con lo que en ese momento no se alcanzó diferencia significativa

Le agradecemos su exhaustividad a la hora de revisar el manuscrito.

Al no haberse publicado todavía los resultados finales del estudio NELSON solo hemos tenido acceso a los resultados preliminares a través de portales web, principalmente *The ASCO Post* y *MedPage Today*. Efectivamente, la reducción del 61% en la mortalidad en mujeres que habíamos reportado no se corresponde con la reducción a 10 años. En línea con lo que nos apunta en su comentario, en http://www.ascopost.com/issues/october-25-2018/nelson-trial/, la información dice lo siguiente: "At year 10, there were 214 lung cancer deaths in the male control arm and 157 deaths in the screened arm. The lung cancer mortality rate ratio for men in the screened vs unscreened arm was 0.74 (26% reduction, P = .0003). At 10 years, the lung cancer mortality rate ratio in women was 0.61 (39% reduction, P = .0054)." Hemos modificado la información en relación al estimador de la razón de tasas de incidencia, que también se corresponde con la información de https://www.medpagetoday.com/meetingcoverage/iaslc/75341, pero no hemos incorporado información de la significación estadística, ya que hemos visto que hay discrepancias en el p-valor entre, al menos, las dos fuentes que mencionamos.

En mi opinión sería de gran interés llevar a cabo con los datos del presente estudio un cálculo de cual sería el número de mujeres que, siguiendo los criterios de inclusión de NLST y Nelson, podrían ser objeto de estudio en un eventual programa de cribado de CP en el Área geográfica analizada. Se podría incluir en el original reduciendo significativamente la información presentada en el texto sobre lo expuesto en la tabla 3, que en buena medida es hipotético.
Se deberá aportar información sobre la teórica población de mujeres susceptibles de entrar en programas de cribado en su área geográfica de estudio. Esto podría ser útil para una eventual previsión de población y recursos precisos en el marco de proyectos futuros de cribado en España.

Muchas gracias por darnos su perspectiva con respecto a estos asuntos. Como nos sugiere el/la revisor/a, hemos optado por retirar la tabla 3 del manuscrito y en su lugar, hemos estimado el número de mujeres que serían elegibles según los criterios NLST y NELSON en el programa de cribado poblacional del cáncer de mama del Instituto Catalán de Oncología si se implementara el cribado de cáncer pulmón. Hemos recogido esta información en el apartado de Resultados del manuscrito de la siguiente forma:

> "Asumiendo estas proporciones, y teniendo en cuenta que aproximadamente 52.000 mujeres participan en el cribado poblacional de cáncer de mama, alrededor de 4.150 participantes según los criterios NLST y de 6.300 participantes según los criterios NELSON serían elegibles en caso de que se implementara el cribado de cáncer de pulmón."

Y también en Discusión del manuscrito:

> "Según nuestras estimaciones, de las 80.000 mujeres invitadas al cribado de cáncer de mama en nuestro centro, cerca de 6.400 según los criterios NLST y

más de 9.700 según los criterios NELSON formarían parte de un hipotético cribado de cáncer de pulmón."

Bibliografía:
Presentación de las referencias bibliográficas. Existen algunas discrepancias con las normas que constan en la "Guía para autores": no es preciso poner el número entre paréntesis que sigue al número de volumen. Por ejemplo cita Nº2: 48(2), la Nº 6: 30 (2), etc...
comprobar, por favor, que se mantiene el acceso a la cita Nº 19. Yo personalmente no he podido acceder. Si no hubiera acceso buscar una cita alternativa

Gracias, de nuevo, por su exhaustividad al revisar el manuscrito.

Hemos eliminado los números entre paréntesis de todas las referencias. Además, la referencia nº19 ha sido actualizada a la siguiente que sí tiene acceso al link:

19. The ASCO Post. Nelson Lung Cancer Screening Study Confirms NLST Results. http://www.ascopost.com/issues/october-25-2018/nelson-trial/.

Reviewer #3:

Estimación del riesgo de cáncer de pulmón en mujeres que participan en el cribado de cáncer de mama.

Estudio interesante que calcula el riesgo de cáncer de pulmón según los criterios de los ensayos clínicos que existen en la actualidad para llevar a cabo el cribado del cáncer de pulmón (NLST y NELSON)

Muchas gracias por el amable comentario a nuestro estudio.

Recomendaciones:

Introducción línea 22.

Recomendaría incluir en el texto as cifras de supervivencia observadas poblacional observadas en España para hombres y mujeres publicadas en la siguiente publicación:
Clin Transl Oncol. 2018 Feb;20(2):201-211. doi: 10.1007/s12094-017-1710-6. Epub 2017 Jul 17. Cancer survival in adult patients in Spain. Results from nine population-based cancer registries. Chirlaque MD1,2, Salmerón D3,4, Galceran J5, Ameijide A5, Mateos A6, Torrella A7, Jiménez R8, Larrañaga N4,9, Marcos-Gragera R10, Ardanaz E4,11, Sant M12, Minicozzi P12, Navarro

C3,4, Sánchez MJ4,13; REDECAN Working Group.

Gracias por su recomendación. Efectivamente, los datos de supervivencia a nivel nacional son pertinentes en nuestro estudio. Como nos recomienda el/la revisor/a, hemos añadido el siguiente extracto en la Introducción del manuscrito:

> "Fumar está asociado a diferentes patologías, incluidos varios tipos de cáncer (vejiga o pulmón, por ejemplo) [61]. Uno de los de mayor letalidad es el cáncer de pulmón [62], con una tasa de supervivencia en España del 37,7% al año del diagnóstico, del 14,9% a los tres años y del 10,7% a los cinco años[6]."

Introducción línea 39, la medidas de prevención primaria no solo disminuyen la mortalidad sino también la incidencia por cáncer de pulmón. Clin Transl Oncol. 2018 Feb;20(2):201-211. doi: 10.1007/s12094-017-1710-6. Epub 2017 Jul 17. Cancer survival in adult patients in Spain. Results from nine population-based cancer registries. Chirlaque MD1,2, Salmerón D3,4, Galceran J5, Ameijide A5, Mateos A6, Torrella A7, Jiménez R8, Larrañaga N4,9, Marcos-Gragera R10, Ardanaz E4,11, Sant M12, Minicozzi P12, Navarro C3,4, Sánchez MJ4,13; REDECAN Working Group.

Gracias por el comentario, que compartimos. Como nos sugiere, hemos completado ese extracto, y queda como sigue:

> "Por la idiosincrasia del cáncer de pulmón, las actividades de prevención primaria (deshabituación tabáquica y prevención del tabaquismo) son esenciales para disminuir la incidencia y, por tanto, las tasas de mortalidad."

En la introducción recomendaría añadir las tendencias del cáncer de pulmón en la mujer en España en los últimos años publicados en la siguiente publicación:

Clin Transl Oncol. 2017 Jul;19(7):799-825. doi: 10.1007/s12094-016-1607-9. Epub 2017 Jan 16. Cancer incidence in Spain, 2015. Galceran J1,2, Ameijide A3, Carulla M3, Mateos A4, Quirós JR5, Rojas D6, Alemán A7, Torrella A8, Chico M9, Vicente M10, Díaz JM11, Larrañaga N12,13, Marcos-Gragera R14,15, Sánchez MJ13,16,17, Perucha J18, Franch P19, Navarro C13,20,21, Ardanaz E13,22, Bigorra J3, Rodrigo P23, Bonet RP24; REDECAN Working Group.

Hemos añadido la información que nos recomienda, quedando ese extracto como sigue:

> "Entre las mujeres, la mortalidad por cáncer de pulmón está en aumento y se ha pronosticado que superará a la de cáncer de mama en los próximos años en diversos países de ingresos medios o altos [63], incluido España [64], consecuencia de una tendencia creciente en la tasa de incidencia de cáncer

de pulmón en mujeres, como se ha podido observar en España, desde un 7% entre 1993 y 1997 hasta un 11,2% entre 2003 y 2007[10]."

Comentario general:

En general mejoraría la redacción del texto

Como nos recomienda el/la revisor/a, hemos cambiado expresiones a lo largo del texto para mejorar el estilo.

Comentarios de la editora y los revisores de Archivos de Bronconeumología (II)

Apreciados autores:

Todos los revisores consideran que la versión revisada de su manuscrito"Estimación del riesgo de cáncer de pulmón en mujeres que participan en un programa de cribado poblacional de cáncer de mama Estimation of the risk of lung cancer in women participating in a population-based breast cancer screening program"(Ref. ARBR-D-19-00071R1 ha sido muy mejorada, sin embargo aún existen algunos problemas que deberán subsanarse en una nueva revisión previamente a la obtención de la aceptación definitiva.

A su vez deberán preparar un documento aparte donde se dé respuesta a todos y a cada uno de los comentarios de los revisores, incluyendo los propios comentarios planteados por todos los revisores. Los cambios introducidos en la versión revisada deberán estar debidamente marcados para ser visualizados fácilmente por los revisores.

Esperamos recibir su versión revisada en los próximos 15 días. En el caso de que no sea así y no se nos notifique por adelantado entenderemos que desestima el envío de la versión revisada de su manuscrito.

Le agradecemos la confianza depositada en nuestra Archivos de Bronconeumología.

Reciba un cordial saludo.

