Determinantes de las concentraciones de cotinina en saliva, dependencia a la nicotina y estadios del cambio en fumadores

Marcela Fu Balboa

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Universitat de Barcelona
Facultat de Medicina
Departament de Ciències Clíniques

DETERMINANTES DE LAS CONCENTRACIONES DE COTININA EN SALIVA, DEPENDENCIA A LA NICOTINA Y ESTADIOS DEL CAMBIO EN FUMADORES

Memoria para optar al título de Doctor

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Programa de Doctorado en Medicina
Barcelona 2011

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Grupo de investigación en Prevención y control del cáncer

– Barcelona 2011 –

AGRADECIMIENTOS

Esta tesis es fruto de un largo trabajo en el cual están involucradas muchas personas, sin cuya contribución individual y colectiva no hubiera sido posible. Quisiera en unas pocas líneas agradecer a todos quienes de una manera directa o indirecta han contribuido a que esto sea una realidad.

Quisiera agradecer en primer lugar a mi director de tesis, Esteve Fernández, por acogerme en su grupo de trabajo; por su profesionalismo, dedicación y su gran paciencia. Gracias Esteve por darme la oportunidad de aprender de ti. Por tu gran calidad humana, por tu apoyo y ayuda en los buenos momentos y en los no tan buenos.

A M. Teresa Anguera, quien me guió en mis primeros pasos del doctorado. Gracias M. Teresa por la oportuna ayuda que siempre me has dado, y sobre todo por el cariño y consideración que siempre me has demostrado.

Al equipo investigador del DCOT, por los consejos y aportes realizados a cada una de las publicaciones derivadas de esta tesis.

A mis compañeras del Programa de Prevención del ICO, especialmente a Gemma Binefa, Núria Díaz, Olga López y Mercè Margalef, por su cariño y ayuda incondicional... *i per la vostra paciència per sentir-me parlar català!* A Carmen Vidal, por su apoyo y generosidad. A Montse García, por los útiles consejos recibidos en más de alguna ocasión. A mis compañeros de la Unidad de Control del Tabaquismo: Anna, Cristina, Esther, Jose, Montse y Xisca, por los buenos ánimos, el espíritu positivo y el compañerismo que hemos logrado crear. Gracias Jose por el trabajo compartido, por tu estímulo para hacer las cosas y también por tu amistad. No puedo olvidar a Anna Schiaffino y Jorge Twose, compañeros que ya no están en

el ICO; gracias por haber confiado en mí y haber permitido que pudiera integrar este grupo de trabajo tan enriquecedor.

A Antonio, Maruja, Rodrigo, Pilar y Tomás, quienes han sido mi familia en Barcelona. Gracias por todo el soporte, cariño y confianza que me han demostrado durante tanto tiempo. Les tendré en mi corazón por siempre.

Finalmente, quisiera agradecer de una manera muy especial a mi familia, quienes confiaron en mí y permitieron que marchara tan lejos de casa a vivir una experiencia inimaginable. Gracias mamá, por tu inmenso amor y por tantos años de dedicación y esfuerzo.

Barcelona, septiembre de 2011.

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Antecedentes

La adicción a los cigarrillos se debe principalmente a la nicotina que contienen, pero poco se conoce sobre su dosificación en fumadores. La medición de la cotinina, el principal metabolito de la nicotina, ayuda a caracterizar la dosis de nicotina recibida por los fumadores, reflejando diferencias en la conducta tabáquica y en la motivación para dejar de fumar, en el tipo de cigarrillos fumados y en el metabolismo de la nicotina en diferentes poblaciones.

Hipótesis

1. El número de cigarrillos fumados será el principal determinante de las concentraciones de cotinina en saliva: las concentraciones de cotinina en saliva se incrementarán al incrementar el consumo de cigarrillos.

2. Las concentraciones de cotinina en saliva serán mayores cuanto menor tiempo haya transcurrido desde que el fumador se despierta hasta que fuma el primer cigarrillo.

3. Los fumadores más dependientes tendrán concentraciones de cotinina en saliva más altas que los fumadores menos dependientes.

4. Los fumadores muy dependientes y con altas concentraciones de cotinina en saliva estarán menos preparados para dejar de fumar.

Objetivos

1. Caracterizar la distribución de las concentraciones de cotinina en saliva en fumadores y los factores que la influencian.

2. Estudiar la asociación entre el tiempo transcurrido hasta el primer cigarrillo fumado después de despertarse y la concentración de cotinina en saliva.

3. Analizar la relación entre la dependencia a la nicotina y las concentraciones de cotinina en saliva.

4. Estudiar la preparación para dejar de fumar (estadios del cambio de Prochaska y DiClemente) de acuerdo al perfil de dependencia y los niveles de cotinina en saliva.

Metodología

Los datos provienen de dos estudios independientes. Uno de ellos es un estudio transversal (2004-2005) de una muestra representativa de la población general de Barcelona (n=1245), en el que se utilizó un cuestionario sobre tabaquismo y exposición pasiva al humo del tabaco, así como una muestra de saliva para determinar la concentración de cotinina. El otro también es un estudio transversal (2006) de una muestra representativa de la población española ≥l8 años (n=2522), en el que se utilizó una entrevista telefónica sobre consumo de tabaco y exposición al humo ambiental del tabaco. Para los análisis se tomaron en consideración tanto a los fumadores diarios como a los fumadores en su conjunto (diarios y ocasionales). Se calcularon medias y desviaciones estándar o medianas y rangos intercuartílicos, según fuera apropiado, para describir los datos. Se utilizaron análisis descriptivos y modelos de regresión múltiple en función de los objetivos propuestos.