Atentamente,

Esther Barreiro
Editora jefe
Archivos de Bronconeumología
www.archbronconeumol.org

Comentarios editoriales:
Los autores deberán mejorar la redacción en general del texto del manuscrito. Se aconseja revisar detenidamente las frases de todas las secciones y evitar el uso de oraciones y expresiones excesivamente coloquiales e innecesarias en un texto científico. En este sentido, expresiones del tipo "así pues" o similares deberán ser eliminadas del texto.

Reviewer #1: En mi opinión se han aceptado adecuadamente las recomendaciones y llevado a cabo los cambios que propusimos con el fin de mejorar el original. Muchas gracias.
Quizá se podría mejorar la redacción del manuscrito.

Reviewer #3: Gracias por incorporar los cambios sugeridos por los revisores.

Respuesta a los revisores (II)

Gracias a los revisores externos por sus amables comentarios, y al Comité Editorial por revisar exhaustivamente el manuscrito.

Los autores hemos vuelto a revisar el manuscrito para mejorar el estilo como nos recomendaron. Adjuntamos la nueva versión con los cambios remarcados en amarillo

Carta de aceptación del manuscrito en Archivos de Bronconeumología

Apreciados autores:

Tras un proceso de revisión por parte de los miembros del Comité Editorial nos es grato comunicarle que el Manuscrito "Estimación del riesgo de cáncer de pulmón en mujeres que participan en un programa de cribado poblacional de cáncer de mama Estimation of the risk of lung cancer in women participating in a population-based breast cancer screening program"(Ref. ARBR-D-19-00071R2) ha sido aceptado bajo el formato actual para su publicación en Archivos de Bronconeumología.

Recuerde que en su momento le remitiremos las pruebas de autor en formato PDF a esta misma dirección electrónica.

Le agradecemos la confianza depositada en nuestra Revista y esperamos que siga contando con ella para futuros trabajos de su grupo.

Reciba un cordial saludo.

Atentamente,

Esther Barreiro
Editora jefe
Archivos de Bronconeumología
www.archbronconeumol.org

ANEXO IV. PROCESO EDITORIAL DEL ARTÍCULO «RELATION BETWEEN TOBACCO CONTROL POLICIES AND POPULATION AT HIGH RISK OF DEVELOPING LUNG CANCER IN THE EUROPEAN UNION»

Carta de presentación a Environmental Research

Dear Editor,

Please find enclosed our manuscript titled "Relation between tobacco control policies and risk of lung cancer in the European Union".

We believe that in this specific moment, in which the possible implementation of lung cancer screening in the European Union is being discussed within the scientific community, the conclusions arising from this manuscript may add more evidence to guide this decision.

All of the authors have read and approved the paper and I confirm it has not been published previously nor is it being considered by any other peer-reviewed journal. Data have been obtained from public sources.

If you deem it necessary, we will be pleased to provide more information on our data and methods.

Thank you for your attention

Jose M Martínez-Sánchez
E-mail: jmmartinez@uic.es

Comentarios del Editor y de los revisores de Environmental Research

Ms. No.: ER-19-762
Title: Relation between tobacco control policies and risk of lung cancer in the European Union
Corresponding Author: Dr. Jose M Martínez-Sánchez
Authors: Adrián González-Marrón; Juan Carlos Martín-Sánchez; Queralt Miró; Nuria Matilla-Santander; Àurea Cartanyà-Hueso; Lorelei Mucci;

Dear Dr. Martínez-Sánchez,

Thank you for submitting your manuscript to Environmental Research. The reviewers have made suggestions which the Editor feels would improve your manuscript. The Editor encourages you to consider these comments and make an appropriate revision of your manuscript. The reviewers' comments are below.

Please submit your revision online within 45 days by logging onto the Elsevier Editorial System for Environmental Research:

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When submitting your revised paper, we ask that you include the following items:

Manuscript and Figure Source Files (mandatory)

REVISED Manuscript (Marked-up with changes)

REVISED Manuscript (Clean version)

We cannot accommodate PDF manuscript files for production purposes. We also ask that when submitting your revision you follow the journal formatting guidelines. Figures and tables may be embedded within the source file for the submission as long as they are of sufficient resolution for Production. For any figure that cannot be embedded within the source file (such as *.PSD Photoshop files), the original figure needs to be uploaded separately. Refer to the Guide for Authors for additional information.
http://www.elsevier.com/journals/environmental-research/0013-9351/guide-for-authors

Highlights (mandatory)

Highlights consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). See the following website for more information
http://www.elsevier.com/highlights

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This takes you to the Author main menu.

You can find the manuscript record listed under "Submissions Needing Revisions." Click "Revise" when you are ready to submit your revision. (If you have forgotten your password, please click the "Forget your password" link located on the log-in screen.) For guidelines on how to submit your revised manuscript please go the following
address: http://help.elsevier.com/app/answers/detail/p/7923/a_id/91

When submitting your revised paper, please include a separate document uploaded as "Response to Reviews" that carefully addresses the issues raised in the below comments, point by point. You should also include a suitable rebuttal to any specific request for change that has not been made.

To facilitate the electronic publication of your manuscript (should it be accepted), we request that your manuscript text, tables and figure legend be submitted in an editable format (Word, WordPerfect, or LaTex only), and all figures uploaded individually as TIF or EPS files.

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see: http://www.elsevier.com/interactiveplots. Interactive Plots provide easy access to the data behind plots. To include one with your article, please prepare a .csv file with your plot data and test it online
at http://authortools.elsevier.com/interactiveplots/verification before submission as supplementary material.

Include interactive data visualizations in your publication and let your readers interact and engage more closely with your research. Follow the instructions here: https://www.elsevier.com/authors/author-services/data-visualization to find out about available data visualization options and how to include them with your article.

MethodsX file (optional)
We invite you to submit a method article alongside your research article. This is an opportunity to get full credit for the time and money you have spent on developing research methods, and to increase the visibility and impact of your

work. If your research article is accepted, your method article will be automatically transferred over to the open access journal, MethodsX, where it will be editorially reviewed and published as a separate method article upon acceptance. Both articles will be linked on ScienceDirect. Please use the MethodsX template available here when preparing your article: https://www.elsevier.com/MethodsX-template. Open access fees apply.

Thank you, and we look forward to receiving your revised manuscript.

With kind regards,

Jose L. Domingo, PhD
Editor-in-Chief
Environmental Research

Environmental Research, Editorial Office
Elsevier
E-mail: er@elsevier.com

Reviewers' comments:

COMMENT of the EDITOR-in-CHIEF:

Please note that while the recommendations on your submission of Reviewers #1 and #3 are positive, that of Reviewer #2 has been Reject it. Taking into account the global comments of the 3 reviewers, I feel that I must give you an opportunity of submitting a revised manuscript. in this sense, I recommend you to pay special attention to the concerns raised by Reviewer #2, to whom I will invite to review your revised submission.

Reviewer #1: This is a very well-designed and well-written paper. It is generally hard to associate tobacco control policies with tobacco-related death and disease, since there are usually few decades of lag between the habit and the disease. The authors, however, designed a study that allowed for such inferences. First, instead of using disease onset, they used disease risk. Second, they correlated most current disease risks with the historical tobacco control policies. In result, they found very interesting associations.
My only comment is that the authors might mention the lag not only in the body of the manuscript but also in the abstract.
All in all, it is a really neat study and the conclusions the authors draw are not overreaching.

Reviewer #2: This is an ecological study analyzing the relationship between the prevalence of high-risk population and the adoption of effective strategies for tobacco control in the European Union. The manuscript is well written and

conclusions are even interesting. However, the present study has several limitations, in particular those inherent to the study design. Authors should address the following comments:

- The title is misleading and must be rephrased, since the analysed relation is not between tobacco control policies and the "risk of lung cancer" but between tobacco control policies and "population at high risk of lung cancer".

- Authors did not consider in the Discussion section the latency period between smoking exposure and lung cancer incidence and mortality (that could last several decades). Also the effects of the adoption of tobacco control policies on the population at high risk of lung cancer may be seen after more than one decade. Authors should further discuss this in the Discussion section.

- Discussion, Lines 29-41: besides "preterm births and low birth weight, tobacco consumption and quitting, secondhand smoke exposure in public and private venues, and attitudes towards smoking regulation" authors should also consider "smoking prevalence" (Martinez-Sanchez et al., 2010, PMID: 21079729; Gallus et al., 2014, PMID: 24441832). Moreover, Martinez-Sanchez et al., 2010 should be cited also with reference to attitudes towards smoking regulation.

- A Table should show for each country the prevalence estimates of people at high risk of lung cancer according to NLST and NELSON criteria, and the TCS score.

Reviewer #3: This is an ecological analysis across the EU of the TCS and smoking prevalence.

It has the limitations of correlational analyses, and - in particular - a reverse causation between smoking prevalence and TCS is possible, i.e. countries with lower proportions of smokers have stricter TCS.

Thus, the interpretation and Discussion should be more cautious.

Respuesta al Editor y a los revisores de Environmental Research

Response to reviewers ER-19-762

Reviewers' comments:

COMMENT of the EDITOR-in-CHIEF:

Please note that while the recommendations on your submission of Reviewers #1 and #3 are positive, that of Reviewer #2 has been Reject it. Taking into account the global comments of the 3 reviewers, I feel that I must give you an opportunity of submitting a revised manuscript. in this sense, I recommend you to pay special attention to the concerns raised by Reviewer #2, to whom I will invite to review your revised submission.

We thank the Editor-in-Chief for letting us submit a revised manuscript. As recommended, we have paid special attention to the comments of the Reviewer #2.

Reviewer #1: This is a very well-designed and well-written paper. It is generally hard to associate tobacco control policies with tobacco-related death and disease, since there are usually few decades of lag between the habit and the disease. The authors, however, designed a study that allowed for such inferences. First, instead of using disease onset, they used disease risk. Second, they correlated most current disease risks with the historical tobacco control policies. In result, they found very interesting associations.
My only comment is that the authors might mention the lag not only in the body of the manuscript but also in the abstract.
All in all, it is a really neat study and the conclusions the authors draw are not overreaching.

We really appreciate the kind comments to our work of Reviewer #1 and thank him/her for the recommendation of adding the lag statement in the abstract, recommendation we have followed. The conclusions in the abstract now read:

> "There is a lag between the implementation of tobacco control policies and the reduction of the rates of high risk of lung cancer. Member states should reinforce comprehensive tobacco control policies to reduce the population at high risk of lung cancer in the EU."

Reviewer #2: This is an ecological study analyzing the relationship between the prevalence of high-risk population and the adoption of effective strategies for tobacco control in the European Union. The manuscript is well written and conclusions are even interesting. However, the present study has several limitations, in particular those inherent to the study design.

We thank Reviewer #2 for her/his relevant and timely comments.

We would like to mention that, apart from the ecological approach, the multilevel GLMM adds for evidence on the likely association between the implementation of the tobacco control policies (aggregated at country level) and the proportion of individuals at high risk of lung cancer (at individual level). As the reviewer mentions, the study design may limit the strength of the conclusions observed. For this reason, we definitely admit these limitations not only in the limitations section, but also throughout the manuscript, for instance in the objective ("the aim of this study was to explore the association between the implementation of tobacco control policies and the risk of lung cancer in the EU") or in the Discussion/conclusions section ("To our knowledge, this is the first study to provide evidence on the likely effect of the implementation of tobacco control policies on the proportion of individuals at high risk of lung cancer in the EU."..."We have observed a possible relation between the level of implementation of tobacco control policies and the proportion of individuals at high risk at the individual level,..."..."We believe that our hypothesis may be confirmed or rejected in a future with further data.").

If the Editor and/or the Reviewer deem necessary to include further comments about the inherent limitations to the study design we are open to provide them.

Authors should address the following comments:

- The title is misleading and must be rephrased, since the analysed relation is not between tobacco control policies and the "risk of lung cancer" but between tobacco control policies and "population at high risk of lung cancer".

Thank you for this interesting comment. We have modified the title to clarify and now it reads as follows:

"Relation between tobacco control policies and population at high risk of lung cancer in the European Union"

Besides, we have modified the wording the reviewer mentions throughout the manuscript.

- Authors did not consider in the Discussion section the latency period between smoking exposure and lung cancer incidence and mortality (that could last several decades). Also the effects of the adoption of tobacco control policies on the population at high risk of lung cancer may be seen after more than one decade. Authors should further discuss this in the Discussion section.

We would like to thank the reviewer for these interesting observations.
On the gap between smoking prevalence and lung cancer mortality, we have added an excerpt based on the reference (Martín-Sánchez JC et al., 2017), which has been also added. Now, the paragraph on the lag between the implementation of the policies and the proportion of individuals at high risk of lung cancer and between smoking exposure and lung cancer mortality reads as follows:

"We suggest that there is a lag between the moment the tobacco control policies come into effect and the impact they have on the smoking reduction, and eventually on the rates of high risk of lung cancer. Being the timeframe shorter between the TCS 2013 and the Special Eurobarometer and the TCS 2016 and the Special Eurobarometer, the effect of the implementation of new policies may not yet be visible. This timeframe between the tobacco control policies come into force and the impact they have on the proportion of individuals at high risk of lung cancer adds to the gap between smoking prevalence and lung cancer mortality, which was estimated elsewhere as around three decades (Martín-Sánchez et al., 2017)."

On the effects of the policies on the population at high risk, we have also added a statement in the Discussion as follows:

"Also, we believe that the timeframe between the TCS in 2013 and 2016 and the Special Eurobarometer 458 is too short to observe statistically significant results for these years. However, and also considering that the full impact of the implementation of tobacco control policies on the proportion of individuals at high risk of lung cancer may be observable well beyond the largest timeframe studied (8 years), we have observed time trends plausible with this likely impact."

- Discussion, Lines 29-41: besides "preterm births and low birth weight, tobacco consumption and quitting, secondhand smoke exposure in public and private venues, and attitudes towards smoking regulation" authors should also consider "smoking prevalence" (Martinez-Sanchez et al., 2010, PMID: 21079729; Gallus et al., 2014, PMID: 24441832). Moreover, Martinez-Sanchez et al., 2010 should be cited also with reference to attitudes towards smoking regulation.

We thank the reviewer for the thorough revision of our manuscript and for the interesting considerations provided which complete the background on the positive effects of tobacco control. We have added the reference (Gallus et al., 2014) and incorporated the recommended information, and now the extract on the effects of tobacco control studied so far reads as follows:

"Previous studies have assessed the impact of tobacco control policies in the EU on smoking prevalence (Gallus et al., 2014) (Martínez-Sánchez et al., 2010), preterm births and low birth weight (Díez-Izquierdo et al., 2018), tobacco consumption and quitting (Feliu et al., 2019)(Lidón-Moyano et al., 2017), secondhand smoke exposure in public (Martínez-Sánchez et al., 2010) (Filippidis et al., 2016) and private venues (Martínez-Sánchez et al., 2013), and attitudes towards smoking regulation (Lidón-Moyano et al., 2018) (Martínez-Sánchez et al., 2010)."

- A Table should show for each country the prevalence estimates of people at high risk of lung cancer according to NLST and NELSON criteria, and the TCS score.

Thank you for your interesting comment. We agree with the reviewer that further descriptive information on the population at high risk and the TCS scores at the country level could add background on the relations later discussed. Hence, we have elaborated and added a Table (Table 1), also mentioned in Results as follows:

> "Table 1 includes country level data on the TCS scores and on the proportion of individuals at high risk of lung cancer according to NLST and NELSON criteria."

Reviewer #3: This is an ecological analysis across the EU of the TCS and smoking prevalence.

It has the limitations of correlational analyses, and - in particular - a reverse causation between smoking prevalence and TCS is possible, i.e. countries with lower proportions of smokers have stricter TCS. Thus, the interpretation and Discussion should be more cautious.

We thank Reviewer #3 for her/his convenient comments.

We would like to mention that, apart from the ecological approach, the multilevel GLMM adds for evidence on the likely association between the implementation of the tobacco control policies and the proportion of individuals at high risk of lung cancer. As the reviewer mentions, the study design may limit the strength of the conclusions observed. We definitely admit these limitations not only in the limitations section, but also throughout the manuscript as mentioned in the response to the second comment of Reviewer #2.

We have found the scenario of reverse causality the reviewer mentions really interesting. Hence, we have added a statement on it in the Discussion section, as follows:

> "Besides, reverse causality cannot be discarded (i.e. countries with lower proportions of smokers have higher scores in the TCS)."

Carta de aceptación del artículo en Environmental Research

Ms. No.: ER-19-762R1
Title: Relation between tobacco control policies and population at high risk of lung cancer in the European Union
Corresponding Author: Dr. Jose M Martínez-Sánchez
Authors: Adrián González-Marrón; Juan Carlos Martín-Sánchez; Queralt Miró; Nuria Matilla-Santander; Àurea Cartanyà-Hueso; Lorelei Mucci;

Dear Dr. Martínez-Sánchez,

We are pleased to inform you that your manuscript referenced above has been accepted for publication in Environmental Research.

Your accepted manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication.

Your article will appear on Elsevier's online journal database ScienceDirect as an "Article in Press" within approximately 4-6 weeks of acceptance. Articles in Press for Environmental Research can be viewed at http://www.sciencedirect.com/science/journal/00139351.

An Article in Press may be cited prior to its publication by means of its unique digital object identifier (DOI) number, which does not change throughout the publication process. At the same time, Medline/PubMed will list the article in its database, linking to the full text of the paper in ScienceDirect. Medline/PubMed is freely accessible to researchers across the world.

You can track the status of your article via the Author Gateway at http://www.elsevier.com/trackarticle. Once you have registered as a user, you will receive e-mail alerts when the publication status of your paper changes, including when the paper is published.

Many thanks for submitting your fine paper to Environmental Research. We look forward to receiving additional papers from you in the future.

With kind regards,

Jose L. Domingo, PhD
Co-Editor in Chief

Environmental Research
Elsevier
E-mail: er@elsevier.com

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at http://help.elsevier.com/app/answers/list/p/7923. Here you can search for solutions on a range of topics, find answers to frequently asked questions and learn more about EES via interactive tutorials. You will also find our 24/7 support contact details should you need any further assistance from one of our customer support representatives.