Resultados

Las concentraciones de cotinina en saliva aumentaron a mayor consumo de cigarrillos hasta llegar aproximadamente a los 20 cigarrillos, nivel donde las concentraciones de cotinina se estabilizaban. El consumo diario de cigarrillos, el momento del día en que se fuma más y el tiempo transcurrido desde que el fumador se despierta hasta que fuma su primer cigarrillo estuvieron significativamente

relacionados con la concentración de cotinina en saliva. Éste último en particular demostró ser un buen indicador de dependencia. Por otra parte, no se observó una asociación entre las concentraciones de cotinina en saliva y los estadios del cambio, si bien en cada estadio se observó que las concentraciones de cotinina aumentaban a mayor consumo de cigarrillos, a mayor nivel de dependencia y a menor tiempo transcurrido hasta fumar el primer cigarrillo del día.

Conclusiones

Las concentraciones de cotinina en saliva están relacionadas con el consumo diario de cigarrillos, el tiempo transcurrido hasta fumar el primer cigarrillo del día y el nivel de dependencia a la nicotina, no así con los estadios del cambio en los que se encuentran los fumadores. El consumo diario de cigarrillos, el tiempo hasta fumar el primer cigarrillo y el momento del día en que se fuma más son buenos indicadores del nivel de dependencia del fumador.

RESUM

Antecedents

L'addicció a les cigarretes és causada principalment per la nicotina que contenen, però no es coneix gaire sobre la seva dosificació en fumadors. La medició de la cotinina, el principal metabòlit de la nicotina, ajuda a caracteritzar la dosi de nicotina rebuda pels fumadors, que reflexa diferències en la conducta tabàquica i en la motivació per deixar de fumar, en el tipus de cigarretes fumades i en el metabolisme de la nicotina en diferents poblacions.

Hipòtesis

1. El nombre de cigarretes fumades serà el principal determinant de les concentracions de cotinina en saliva: les concentracions de cotinina en saliva s'incrementaran en incrementar el consum de cigarretes.

2. Les concentracions de cotinina en saliva seran més altes quant menys temps hagi transcorregut des que el fumador es desperta fins que fuma la primera cigarreta.

3. Els fumadors més dependents tindran concentracions de cotinina en saliva més altes que els fumadors menys dependents.

4. Els fumadors molt dependents i amb altes concentracions de cotinina en saliva estaran menys preparats per deixar de fumar.

Objectius

1. Caracteritzar la distribució de les concentracions de cotinina en saliva en fumadors i els factors que la influencien.

2. Estudiar l'associació entre el temps transcorregut fins a la primera cigarreta fumada després de despertar-se i la concentració de cotinina en saliva.

3. Analitzar la relació entre la dependència a la nicotina i les concentracions de cotinina en saliva.

4. Estudiar la preparació per deixar de fumar (estats del canvi de Prochaska i DiClemente) d'acord al perfil de dependència i els nivells de cotinina en saliva.

Metodologia

Les dades provenen de dos estudis independents. Un d'ells és un estudi transversal (2004-2005) d'una mostra representativa de la població general de Barcelona (n=1245), en el qual es va utilitzar un qüestionari sobre tabaquisme i exposició passiva al fum del tabac, així com una mostra de saliva per determinar la concentració de cotinina. L'altre també és un estudi transversal (2006) d'una mostra representativa de la població espanyola ≥18 anys (n=2522), en el qual es va utilitzar una entrevista telefònica sobre consum de tabac i exposició al fum ambiental del tabac. Per a les anàlisis es van considerar tant als fumadors diaris com als fumadors en el seu conjunt (diaris i ocasionals). Es van calcular mitjanes i desviacions estàndard o medianes i rangs interquartílics, segons fos apropiat, per descriure les dades. Es van utilitzar anàlisis descriptives i models de regressió múltiple en funció dels objectius proposats.

Resultats

Les concentracions de cotinina en saliva augmentaven a més consum de cigarretes fins a arribar aproximadament a les 20 cigarretes, nivell on les concentracions de cotinina s'estabilitzaven. El consum diari de cigarretes, el moment del dia en que es fuma més i el temps transcorregut des que el fumador es desperta fins que fuma la seva primera cigarreta varen estar significativament relacionats amb la concentració de cotinina en saliva. Aquest últim en particular va demostrar ésser un bon

indicador de dependència. Per una altra banda, no es va observar una associació entre les concentracions de cotinina en saliva i els estadis del canvi, malgrat que en cada estadi es va observar que les concentracions de cotinina augmentaven a més consum de cigarretes, a major nivell de dependència i a menor temps transcorregut fins a fumar la primera cigarreta del dia.