ANEXO V. PROCESO EDITORIAL DE LA EDITORIAL «TOBACCO CONTROL - PROTECTING FUTURE GENERATIONS' LUNGS»

Comentarios del Editor y de los revisores de Expert Review in Respiratory Medicine

De: Expert Review of Respiratory Medicine <onbehalfof@manuscriptcentral.com>
Fecha: 8 de abril de 2019, 14:40:05 CEST
Para: jmmartinez@uic.es
Asunto: Expert Review of Respiratory Medicine - Decision on Manuscript ID ERRX-2019--0025
Responder a: IERX-peerreview@journals.tandf.co.uk

08-Apr-2019

Dear Dr Martínez-Sánchez,

Thank you for your patience while your manuscript was under review. Your manuscript, entitled "Tobacco control - protecting future generations' lungs", which you submitted to Expert Review of Respiratory Medicine, has now been reviewed. The referee comments are included at the bottom of this letter along with some essential editorial revisions.

The reviews are in general favourable and suggest that, subject to minor revisions, your paper could be suitable for publication. Please consider these suggestions and submit your revised manuscript by 15th April 2019. I look forward to receiving your revision.

PLEASE NOTE: When you revise your manuscript please highlight the changes you make in the manuscript by using the track changes mode in MS Word or by using bold or coloured text.

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https://mc.manuscriptcentral.com/errx?URL_MASK=97063287a38e4fedaa53aa6c42dad455

This will direct you to the first page of your revised manuscript. Please enter your responses to the comments made by the referees and editorial office in the space provided. You can use this space to document any changes you made to the original manuscript. Please be as specific as possible in your response to the referees.

This link will remain active until the due date stated above. If you begin a revision and intend to finish it at a later time, please note that your draft will appear in the "Revised Manuscripts in Draft" queue in your Author Centre.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the

submission.

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into https://mc.manuscriptcentral.com/errx: Click on 'Author Centre' >
'Manuscripts with Decisions' > 'Create a Revision'.

Because we are trying to facilitate timely publication of manuscripts submitted to Expert Review of Respiratory Medicine, your revised manuscript should be uploaded by the due date specified above. If it is not possible for you to submit your revision by this date, please do let me know as soon as possible.

Once again, thank you for submitting your manuscript to Expert Review of Respiratory Medicine and I look forward to receiving your revision.

Sincerely,

Edward Spofford
Commissioning Editor
Edward.Spofford.GB1@tandf.co.uk

Ref 1:
It is a very well-written, short summary on the key issues that tobacco control community currently faces. My only comment is that, while the authors accurately present the very real and looming harms of the novel tobacco products, they avoid discussing the arguments of those who see some potential of those products to reduce tobacco-related harm. This lack of balance in presenting the arguments needs to be corrected, especially in the following few places:
1) P. 2. Authors write that the industry has "no real intention to improve public health". That's right, but the industry has no real intention to harm public health either. The industry is programmed to maximize the profit to its stakeholders in a given market and regulatory environment. If it happens that selling novel product is more profitable for the industry (e.g. due to lower taxes), they will stop selling cigarettes (e.g. as signaled in New Zealand few days ago).
2) P2. The sentence starting with "The fact is that, as of today,…" needs to be corrected. I find it troubling that the authors diminish the validity of existing evidence, even though the evidence has been accepted by large organizations, such as Public Health England or CDC.
3) P3. One sentence calls for "equalizing prices for all tobacco products (traditional and new products)". Chaloupka, Sweanor and Wrner proposed a different approach, which was to increase the prices of e-cigarettes to the point that the price discourages initiation, while, at the same time, tax the hell out of regular cigarettes, so that smokers of regular cigarettes are encouraged to completely switch to the reduced-risk products. Their proposal seems quite reasonable to me. I think it is worth mentioning.
Apart from the need to merely acknowledge the potential of some of those new products to save lives of those who are unable or unwilling (sic!) to quit, I think this is a great piece.

Ref 2:
Good job.

Ref 3:
Really a very interesting editorial that provides those points in which we must continue fighting against tobacco.
- Just a note: are the references number 4, 12 and 17 adequately written? A reference should start with the authors and then with the title of the work, etc.

Editorial Office Revisions:

1. Please note that our editorial articles should not have abstracts, in this case please include your abstract as part of your main text.

Respuesta al Editor y a los revisores de Expert Review in Respiratory Medicine

RESPONSE TO REVIEWERS ERRX-2019--0025

We would like to thank the reviewers for their feedback and kind comments on our editorial.

We provide a point-by-point response to all of them.

Ref 1:
It is a very well-written, short summary on the key issues that tobacco control community currently faces.

Thank you for your nice feedback and for the exhaustiveness reviewing the manuscript.

My only comment is that, while the authors accurately present the very real and looming harms of the novel tobacco products, they avoid discussing the arguments of those who see some potential of those products to reduce tobacco-related harm. This lack of balance in presenting the arguments needs to be corrected, especially in the following few places:

1) P. 2. Authors write that the industry has "no real intention to improve public health". That's right, but the industry has no real intention to harm public health either. The industry is programmed to maximize the profit to its stakeholders in a given market and regulatory environment. If it happens that selling novel product is more profitable for the industry (e.g. due to lower taxes), they will stop selling cigarettes (e.g. as signaled in New Zealand few days ago).

Thank you for this timely and interesting comment. We agree with you in this aspect, and have modified this excerpt, now reading as follows:

> *"On the one hand, this strategy has been broadly described as a way of the tobacco industry to clean their corporate image and bypass modifications in policies with the aim of increasing their sales in a new market niche* [65]*, since industry considers the diverse products containing nicotine a complement to its traditional business* [66]*."*

2) P2. The sentence starting with "The fact is that, as of today,…" needs to be corrected. I find it troubling that the authors diminish the validity of existing evidence, even though the evidence has been accepted by large organizations, such as Public Health England or CDC.

Thank you for your feedback on this sensitive issue. We have relaxed this statement, and now it reads as follows:

> *"As of today, there is still limited evidence on the real and long-term effects of the use of these products. However, a large number of entities have already*

adhered to the THR strategy. One of the most relevant is Public Health England, organization that concluded in a review in 2015 that vaping is around 95% safer than smoking [67], although a number of experts questioned the transparency of this review [68]."

3) P3. One sentence calls for "equalizing prices for all tobacco products (traditional and new products)". Chaloupka, Sweanor and Wrner proposed a different approach, which was to increase the prices of e-cigarettes to the point that the price discourages initiation, while, at the same time, tax the hell out of regular cigarettes, so that smokers of regular cigarettes are encouraged to completely switch to the reduced-risk products. Their proposal seems quite reasonable to me. I think it is worth mentioning.

Thank you for mentioning this interesting approach. We have commented it as follows:

"Based on this evidence, increasing taxes, and equalizing prices for all tobacco products (traditional and new products) should be a pivotal measure to limit tobacco purchase in adolescents. Other authors supporting the THR approach, however, have advocated for a differential taxing taking into account the supposedly different risks of the nicotine products [69]. In any case, we consider that a debate should be opened to discuss if new nicotine products should be limited only to current smokers who want to quit or reduce their consumption to avoid them being a gateway to nicotine for adolescents as we mentioned before."

Apart from the need to merely acknowledge the potential of some of those new products to save lives of those who are unable or unwilling (sic!) to quit, I think this is a great piece.

Again, thank you for kind comments.

Ref 2:
Good job.

Thank you for your feedback.

Ref 3:
Really a very interesting editorial that provides those points in which we must continue fighting against tobacco.
- Just a note: are the references number 4, 12 and 17 adequately written? A reference should start with the authors and then with the title of the work, etc.

Thank you for your very nice comments.
Regarding the format of the references 4, 12 and 17, we have moved the information on the papers we consider interesting at the end of the reference.

Editorial Office Revisions:

1. Please note that our editorial articles should not have abstracts, in this case please include your abstract as part of your main text.

Thank you. We have deleted the abstract, since all the information was already included in the introduction of the text.

Carta de aceptación de la editorial en Expert Review in Respiratory Medicine

12-Apr-2019
Ref: Tobacco control - protecting future generations' lungs

Dear Dr Martínez-Sánchez,

Thanks again for submitting your revised manuscript and for your time spent making the revisions. We are delighted to now accept your paper in its current form for publication in Expert Review of Respiratory Medicine. It will now be forwarded to our Production team for copy editing and typesetting. You will receive the proofs from them for checking, and instructions for transfer of copyright in due course. The publisher requests that proofs are checked and returned within 48 hours of receipt. The publisher will contact you, as part of the acceptance process, for confirmation on any colour figure requirements.

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We regularly promote our published articles on social media, particularly via Twitter and LinkedIn, and we encourage authors to do the same. This can prove an excellent opportunity to share your article with a wider audience. Please visit https://authorservices.taylorandfrancis.com/ensuring-your-research-makes-an-impact/for ten top tips to maximize the impact of your research.

Thank you for your contribution to Expert Review of Respiratory Medicine. I hope you've had a pleasurable experience publishing with us and I hope to receive further submissions from you.

Best wishes,

Edward Spofford
Expert Review of Respiratory Medicine
Taylor & Francis, London, UK
Edward.Spofford.GB1@tandf.co.uk

ANEXO VI. ARTÍCULO DERIVADO DE LA FORMACIÓN PREDOCTORAL - «CONFIDENCE INTERVAL REPORTING FOR MEASURES OF ASSOCIATION IN MULTIVARIABLE REGRESSION MODELS IN OBSERVATIONAL STUDIES»

Med Clin (Barc). 2019;153(6):239–242

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Original breve

Confidence interval reporting for measures of association in multivariable regression models in observational studies

Adrián González-Marrón[a], Jordi Real[b,c,d], Carles Forné[e,f], Albert Roso-Llorach[g], Eva María Navarrete-Muñoz[h,i,j], Jose M. Martínez-Sánchez[a,*]

[a] Group of Evaluation of Health Determinants and Health Policies, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Spain
[b] Research support unit Barcelona, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain
[c] Epidemiology and Public Health, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Spain
[d] CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Spain
[e] Biostatistics Unit, Institut de Recerca Biomèdica de Lleida (IRBLleida), Lleida, Spain
[f] Department of Basic Medical Sciences, Universitat de Lleida, Lleida, Spain
[g] University Institute in Primary Care Research Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain
[h] CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain
[i] Unit of Nutritional Epidemiology, Department of Public Health, History of Medicine and Gynecology, Universidad Miguel Hernández, Alicante, Spain
[j] Institute for Health and Biomedical Research (ISABIAL - FISABIO Foundation), Alicante, Spain

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P-value
STROBE guideline

ABSTRACT

Background/Objectives: To assess the adherence to reporting confidence intervals (CI) for measures of association in multivariable regression models (MRM) in articles with observational design indexed in MEDLINE.
Material and methods: A literature search was conducted using the MEDLINE bibliographic database to obtain a representative sample of studies with observational design and applying MRM (logistic, linear, and Cox regression) ($n = 428$). Proportions and 95% CI of articles reporting CI for measures of association in MRM were calculated. Percentage ratios (PRs) were also calculated to describe the change in CI reporting before and after the publication of the STROBE statement.
Results: 188 of the 236 abstracts with measures of association (79.7%; 95% CI 74.5, 84.8) and 360 of the 428 main texts (84.1%; 80.6, 87.6) were provided with CI. A non-significant increase of 1% in the abstract, PR = 1.01 (0.77, 1.29), and 7% in the main text, PR = 1.07 (0.87, 1.28), occurred in the CI reporting after the publication of the STROBE guideline.
Conclusions: The STROBE guideline recommendation on reporting CI should be more thoroughly followed.

Reporte de los intervalos de confianza en medidas de asociación en modelos de regresión multivariable en estudios observacionales

Palabras clave:
Intervalo de confianza
P-valor
Guía STROBE

RESUMEN

Antecedentes/objetivos: Evaluar la adherencia al reporte de los intervalos de confianza (IC) en medidas de asociación en modelos de regresión multivariable (MRM) en artículos con diseño observacional indexados en MEDLINE.
Material y métodos: Se realizó una búsqueda bibliográfica usando la base de datos bibliográfica MEDLINE para obtener una muestra representativa de estudios con diseño observacional y que aplicaran MRM (regresión logística, lineal y Cox) (n = 428). Se calcularon las proporciones e IC 95% de los artículos que reportaban IC en las medidas de asociación en MRM. También se calcularon las razones de porcentaje (RP) para describir el cambio en el reporte de los IC antes y después de la publicación de la declaración STROBE.

* Corresponding author.
E-mail address: jmmartinez@uic.es (J.M. Martínez-Sánchez).

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Resultados: 188 de los 236 resúmenes con medidas de asociación (79,7%; IC 95% 74,5-84,8) y 360 de los 428 textos principales (84,1%; 80,6-87,6) estaban provistos de IC. Un incremento no significativo del 1% en el resumen, RP = 1,01 (0,77-1,29), y del 7% en el texto principal, RP = 1,07 (0,87-1,28), tuvo lugar en el reporte de los IC después de la publicación de la guía STROBE.
Conclusiones: La recomendación de reportar IC dada por la guía STROBE debería ser seguida más exhaustivamente.

Introduction

Multivariable regression models (MRM), especially logistic regression, have progressively been adopted as invaluable statistical tools in epidemiological studies in recent years.[1] From a methodological point of view, MRM are among the techniques applied to control confounding,[2] as long as some strict assumptions are accomplished (e.g., normality, homoscedasticity), while a diversity of response variables—continuous, time-dependent, dichotomous—are analyzed in the linear, Cox and logistic models, respectively.[3]

Two methods have been classically applied to report and statistically assess results arising from MRM and other models: hypothesis testing or NHST (null hypothesis significance testing, also known as *P*-value determination) and confidence interval calculation (estimation). Although both approaches are complementary,[4] confidence intervals (CI) are mainly preferred nowadays [5]because in addition to statistical significance, the size and uncertainty of the effect is also obtained. Besides, *P*-values are not frequently used and interpreted properly,[5] facts that have led to new proposals when assessing statistical significance, such as lowering the threshold from 0.05 to 0.005.[6]

In 2007, the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement[7] was published. This initiative has become so widely popular among researchers that other extensions (e.g., STROBE-nut)[8] have imitated its features. The goal of STROBE is to provide a checklist and recommendations for researchers to improve the quality of reporting in observational studies. For that purpose, the 16th item in its checklist states that estimates should be given along with their 95% CI, while *P*-value determination per se does not appear throughout the text.

The objective of this study was to assess the adherence to reporting CI for measures of association in observational studies using MRM (linear, logistic and Cox regression) and indexed in MEDLINE and to compare the reporting of CI before and after the publication of the STROBE guideline in 2007.

Methods

We reviewed the reporting of CI in the abstract and main text of a representative random sample of articles indexed in MEDLINE using the PubMed search engine. The search was specifically designed to identify original studies with an analytical observational design that stated their use of logistic, Cox, or linear multivariable regression models. Further information on the search strategy, which eventually yielded 428 papers to review, may be found elsewhere.[1,9]

The selected articles were randomly distributed among the three designated reviewers (JR, CF, ARLl) on the research team. Any doubts were shared and resolved by consensus. In addition, the three reviewers randomly selected 12 articles for blinded evaluation of inter-rater agreement. The agreement was ≥91.6%, with Kappa indexes between reviewers ≥0.80.

We calculated the proportion and 95% CI of the articles that reported CI for measures of association in the MRM. We considered that an article reported CI for the measures of association when at least one measure of association was reported along with the CI. All analyses were stratified in groups according to the impact factor (IF) of the journal in the year of publication (≤2, 2.01–4, ≥4.01), sample size (≤500, 501–1500, ≥1501), design (cross-sectional, cohort, case-control), data source (ad hoc, clinical/administrative records, both or "mixed"), and the type of MRM (logistic, linear, Cox). Pearson χ^2 and Cochran–Armitage test for trend were used to assess the association between the proportion of the reporting of CI and the categorizing variables. We calculated the percentage ratio (PR) and 95% CI of the reporting before and after the publishing of the STROBE guideline (2003–2007, 2008–Feb. 2014).

Besides, we performed a joinpoint regression to identify any change in the trend, and a segmented regression to calculate the increase in the reporting of CI before and after the publication of the STROBE statement.

Results

Table 1 shows the proportion of measures of association the abstract and the proportion of CI reporting in the articles reviewed. Of the 428 main texts, 360 (84.1%; 95% CI 80.6, 87.6) were provided with CI. According to point estimates, the highest proportions of CI reporting in the main text within each categorizing variable corresponded to case–control studies (93.1%; 87.2, 98.9), mixed data sources (91.2%; 86.0, 96.4), sample size ≥1501 (94.0%; 89.9, 98.0), IF ≥4.01 (87.8%; 81.8, 93.8) and logistic regression models (90.6%; 87.0, 94.1). On the other hand, measures of association were reported in 236 of 428 (55.1%; 50.4, 59.9) of the abstracts, of which 188 (79.7%; 74.5, 84.8) were completed with their CI. Within each categorizing variable, a positive correlation was found between the point estimates of CI reporting in the abstract and the main text (i.e., the highest proportion found in the abstract for a category also corresponded to the highest in the main text), with the exception of the variable data source. A positive correlation was also found between the reporting of CI and the variables sample size and IF of the journal, at least according to point estimates (i.e., for larger sample sizes and higher IF, a higher proportion of CI reporting was observed). The reporting of CI increased according to the variable IF even after adjusted by the variable sample size, although there was not statistical significance.

Table 2 shows the proportion of CI reporting in MRM in the abstract and main text of the articles reviewed before and after the publication of the STROBE statement in 2007. The reporting of CI increased 1% (PR 1.01; 0.77, 1.29) and 7% (PR 1.07; 0.87, 1.28) in the point estimates only for the abstract and the main text, respectively, after the publication of the STROBE guideline, although statistically significant differences were not observed. When stratifying, data did not show statistically significant differences, either.

The joinpoint regression did not show any change in trend in the reporting of CI before and after the publication of the STROBE statement (data not shown). However, we observed a higher increase in the percentage of CI reporting per year after the publication of the STROBE statement (1.72 points per year) than before the publication of the STROBE statement (1.36 points per year).

Table 1
Report of measures of association and confidence intervals (CI) in the abstract and main text of the reviewed articles.