Conclusions

Les concentracions de cotinina en saliva estan relacionades amb el consum diari de cigarretes, el temps transcorregut fins a fumar la primera cigarreta del dia i el nivell de dependència a la nicotina, no així amb els estadis del canvi en els quals es troben els fumadors. El consum diari de cigarretes, el temps fins a fumar la primera cigarreta i el moment del dia en què es fuma més són bons indicadors del nivell de dependència del fumador.

ABSTRACT

Background

Addiction to cigarettes is caused mainly by the nicotine contained in them, but little is known about its dosage in smokers. Measurement of cotinine, the main metabolite of nicotine, helps to characterise the nicotine dose taken by smokers, indicating differences in the smoking behaviour and in the motivation to quit smoking, in the type of cigarettes smoked, and in the metabolism of nicotine in different populations.

Hypotheses

1. The number of cigarettes smoked will be the main determinant of salivary cotinine concentration: salivary cotinine concentration will increase as cigarette consumption increases.

2. Salivary cotinine concentration will be higher at lesser time elapsed since the smoker wakes-up until he/she smokes his/her first cigarette.

3. High-dependent smokers will have higher salivary cotinine concentration than less-dependent smokers.

4. High-dependent smokers with high salivary cotinine concentration will be less prepared to quit smoking.

Objectives

1. To characterise the distribution of salivary cotinine concentration in smokers as well as the factors influencing it.

2. To study the association between time to first cigarette smoked after waking-up and salivary cotinine concentration.

3. To analyse the relation between nicotine dependence and salivary cotinine concentration.

4. To study the readiness to quit smoking (stages of change by Prochaska and DiClemente) according to the profile of dependence and salivary cotinine levels.

Methods

Data are derived from two independent studies. One of them is a cross-sectional study (2004-2005) of a representative sample of the general population of Barcelona, Spain (n=1245), where a questionnaire on smoking and exposure to second-hand smoke as well as a saliva specimen for determination of cotinine concentration was used. The other one is also a cross-sectional study (2006) of a representative sample of the Spanish general population ≥18 years old (n=2522), where a telephone interview on smoking and second-hand smoke exposure was used. We considered for the analyses both daily smokers and all smokers (daily and occasionally smokers). We calculated means and standard deviations or medians and interquartile ranges, as appropriate, to describe the data. We used descriptive analyses and multiple regression models according to the objectives.

Results

The more the cigarette consumption the higher the salivary cotinine concentration up to approximately 20 cigarettes, the level where cotinine concentrations flattened. Cigarette consumption, the moment of the day the smoker smokes more, and the time elapsed since the smoker wakes up until he/she smokes his/her first cigarette were significantly related to salivary cotinine concentration. Particularly, time to first cigarette was a good indicator of dependence. On the other hand, we observed no association between salivary cotinine concentration and stages of change,

although in every stage we observed that cotinine concentrations were higher with higher cigarette consumption, higher nicotine dependence, and lesser time to the first cigarette of the day.

Conclusions

Salivary cotinine concentrations were related to daily cigarette consumption, time to first cigarette, and level of nicotine dependence, but not to stages of change of smokers. Daily cigarette consumption, time to first cigarette and the moment of the day the smoker smokes more are good indicators of smoker's dependence level.

1. INTRODUCCIÓN

El tabaquismo constituye la primera causa de muerte prevenible en los países desarrollados. Es el principal factor de riesgo para seis de las ocho causas más importantes de muerte en el mundo: enfermedad coronaria isquémica, enfermedades cerebrovasculares, infecciones del aparato respiratorio inferior, enfermedad pulmonar obstructiva crónica, tuberculosis y cáncer de pulmón[1]. La Organización Mundial de la Salud ha estimado que el consumo de tabaco hoy en día es el causante de más de cinco millones de muertes anuales en todo el mundo, y para el año 2030 se estima que esta cifra superará los ocho millones[1]. Sin embargo, el tabaquismo y sus efectos para la salud afectan no sólo a quienes fuman, sino también a quienes están expuestos pasivamente al humo del tabaco. Esta exposición constituye la principal causa de enfermedades como cáncer de pulmón o enfermedades coronarias en personas sanas no fumadoras, y es la causante de otros problemas respiratorios. Se ha estimado que en 2004 la exposición pasiva al humo del tabaco causó 603.000 muertes prematuras causadas principalmente por enfermedad coronaria isquémica y asma en adultos e infecciones del tracto respiratorio en niños[2]. En España, 53.155 muertes ocurridas en el año 2006 fueron atribuibles al consumo de tabaco en la población adulta de 35 y más años, cifra que representa el 14,7% de todas las muertes ocurridas en esos adultos durante ese año[3], mientras que la mortalidad atribuible a la exposición pasiva al humo del tabaco en casa y en el lugar de trabajo en 2002 se estimó entre 1.228 y 3.237 muertes anuales por cáncer de pulmón y enfermedades coronarias[4].

Los efectos nocivos del tabaco se reconocen desde hace décadas, desde los informes del *Royal College of Physicians of London* de 1962 en Inglaterra[5] y del *Surgeon General* de 1964 en Estados Unidos[6]. Se ha descrito una fuerte relación dosis-respuesta entre la cantidad y duración del consumo de tabaco y diversos efectos para la salud, de tal forma que un mayor consumo de tabaco y una mayor duración del mismo se relacionan con un mayor riesgo de enfermedad[7,8]. Aunque la

evidencia indica que los fumadores de pocos cigarrillos al día tienen un menor riesgo de enfermedad que quienes fuman más cigarrillos al día, se ha constatado que no existe un nivel "seguro" de consumo[9].