Variable	Measures of association in the abstract				CI for measures of association in the abstract			CI for measures of association in the main text		
Category	*N*	%	95% CI	*P*-value	%[d]	95% CI	*P*-value	%	95% CI	*P*-value
Overall	428	55.1	50.4–59.9		79.7	74.5–84.8		84.1	80.6–87.6	
Design[a]				<0.001			0.255			0.006
Cross-sectional	108	**39.8**	30.6–49.0		72.1	58.7–85.5		**75.9**	67.9–84.0	
Cohort	212	**58.5**	51.9–65.1		79.0	71.9–86.2		**85.8**	81.2–90.5	
Case–control	72	**69.4**	58.8–80.1		86.0	76.4–95.6		**93.1**	87.2–98.9	
Data source[a]				0.003			0.219			0.001
Ad hoc	195	**47.2**	40.2–54.2		76.1	67.4–84.8		**77.4**	71.6–83.3	
Clinical record	106	**59.4**	50.1–68.8		87.3	79.1–95.5		**89.6**	83.8–95.4	
Mixed	114	**66.7**	58.0–75.3		78.9	69.8–88.1		**91.2**	86.0–96.4	
Sample size				<0.001			0.001			<0.001
≤500	205	**45.4**	38.6–52.2		**67.7**	58.2–77.2		**76.1**	70.3–81.9	
501–1500	90	**61.1**	51.0–71.2		**85.5**	76.1–94.8		**87.8**	81.0–94.5	
≥1501	133	**66.2**	58.1–74.2		**88.6**	82.0–95.3		**94.0**	89.9–98.0	
IF[b]				0.089			0.034			0.064
≤2.00	147	49.7	41.6–57.7		**69.9**	59.3–80.4		79.6	73.1–86.1	
2.01–4.00	166	56.6	49.1–64.2		**84.0**	76.6–91.4		85.5	80.2–90.9	
≥4.01	115	60.0	51.0–69.0		**84.1**	75.4–92.7		87.8	81.8–93.8	
Model[c]										
Logistic	289	55.5	49.4–61.6	0.335	**86.5**	80.9–92.2	0.001	**90.6**	87.0–94.1	<0.001
Linear	77	43.9	31.0–56.7	0.102	**40.0**	20.8–59.2	<0.001	**49.1**	36.1–62.1	<0.001
Cox	98	57.3	46.6–68.0	0.168	80.9	69.6–92.1	0.901	84.1	76.2–92.1	0.621
Period				0.961			0.901			0.137
2003–2007	131	55.0	46.4–63.5		79.2	69.8–88.5		80.2	73.3–87.0	
2008–Feb. 2014	297	55.2	49.6–60.9		79.9	73.7–86.0		85.9	81.9–89.8	

[a] It excludes category with undefined information.
[b] Impact factor of the journal when the article was published.
[c] The model type categories are not mutually exclusive.
[d] Proportions calculated over the total of studies reporting measures of association in the abstract.

Table 2
Reporting of confidence intervals (CI) before and after the publishing of the STROBE guideline.

Variable	CI of measures of association in Abstract				CI of measures of association in Main text[a]			
	Before	After			Before	After		
Category	%	%	PR	95% CI	%	%	PR	95% CI
Overall	79.2	79.9	1.01	0.77–1.29	80.9	86.2	1.07	0.87–1.28
Design[b]								
Cross-sectional	75.0	71.0	0.95	0.45–1.68	80.0	74.0	0.92	0.62–1.30
Cohorts	75.0	80.7	1.08	0.72–1.53	79.0	90.0	1.14	0.85–1.48
Case–control	90.0	83.3	0.93	0.56–1.40	88.9	95.6	1.08	0.69–1.55
Data source[b]								
Ad hoc	84.0	73.1	0.87	0.55–1.28	77.4	78.2	1.01	0.75–1.32
Clinical record	85.7	88.1	1.03	0.62–1.56	89.3	91.0	1.02	0.67–1.46
Mixed	68.2	83.3	1.22	0.71–1.94	82.9	94.9	1.15	0.77–1.60
Sample size								
≤500	59.3	71.2	1.20	0.71–1.89	71.9	78.7	1.10	0.81–1.44
501–1500	82.4	86.8	1.05	0.59–1.68	84.0	89.2	1.06	0.67–1.57
≥1501	96.4	85.0	0.88	0.58–1.24	92.9	95.6	1.03	0.73–1.38
IF[c]								
≤ 2.00	63.0	73.9	1.17	0.70–1.82	80.9	80.0	0.99	0.71–1.33
2.01–4.00	92.9	80.3	0.86	0.57–1.23	79.2	89.4	1.13	0.82–1.50
≥4.01	82.4	84.6	1.03	0.57–1.64	83.9	89.3	1.06	0.70–1.51
Model[d]								
Logistic	86.0	86.8	1.01	0.73–1.34	89.7	91.5	1.02	0.80–1.27
Linear	50.0	36.8	0.74	0.20–1.94	44.4	51.3	1.15	0.55–2.18
Cox	81.8	80.6	0.98	0.47–1.73	76.9	89.3	1.16	0.72–1.73

PR, percentage ratio.
[a] Only one article showing CI in the abstract did not show CI in the main text.
[b] It excludes category with undefined information.
[c] Impact factor of the journal when the article was published.
[d] The model type categories are not mutually exclusive.

Discussion

Around eight out of ten studies with observational design conducting a MRM published in medical journals and indexed in MEDLINE were reported with CI in the measures of association. A low reporting of measures of association in the abstract (around 55%) was also observed. Furthermore, CI reporting for measures of association increased slightly according to the point estimates after the publishing of the STROBE statement, although statistical significance was not observed (the CI of the PR includes one). Our results also show differences in underreporting for both measures of association and CI according to some categorizing variables such

as design, sample size of the study or IF of the journal. In a previous study, other recommendations from STROBE have been observed not to be followed either,[10] although the reporting of CI is becoming more common in abstracts, particularly in epidemiology journals.

Remarkably, we observed an increase in the point estimate for the proportion of CI reporting proportional to the IF of the journal, only statistically significant in the abstract. This may be explained by the fact that journals with higher IF would require manuscripts with higher statistical proficiency. Moreover, some of these journals require a checklist following the STROBE recommendations. Nevertheless, other studies suggest that editorial policy is more influential on this matter than the IF itself.[11] We also observed a high proportion in the reporting of measures of association and CI in studies with large sample sizes. On the other hand, in studies with smaller sample sizes, for which the confidence in the estimate is lower, the reporting of CI was less common. However, this relationship was found to be partially confounded by the IF of the journal.

Convenience of the use of *P*-values or CI has been broadly discussed. Experts' opinions,[8] groups such as CONSORT (CONsolidated Standards of Reporting Trials) [12]or STROBE and guidelines for authors to submit articles to journals recommend the use of CI over NHST (or NHST as a complement to CI). In this sense, we did not observe a statistically significant increase in the reporting of CI either in the abstract or the main text of the article after the publication of the STROBE guideline.

One of the limitations of our study is that the primary source of data was the abstracts accessed in MEDLINE via the PubMed search engine. Therefore, the universe of potential studies for analysis was limited to that repository. Also, our search strategy [1,9] was highly specific and only articles that included the MRM term within the abstract were retrieved. In addition, we believe that the length of the pre- and, especially, post-STROBE period in which the search strategy was delimited may have an impact in the proportion of measures of association provided with their CI. However, we consider that with this time frame we have gathered all the variation attributable to the publishing of the STROBE guideline. Besides, the reporting of CI could be overestimated because we considered the reporting was positive when at least one of the measures of association was completed with its CI. We would also like to point out that the IF of journals when assessing the quality of publications has downsides (e.g., inaccurate inter-field comparisons), which may have hampered the conclusions arising from the use of this variable.

In summary, although we observed a relatively high reporting of CI for measures of association in observational studies that used MRM and were published in biomedical journals, there were a worrying number of studies that did not provide CI. Given the importance of the reporting of CI for measures of association, biomedical researchers should follow the STROBE guideline recommendations.

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Conflicts of interest

None

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ANEXO VII. ARTÍCULO DERIVADO DE LA FORMACIÓN PREDOCTORAL - «VALIDITY OF SELF-REPORTED INTENSITY OF EXPOSURE TO SECOND-HAND SMOKE AT HOME AGAINST ENVIRONMENTAL AND PERSONAL MARKERS»

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Metodological note

Validity of self-reported intensity of exposure to second-hand smoke at home against environmental and personal markers

José M. Martínez-Sánchez[a,b,c,*], Adrián González-Marrón[a], Juan Carlos Martín-Sánchez[a], Xisca Sureda[d], Marcela Fu[b,c,e], Raúl Pérez-Ortuño[f], Cristina Lidón-Moyano[a], Iñaki Galán[g,h], José Antonio Pascual[f,i], Esteve Fernández[b,c,e]

[a] Group of Evaluation of Health Determinants and Health Policies, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Barcelona, Spain
[b] Tobacco Control Unit, Cancer Prevention and Control Programme, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain
[c] Cancer Control and Prevention Group, Bellvitge Biomedical Research Institute-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[d] Social and Cardiovascular Epidemiology Research Group, School of Medicine, University of Alcalá, Alcalá de Henares, Madrid, Spain
[e] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona, Barcelona, Spain
[f] Group of Integrative Pharmacology and Systems Neuroscience, Neurosciences Programme, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain
[g] National Centre for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain
[h] Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain
[i] Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain

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ABSTRACT

The objective of this study was to assess the validity of two questions about the perception of intensity of exposure to secondhand smoke (SHS) at home using as a reference environmental markers (airborne nicotine and benzene) and biomarkers of exposure (cotinine in saliva and urine). This was a cross-sectional study in a convenience sample of 49 non-smoking volunteers. We found a high correlation between self-reported SHS exposure and airborne nicotine (r_{sp} = 0.806, p < 0.05), salivary cotinine (r_{sp} = 0.752, p < 0.05), and urinary cotinine (r_{sp} = 0.626, p < 0.05). We did not find differences between the score question and the conventional ones (p > 0.05). In conclusion, the significant correlation of the two questions proposed with environmental markers and personal markers indicates their potential validity to assess exposure to SHS at home.