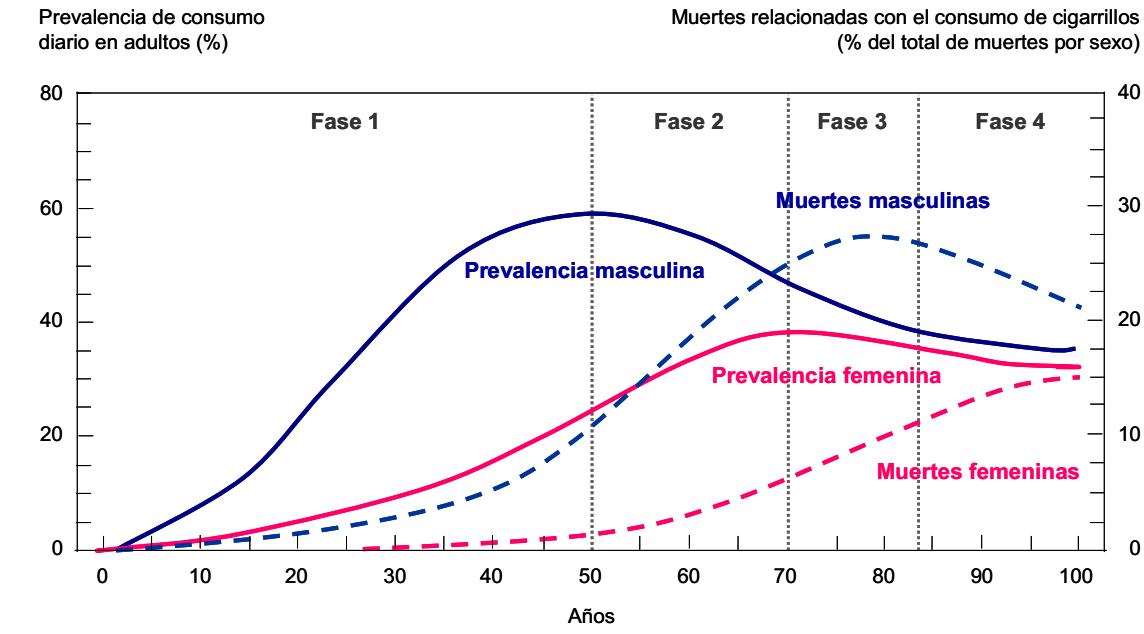
1.1. La epidemia del tabaquismo

Si bien los efectos del consumo de tabaco para la salud se pueden apreciar al poco tiempo de haberse iniciado éste, la mayor parte de los efectos nocivos no se hacen evidentes sino hasta años o incluso décadas después de haberse iniciado el consumo. Así, mientras el uso del tabaco se está elevando a nivel mundial y se han comenzado a desarrollar políticas para controlar su consumo en los países desarrollados, la epidemia de enfermedad y muerte relacionada con el tabaco apenas ha comenzado[1]. Por tanto, resulta de gran relevancia estudiar la dinámica del tabaquismo en las poblaciones para afrontar de mejor manera la evolución de la misma.

Se ha observado que la prevalencia de tabaquismo tiene unas características que varían a través del tiempo según diversas variables sociodemográficas. Esto ha llevado a proponer algunos modelos de la epidemia del tabaquismo en los países desarrollados[10-12]. Posiblemente el más extendido es el modelo propuesto por Lopez y cols.[13], que describe una serie de fases que pueden ser caracterizadas por los cambios producidos en tres variables: la prevalencia de fumadores regulares en la población adulta, la cantidad fumada por adulto en un período dado, y la mortalidad atribuible al tabaquismo[13]. Estas fases están representadas en la figura 1, y son las siguientes:

Fase I: Dura una o dos décadas y define los inicios de la epidemia del tabaquismo en una población. En esta fase, la prevalencia de consumo en los hombres es inferior al 15% y en las mujeres prácticamente no supera el 10%. El consumo de

Figura 1. Modelo de la epidemia del tabaquismo propuesto por Lopez y cols.



Adaptado de Lopez y cols.[13].

cigarrillos *per capita* es también relativamente bajo, inferior a los 500 cigarrillos al año por adulto, consumidos en su mayoría por los hombres. En esta fase, la enfermedad y muerte asociadas al tabaquismo aún no son evidentes.

Fase II: Puede abarcar dos o tres décadas. En esta fase, la prevalencia de tabaquismo en los hombres continúa ascendiendo rápidamente, alcanzando un pico que puede variar entre el 50 y el 80%, mientras que la proporción de ex-fumadores es relativamente baja. La prevalencia de tabaquismo en las mujeres tiene un desfase de una a dos décadas respecto a la de los hombres, pero su incremento es rápido. El consumo de cigarrillos por adulto varía entre 1000 y 3000 unidades al año, siendo en su mayoría también consumidos por los hombres, entre quienes el consumo podría estar entre los 2000-4000 cigarrillos anuales. Las actividades de control del tabaquismo son incipientes. Hacia el final de esta fase el tabaquismo causa alrededor del 10% de las muertes en los hombres y muy pocas en las mujeres.

Fase III: Se extiende unas tres décadas. La prevalencia de consumo en los hombres comienza a disminuir, posiblemente después de exceder el 60% durante un extenso período, alcanzando aproximadamente el 40% hacia el final de esta fase. La prevalencia de consumo tiende a ser más baja entre los hombres a partir de la mediana edad, muchos de los cuales se han vuelto ex-fumadores. El final de esta fase está caracterizado por un declive inicial en la prevalencia del consumo en las mujeres, al que le sigue una meseta que puede ser incluso más larga que aquélla propuesta en los hombres. El pico en la prevalencia de consumo en las mujeres es considerablemente menor, entre un 35 y 45%, gracias al mayor conocimiento de los efectos nocivos del tabaco para la salud. La disminución de la prevalencia de consumo sería significativamente mayor en las personas de mayor nivel educativo, quienes responden más favorablemente a las campañas de promoción de la salud sobre los efectos nocivos del consumo de tabaco. En promedio, el consumo entre los hombres adultos podría variar entre 3000 y 4000 cigarrillos por año, más cercano a 3000 al final del período, mientras que en las mujeres estaría probablemente en el rango de 1000 a 2000 cigarrillos por año. Quizás la característica más dominante de este período es el aumento de la mortalidad atribuible al tabaquismo, siendo del 10% al 25-30% de todas las muertes en los hombres, mientras que en las mujeres es aún comparativamente baja (alrededor del 5% de todas las muertes), pero va en aumento. Hacia el final de esta fase, las tasas de cáncer de pulmón en los hombres deberían haber alcanzado un pico de alrededor de 110-120/100.000 hombres. Las tasas de muerte por enfermedades relacionadas con el tabaquismo entre las mujeres deberían también aumentar bruscamente, a niveles alrededor de 25-30/100.000 mujeres. Existen condiciones más favorables para promulgar e implementar leyes integrales de control del tabaquismo.

Fase IV: La prevalencia de tabaquismo en ambos sexos continúa disminuyendo lentamente, más o menos en paralelo. La prevalencia de consumo en las mujeres debería estar alrededor del 30%, mientras que en los hombres se espera que sea ligeramente más alta, quizás de un 33-35%. El incremento de la mortalidad asociada al consumo de tabaco en los hombres puede alcanzar el 30-35% de todas las

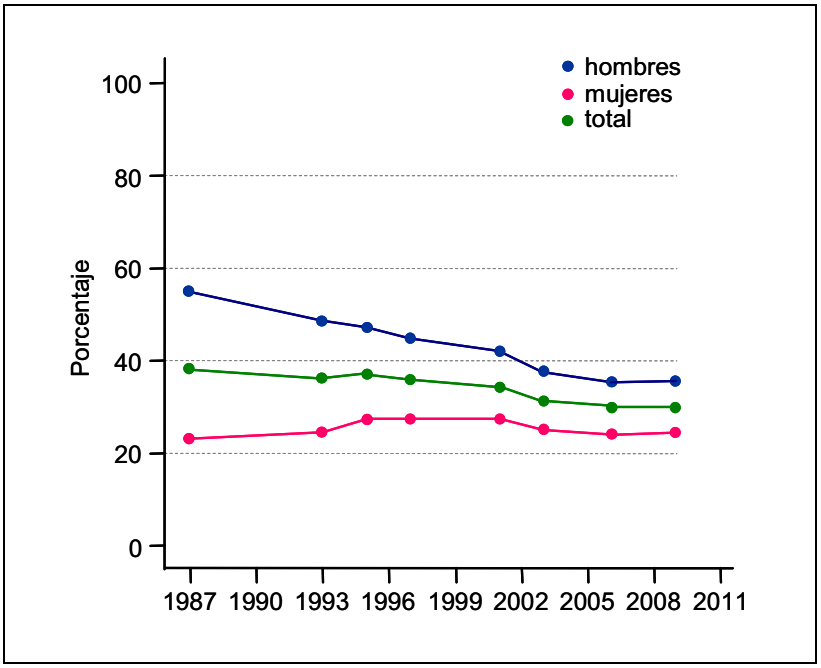
muertes, alcanzando el 40-45% de las muertes producidas en edades medias, y se espera que dentro de diez años comience a caer progresivamente. En las mujeres, las muertes debidas al tabaquismo deberían incrementarse rápidamente, aunque será proporcionalmente inferior a las de los hombres debido a su menor exposición acumulativa, esperándose un pico de alrededor del 20-25% de todas las muertes durante dos o tres décadas. A partir de entonces, la mortalidad atribuible al tabaquismo en ambos sexos declinaría progresivamente. El establecimiento de ambientes libres de humo comienza a ser un tema importante en esta fase. Las políticas necesitan abordar el problema de los fumadores dependientes a la nicotina que quieren dejar de fumar, pero no son capaces de hacerlo por sí mismos. Las diferencias sociales en la prevalencia de tabaquismo persisten e incluso pueden ampliarse.