Validación de la intensidad de la exposición pasiva al tabaco en el hogar reportada mediante cuestionario

Palabras clave:
Humo de tabaco ambiental
Hogares
Validación
Cotinina
Nicotina
Marcadores personales

RESUMEN

El objetivo de este trabajo es evaluar la validez de dos preguntas sobre la exposición al humo ambiental de tabaco (HAT) en el hogar utilizando como referencia marcadores ambientales (nicotina y bencenos en el aire) y biomarcadores específicos (cotinina en saliva y orina) de la exposición pasiva al tabaco. Para ello se realizó un estudio transversal de una muestra de conveniencia de 49 voluntarios no fumadores mayores de edad de la ciudad de Barcelona. Se encontró una alta correlación entre la pregunta de intensidad de la exposición pasiva autodeclarada en casa y la nicotina en el aire (r_{sp} = 0,806, p < 0,05), la cotinina en saliva (r_{sp} = 0,752, p < 0,05) y la cotinina en orina (r_{sp} = 0,626, p < 0,05). No encontramos diferencias entre las preguntas puntuables y las convencionales (p >0,05). En conclusión, la alta correlación de las preguntas propuestas con los marcadores ambientales y los biomarcadores indica su validez para evaluar la intensidad de la exposición pasiva al tabaco en el hogar.

Introduction

World Health Organization proposed the MPOWER package in order to achieve a world where no child and adult will be exposed to second hand smoke (SHS).[1] Among the measures of MPOWER, WHO encourages the *monitoring* (the M of MPOWER acronym) of the tobacco epidemic.

Monitoring and measurement of SHS exposure can be performed by direct and indirect methods. Among the direct methods, environmental markers (e.g., airborne nicotine and benzene) and/or personal biomarkers such as cotinine in biological matrices can be measured. Although direct methods are the most

* Corresponding author.
E-mail address: jmmartinez@uic.es (J.M. Martínez-Sánchez).

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reliable to measure the SHS exposure, indirect methods –such as questionnaires– are the most commonly used in the scientific literature[2,3] because they are low cost and simple to implement.[4]

In a previous study,[5] two new questions were included to self-report the perception of intensity of exposure to SHS in hospitality venues. The main objective of this study was to assess the validity of these two questions to measure the intensity of exposure to SHS at home using environmental markers (nicotine and benzene) and personal biomarkers (salivary and urinary cotinine) as reference.

Methods

We conducted a cross-sectional study in a convenience sample of 49 non-smoking volunteers from different houses: 25 non-smokers who lived with at least one smoker and 24 non-smokers who lived in totally smoke-free homes. The fieldwork was conducted between November 2011 and February 2012.

After an initial telephone or direct approach, a member of the research team went to the volunteer's home to explain the objective and procedures of the study. In that visit, the researcher installed two devices to passively collect nicotine and benzene in the main room of the house (usually the living room). In the second visit, one week later, the researcher returned to the volunteer's home to remove both devices from the room, to obtain saliva and urine samples from the volunteer, and to administrate a face-to-face questionnaire on SHS exposure at home. The research and ethics committee of the Bellvitge University Hospital provided ethical approval for the study protocol.

The two questions validated were: 1) "How would you describe, during the last week, secondhand smoke exposure in the room of your home where the devices were installed?" (Likert scale-based question with four possible answers: high, medium, low, and very low intensity); and 2) "What score from 0 to 10 would you give the room where devices were installed regarding the amount of secondhand smoke exposure during the last week, bearing in mind that 0 would be minimum contamination and 10 maximum contamination?". The questionnaire also included three conventional questions to measure the intensity and duration of SHS exposure at home:[3] 1) "During the past week, how many persons per day usually smoked inside your home?"; 2) "During the past week, how many cigarettes (per day) have been smoked in your presence in the room where devices were installed?"; and 3) "During the past week, how many hours (per day) have you been exposed in the room where the devices were installed?".

The sampling devices were installed in the main room following a standard protocol.[6] Nicotine and benzene were extracted and analyzed by gas chromatography with detection by mass spectrometry (GC/MS) at the Laboratory of the Public Health Agency of Barcelona (Spain). The analysis of the samples of saliva and urine were performed at IMIM Hospital del Mar Medical Research Institute in Barcelona. Salivary and urinary cotinine were measured by liquid chromatography coupled to tandem mass spectrometry with multiple reactions monitoring (LC/MS/MS).

Medians and interquartile ranges (IQR) were calculated. We performed a Kruskal-Wallis test and a linear trend test to compare the concentrations of the environmental markers and personal biomarkers with the answers to the Likert scale question proposed.

Spearman correlation coefficients (r_{sp}) were computed to assess the relationship between the intensity of exposure elicited by the score question and the markers of exposure. We compared the correlations between the scores of perceived SHS exposure proposed and the concentrations of airborne markers and biomarkers were statistically compared with those correlations between the conventional questions and the concentrations of airborne markers and biomarkers using the Meng's test.[7]

Results

Table 1 presents the median concentrations and IQR of environmental and personal markers categorized according to the Likert scale-based question ($p < 0.05$). We observed a positive linear relationship between the perception of SHS exposure and each of the direct measures ($p < 0.05$).

We found a high correlation of the score question with airborne nicotine ($r_{sp} = 0.806$, $p < 0.05$) and moderate with benzene ($r_{sp} = 0.464$, $p < 0.05$). We also found a high correlation of the score question with salivary cotinine ($r_{sp} = 0.752$, $p < 0.05$) and urinary cotinine ($r_{sp} = 0.626$, $p < 0.05$). We did not find statistically significant differences between the correlations of the score question proposed and the conventional ones (Table 2). When we stratified the data according to sex, age (<30 and ≥30 years), and size of the room where the devices were installed (<20 and ≥20 m^2) all the correlations were similar (data not shown).

Discussion

Our results show that the questions proposed to self-report the intensity of SHS exposure at home were valid when assessed against concentrations of selected markers of SHS exposure (airborne nicotine and cotinine in body fluids). Moreover, the correlations between the score question and all objective markers were statistically similar to those between the conventional questions and the objective markers. In this sense, the proposed question was at least as good as the conventional quantitative questions at assessing the exposure to SHS at home. The poorest discrimination was obtained for benzene concentrations for both the conventional questions and the new questions to validate. This may be because benzene is a less specific airborne marker of SHS exposure.

Previous studies showed similar results in the assessment of self-reported SHS exposure against biomarkers[8] and against airborne markers in other settings such as workplaces.[9] However, many of the studies reported lower correlations to the ones obtained in ours. These differences may be explained by the fact that our questionnaire was applied immediately after the week the markers were collected, avoiding a recall bias.

The main limitation of our study is related to the use of an opportunistic limited-sized sample of volunteers. In this sense, external validity could be hampered by the non-random sample selection and the power of the experiment could be relatively low. Nevertheless, the use of an opportunistic sample allowed us to include those participants who confirmed no other potential sources of tobacco exposure in other settings. Other potential limitation is the lack of assessment of other potential sources of nicotine and benzene, such as those cumulated in the dust of homes (thirdhand smoke) from previous tobacco consumption in the homes of smokers.[10] Finally, as a strength, whereas many of the previous studies measured either biomarkers or environmental markers, we were able to compare our questions to both types of markers and other conventional questions of SHS exposure.

In conclusion, the questions proposed to evaluate the perceived intensity of SHS exposure at home distinguished between different concentrations of nicotine in air and cotinine in saliva and urine. Moreover, we observed a similar discrimination with conventional questions of SHS exposure. These questions may be valid for use in future investigations to characterize SHS exposure at home, although further research in larger and more diverse samples should be conducted.

Table 1
Median concentrations and IQR of airborne markers and personal markers according to the perception of exposure to secondhand smoke at home through a Likert scale question.

Perceived intensity of exposure to SHS	n	Airborne nicotine ($\mu g/m^3$) Median (IQR)	Airborne benzene ($\mu g/m^3$) Median (IQR)	Salivary cotinine (ng/ml) Median (IQR)	Urinary cotinine (ng/ml) Median (IQR)
High	1	9.49	4.75	0.94	7.59
Medium	4	2.35 (0.55, 5.43)	0.38 (0.31, 4.90)	0.95 (0.41, 1.18)	3.57 (2.08, 6.16)
Low	17	1.03 (0.30, 1.92)	0.46 (0.39, 3.76)	0.29 (0.19, 0.45)	1.25 (0.71, 2.57)
Very low	27	0.01 (0.01, 0.12)	0.32 (0.24, 0.50)	0.05 (0.05, 0.18)	0.44 (0.28, 1.23)
	p-value[a]	<0.001	0.016	<0.001	0.002
	p-value[b]	<0.001	0.004	<0.001	<0.001

IQR: interquartile range.
[a] Kruskal-Wallis test.
[b] Linear trend test.

Table 2
Spearman correlations (r_{sp}) and 95%CI between airborne markers, personal markers and the score question for the perception of exposure to secondhand smoke (SHS) at home and two conventional questions for SHS assessment.