1.2. Situación de la epidemia del tabaquismo en España

Mediante el análisis de las tres variables implicadas en el modelo de la epidemia del tabaquismo de Lopez y cols. (prevalencia de consumo, consumo de cigarrillos *per capita* y mortalidad atribuible al consumo de tabaco) es posible afirmar que España se encuentra en el inicio de la fase IV de la epidemia. En nuestro país, la prevalencia de consumo de tabaco en los hombres ha seguido una tendencia creciente y constante durante la primera mitad del siglo XX, alcanzando una prevalencia máxima de 59,1% en la década de 1970. Este pico fue seguido por una década de estabilización de la prevalencia, que luego disminuyó de manera continua y progresiva. En las mujeres el patrón de difusión del tabaquismo es diferente, con una prevalencia muy baja de consumo, que era del 5% a principios de la década de 1970, época en la cual comienza a aumentar hasta alcanzar una meseta en torno al 22% en la década de 1990, para luego comenzar a disminuir lentamente[14]. En estos últimos años, la prevalencia de fumadores presenta un descenso relativo promedio anual del 2,2% en los hombres entre los años 1987 y 2006, mientras que en las mujeres se detecta un incremento del 1,2% de 1987 a 2001, año a partir del cual se

produce un descenso anual del 2,9%[15] (figura 2). Los últimos datos de la Encuesta Europea de Salud en España de 2009 indican que, en ese año, el 29,9% de la población adulta española de 16 y más años eran fumadores diarios u ocasionales (35,3% de los hombres y 24,6% de las mujeres)[16].

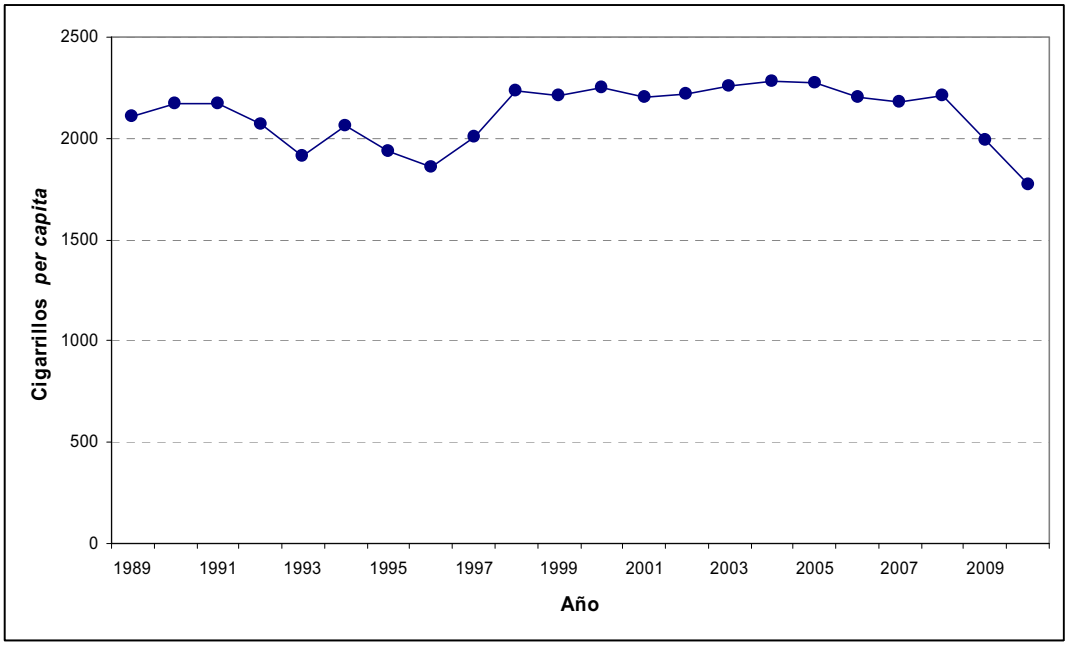
Figura 2. Evolución de la prevalencia de fumadores en la población adulta española ≥16 años (1987-2009).



Elaboración propia a partir de los datos de Nebot y Fernández[15] y de la Encuesta Europea de Salud en España[16].

El consumo de cigarrillos *per capita* puede ser estimado mediante las tendencias en las ventas de los mismos. En un análisis de las ventas de cigarrillos en España durante el período comprendido entre 1989 a 2008[15] se pudo apreciar que en un comienzo las ventas experimentaron un descenso anual del 1,6%; luego se produce un incremento anual del 4,9% entre los años 1996 y 2000, y a partir de entonces se recupera el descenso del 1,6% anual (figura 3). Esta tendencia no es homogénea en todas las comunidades autónomas: en la mayoría de ellas se aprecia una disminución de las ventas de cigarrillos que comienza en la década de 1990 y se mantiene estable desde entonces, de manera similar a la evolución de la prevalencia

Figura 3. Evolución de la venta de cigarrillos en la Península y Baleares (1989-2010).



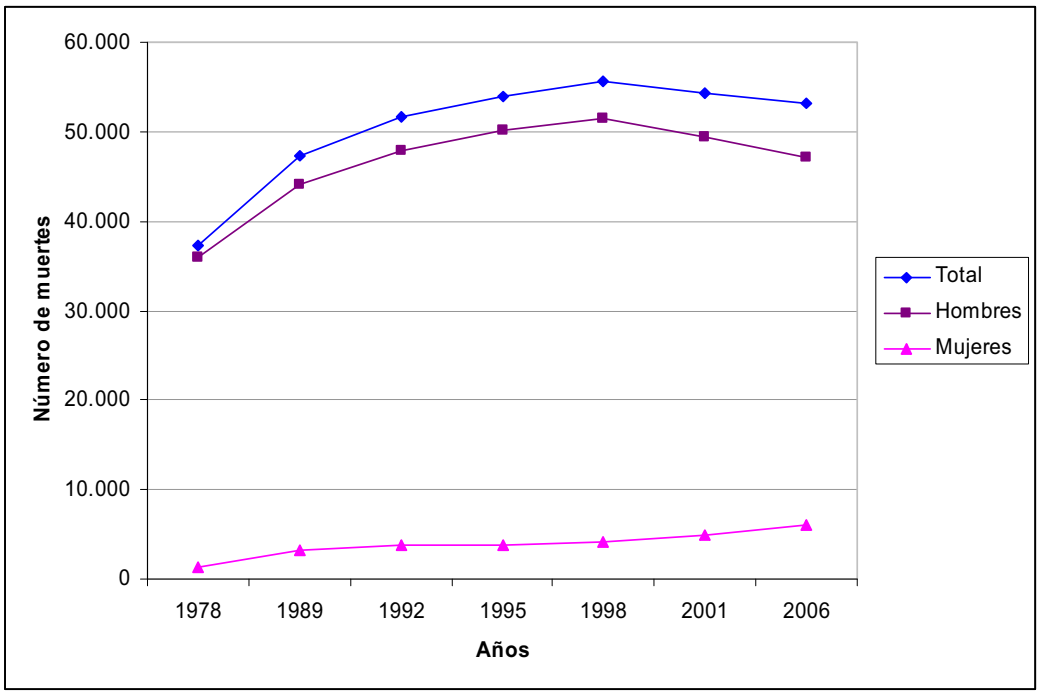
Elaborado a partir de los datos del Comisionado para el Mercado de Tabacos[18].

de consumo de tabaco; mientras que en las comunidades autónomas vecinas a Francia y Portugal las ventas siguen una tendencia creciente que parece tener relación con la compra de tabaco por parte de ciudadanos de dichos países. A partir de 2005, año en que entró en vigor la ley 28/2005[17], la tendencia en las ventas de cigarrillos en estas comunidades autónomas alcanza un punto de inflexión que puede ser explicado por las limitaciones a la venta y el suministro de tabaco establecidas en dicha ley[15]. A nivel estatal se destaca otro punto de inflexión en el año 2008, en donde se produce un descenso pronunciado en la venta de cigarrillos, probablemente debido a un descenso real en el consumo de cigarrillos *per capita*, o bien al aumento del consumo de otro tipo de tabaco (por ejemplo, tabaco de liar).

En cuanto a las muertes atribuibles al consumo de tabaco en España, se ha observado un incremento progresivo de estas muertes a expensas de un incremento en el número de muertes atribuibles en los hombres, si bien entre éstos se constata un ligero descenso de la tendencia observada a partir del año 2001. En las mujeres, el ascenso de las muertes atribuibles al consumo de tabaco es continuo, aunque

discreto[3] (figura 4). En 2006, las muertes atribuibles al consumo de tabaco fueron 47.174 en hombres de 35 y más años y 5.981 en mujeres de la misma franja de edad.

Figura 4. Muertes atribuibles al consumo de tabaco en individuos de 35 y más años. España, 1978-2006.



Elaborado a partir de los datos de Banegas y cols.[3].

1.3. Inicio del consumo

La mayor parte de las consecuencias del consumo de tabaco en la salud de los fumadores no se manifiestan sino hasta varios años después de que éste se ha iniciado[1]. Se ha descrito que quienes comienzan a fumar a temprana edad con mucha probabilidad llegarán a ser grandes fumadores en el futuro y serán altamente dependientes[19,20]. Considerando que entre un tercio y la mitad de los escolares en los países desarrollados experimentan con el tabaco antes de finalizar la escolarización secundaria[21], es importante intervenir en edades tempranas para evitar o al menos retardar el inicio del consumo[22].

En España, la iniciación al consumo se produce fundamentalmente en edad escolar entre los 12 y 18 años[23-25]. Diversas encuestas de salud de ámbito estatal, autonómico y local indican que la prevalencia de consumo en los jóvenes oscila entre 8,5 y 13,3% en los chicos y entre 12,7 y 16,4% en las chicas, observándose un descenso de la prevalencia en el tiempo: se ha estimado que en los últimos años el declive ponderado ha sido del 6,5% anual en los chicos y del 7,0% en las chicas[26].