	Airborne nicotine r_{sp} 95%CI	Airborne benzene r_{sp} 95%CI	Salivary cotinine r_{sp} 95%CI	Urinary cotinine r_{sp} 95%CI
Score question for the perception of exposure to SHS[a]	0.806 (0.679, 0.886)[c]	0.464 (0.210, 0.659)[c]	0.752 (0.597, 0.853)[c]	0.626 (0.418, 0.771)[c]
Number of cigarettes smoked at home	0.796 (0.663, 0.880)[c]	0.396 (0.129, 0.609)[c]	0.713 (0.540, 0.828)[c]	0.602 (0.386, 0.755)[c]
p-value[b]	0.792	0.255	0.375	0.643
Number of hours of exposure at home	0.793 (0.659, 0.878)[c]	0.448 (0.191, 0.648)[c]	0.703 (0.526, 0.822)[c]	0.601 (0.385, 0.755)[c]
p-value[b]	0.724	0.777	0.250	0.615
Number of smokers at home	0.854 (0.754, 0.915)*	0.525 (0.286, 0.702)*	0.807 (0.680, 0.887)*	0.652 (0.454, 0.789)*
p-value[b]	0.173	0.295	0.173	0.610

CI: confidence interval; SHS: secondhand smoke.
[a] Score scale for the perception of exposure to SHS from 0 (not contaminated) to 10 (highly contaminated).
[b] Meng's Z-test for correlated correlation coefficients.
[c] $p < 0.05$.

Authorship contributions

J.M. Martínez-Sánchez, E. Fernández and I. Galán conceived the study and questions proposed to measure second hand smoke exposure. X. Sureda, M. Fu, E. Fernández and J.M. Martínez-Sánchez conducted the fieldwork. R. Pérez-Ortuño and J.A. Pascual developed the analytical method to quantify the cotinine in saliva and urine and also performed the analyses of biological samples. J.C. Martín-Sánchez and C. Lidón-Moyano prepared and analyzed the database. J.M. Martínez-Sánchez and A. González-Marrón drafted the first draft of the manuscript. All authors contributed substantially to the conception, design, and interpretation of data. All authors contributed to the manuscript and approved its final version. J.M. Martínez-Sánchez is the guarantor.

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Conflicts of interest

None.

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ANEXO VIII. CARTA AL EDITOR DERIVADA DE LA FORMACIÓN PREDOCTORAL - «QUIS CUSTODIET IPSOS CUSTODES?»

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CARTA AL DIRECTOR

Quis custodiet ipsos custodes?

Who will guard the guardians?

Quis custodiet ipsos custodes?
Sátiras de Juvenal

Un artículo publicado recientemente en *The British Medical Journal*[1] ha puesto de manifiesto que la mitad de los editores de diferentes revistas médicas estadounidenses (50,6% de 713 editores de 52 revistas) reciben pagos sistemáticos de la industria farmacéutica y que hasta en dos tercios de las revistas incluidas en el estudio no se incluye una sección de conflictos de intereses del comité editorial.

Investigación y publicación deberían ser procesos asépticos, en los que autores, revisores y editores trabajaran con ética y rigor. Sin embargo, con frecuencia, estos procesos se ven cuestionados por la participación de actores externos (frecuentemente *stakeholders*, como inversores o patrocinadores) que pueden suponer una injerencia negativa, dando lugar a los mencionados conflictos de intereses.

En la mayoría de revistas científicas, en el momento de aceptar un manuscrito para su revisión, se requiere la declaración del autor o de los autores de los conflictos de intereses, los cuales pueden abarcar tanto aspectos financieros como no financieros[2]. Sin embargo, la revelación de dichos conflictos cuando afectan a revisores o a miembros del comité editorial no está tan extendida[1,2].

Esta situación de «caja negra» en la que se puede convertir el proceso de revisión de un manuscrito podría tener al menos dos consecuencias. Por un lado, la confianza de los lectores puede verse afectada ante la posibilidad de que la presencia de conflictos de intereses esté, efectivamente, sesgando la información que reciben. Relacionado con este aspecto nos encontramos el «ruido» que se introduce en la evidencia científica y al que se ve sometido el lector al contemplar conclusiones antagónicas ante preguntas de investigación idénticas, como ha ocurrido en epidemiología nutricional[3] o control del tabaquismo[4]. Este «ruido» puede incluso alcanzar a la clase política y al imaginario colectivo de la opinión pública, creando interferencias a la hora de implementar nuevas políticas de salud pública basadas en la evidencia científica. Por otro lado, los miembros del comité editorial, como responsables finales de las revistas, toman la decisión final de qué manuscritos acaban convirtiéndose en artículos, hecho que supone la visualización en positivo de todas las contingencias por las que transita un investigador hasta conseguir que sus hallazgos se incorporen a la evidencia científica en su campo, y cuáles no. Esta segunda situación, el rechazo *(rejection)*, se podría estar dando en algunas situaciones por pura arbitrariedad, pudiendo estar llevando trabajos de investigación que en condiciones objetivas en las cuales aspectos como la calidad, innovación o impacto en la población se tuvieran en consideración, temporalmente a la basura y generando frustraciones[5].

En definitiva, la investigación en cualquier disciplina es un proceso arduo y complejo y los rechazos y aceptaciones tendrían que basarse en decisiones meramente objetivas por parte de los editores, garantes de su publicación. Pero, ¿quién vigila a los propios vigilantes?

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A. González-Marrón*, J.M. Martínez-Sánchez, J.C. Martín-Sánchez, N. Matilla Santander y À. Cartanyà-Hueso

Grupo de Evaluación de Determinantes de Salud y Políticas Sanitarias, Facultad de Medicina y Ciencias de la Salud, Universidad Internacional de Cataluña, Sant Cugat del Vallés, Barcelona, España

* Autor para correspondencia.
Correo electrónico: agonzalezm@uic.es
(A. González-Marrón)

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ANEXO IX. CARTA AL EDITOR DERIVADA DE LA FORMACIÓN PREDOCTORAL - «SARAMPIÓN EN EUROPA: NECESIDAD DE ACCIÓN GLOBAL Y LOCAL PARA SU ERRADICACIÓN»

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Miguel López Gobernado*, Jaime Hernández Bartolomé, David Villalba Gil y Alberto Castellanos Asenjo

Servicio de Prevención de Riesgos Laborales, Hospital Clínico Universitario de Valladolid, Valladolid, España

* Autor para correspondencia.
Correo electrónico: mlopezgob@saludcastillayleon.es (M. López Gobernado).

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Sarampión en Europa: necesidad de acción global y local para su erradicación

Measles in Europe: necessity of global and local action to achieve its eradication

Sr. Director:

Uno de los objetivos actuales de la Organización Mundial de la Salud (OMS) es la erradicación del sarampión y la rubéola en al menos cinco regiones de la OMS para el año 2020, como se recoge en el Plan Estratégico Mundial encabezado por la Iniciativa Sarampión y Rubéola[1]. Sin embargo, en los últimos meses, el sarampión se ha convertido en un importante problema de salud pública en Europa debido al aumento de casos registrados en diversos brotes[2]. Atendiendo a la definición de «enfermedad emergente» de la OMS[3], en la actualidad podríamos incluso considerar este proceso como tal.

Cabe destacar que la mayor incidencia de casos se está registrando en países con una cobertura de vacunación con la segunda dosis de vacuna triple vírica muy por debajo del objetivo marcado del 95% para conseguir la inmunidad de grupo o comunitaria[4]. Este hecho está permitiendo que el elevado número básico de reproducción del sarampión, el más alto entre las enfermedades transmisibles, se manifieste en bolsas de población susceptible y resulte en largas cadenas de transmisión. Sin embargo, también se han registrado recientemente brotes en países como España, donde la cobertura de vacunación se alcanza o es cercana al 95% para el global nacional, pero no es así en el ámbito autonómico[5], tal como demuestra el brote que tuvo lugar en el primer trimestre de 2017 en Barcelona y que, a fecha 7 de abril, había afectado a 46 personas[2].

Disponer de una vacuna del sarampión tremendamente eficaz nos obliga a identificar los obstáculos reales con que se encuentran los sistemas de salud para controlar y erradicar una enfermedad ya descrita en el siglo IX. Uno de ellos es el movimiento antivacunas, que en nuestro país afortunadamente se puede considerar anecdótico[6]. Por otro lado, hay que referirse a los determinantes sociales de la salud. La desigualdad y la falta de acceso a los recursos sanitarios con origen en la marginalidad y la discriminación de determinados grupos se han demostrado en el pasado como un elemento clave para favorecer la circulación del sarampión[7]. Este hecho nos debe llevar a aproximar el *zoom* al ámbito local e implementar actividades de promoción de la salud a través de programas de educación sanitaria que tengan como objetivo la repesca de los individuos más vulnerables. Finalmente, no podemos olvidar la actual perspectiva global de las enfermedades transmisibles, en la que los agentes infecciosos recorren distancias que eran impensables en el pasado, reforzando los sistemas de vigilancia. Es posible que solo un correcto balance entre ambas pueda permitir la erradicación de esta enfermedad.

Declaraciones de autoría

Los dos autores declaran haber contribuido por igual a la redacción de esta carta.

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Adrián González-Marrón* y José M. Martínez-Sánchez

Grupo de Evaluación de Determinantes de Salud y Políticas Sanitarias, Facultad de Medicina y Ciencias de la Salud, Universidad Internacional de Cataluña, Sant Cugat del Vallés (Barcelona), España

* Autor para correspondencia.
Correo electrónico: agonzalezm@uic.es (A. González-Marrón).

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