Diversos factores operan en el inicio del consumo. Sin duda, uno de ellos es el papel modélico que juega el entorno social, ya sea la familia, amigos, educadores, compañeros de estudios o de trabajo. Las actitudes permisivas hacia el tabaquismo por parte de los pares y personas significativas, la existencia de modelos fumadores y la accesibilidad al tabaco pueden favorecer el inicio del consumo[27]. En los jóvenes, el consumo de tabaco puede representar una vía para la integración grupal. La experimentación con el tabaco puede ser una forma de probar límites al hacer algo que les está prohibido. Se ha asociado el inicio del consumo de tabaco en los jóvenes con la realización de actividades propias de los adultos, tal como frecuentar bares o discotecas, en donde es posible (en ausencia de políticas de control tal como la implementación de espacios sin humo) la experimentación con el tabaco en ausencia del control parental[28]. La percepción de beneficios asociados al consumo del tabaco, tal como relajación[29], el control del peso, o bien la percepción de lejanía de las consecuencias negativas del consumo generan una falsa sensación de autocontrol que facilita el inicio del consumo[30]. Además, los mensajes transmitidos por la publicidad de la industria tabaquera asocian el consumo de tabaco con valores tales como el éxito, la distinción o la modernidad[31]. Durante años la publicidad ha dirigido sus esfuerzos no sólo a conseguir nuevos consumidores de tabaco, sino también a hacer que quienes fuman lo continúen haciendo y que los ex-fumadores vuelvan a consumir. Para ello centra sus esfuerzos en los grupos vulnerables, como los jóvenes[30], las mujeres[32], y en general las poblaciones más desfavorecidas[1]. La publicidad fomenta las actitudes positivas hacia el consumo, favoreciendo la predisposición a fumar y consecuentemente la experimentación[30].

Por otra parte, existen también factores psicológicos asociados al inicio del consumo. En los jóvenes, se ha visto que la iniciación en el consumo de tabaco está frecuentemente ligada a la extroversión, al carácter impulsivo y ansioso, a la tendencia a asumir riesgos, etc. También se ha descrito una asociación entre el consumo y problemas de integración, baja autoestima, búsqueda de sensaciones novedosas, pobre rendimiento escolar y rebeldía[23].

Otro factor que también se ha relacionado con el inicio del consumo es el genético. Estudios de cohortes de gemelos sugieren que los factores genéticos juegan un rol importante en la iniciación, el mantenimiento, la magnitud del consumo y la dependencia. Los resultados de un metaanálisis indicaban que el 48,6% de la iniciación al consumo y el 28,3% del consumo continuado son atribuibles a factores genéticos, existiendo diferencias por sexo[33]. Asimismo, se ha debatido sobre la relación existente entre los condicionantes genéticos y sociales del consumo, donde los condicionantes sociales pueden facilitar o inhibir la predisposición genética al consumo y la adicción, y a su vez la expresión genética puede acelerar o ralentizar los cambios sociales en el consumo[34]. En este sentido, cuando el consumo de tabaco se vuelve socialmente no aceptado en la población, las influencias genéticas pueden predecir mejor el consumo de tabaco, pues los fumadores sociales, con una menor dependencia, harán más acciones por evitar el consumo que aquéllos con una predisposición genética a la dependencia. Y al revés, la predisposición genética puede llegar a afectar los patrones de consumo: durante las fases iniciales de la epidemia del tabaquismo la predisposición genética hace más difícil para algunos fumadores evitar el consumo, ralentizando el ritmo del cambio social; mientras que en estadios más avanzados de la epidemia, las políticas de control del tabaquismo y las restricciones sociales aceleran las tasas de abandono en ambos grupos de fumadores[34].

1.4. Mantenimiento del consumo

Un factor clave que interviene en el mantenimiento del consumo es el componente conductual asociado al consumo regular y continuado: el fumador comienza a asociar estados de ánimo, situaciones o factores ambientales específicos con los efectos de recompensa de la nicotina[35]. Muchas veces se fuma mientras se toma el café o después de la comida, y esta conducta repetitiva refuerza y condiciona el consumo. Algunas circunstancias tales como el estrés, presión laboral, problemas familiares, etc. también favorecen el consumo, por la mera repetición del acto de fumar en tales circunstancias. Por otra parte, las sensaciones placenteras a nivel del tacto, gusto, olfato y sensaciones visuales asociadas al consumo (manipulación oral y manual, ceremonial del encendido, sabor y aroma, etc.) también refuerzan el consumo continuado[35].

También se han descrito factores genéticos que intervienen en el mantenimiento del consumo. Estudios en gemelos evidencian las influencias genéticas no sólo en la iniciación, sino también en el uso prolongado de tabaco y en muchas medidas indirectas de dependencia del tabaco, incluyendo la cantidad consumida y la persistencia[36,37]. Los hallazgos encontrados parecen indicar que la plasticidad neuronal y el aprendizaje son aspectos determinantes de las diferencias individuales en la vulnerabilidad a la dependencia a la nicotina[35]. Las nuevas tecnologías genómicas, junto con métodos avanzados de investigación en los frentes experimental, bioinformático, estadístico y epidemiológico, prometen un amplio campo de investigación, cuyos avances permitirán la mayor integración de los mecanismos neurobiológicos en los esfuerzos de prevención y control en salud pública[38].

Finalmente, existen factores farmacológicos asociados al mantenimiento del consumo. Entre ellos destacan los efectos producidos por la nicotina, una de las sustancias más relevantes del humo del tabaco, como se revisa brevemente a continuación.

1.5. Adicción a la nicotina

La adicción al tabaco es compleja, debido a la interacción de diversos factores farmacológicos, genéticos, conductuales y socio-ambientales. El determinante más importante de la adicción al tabaco es la nicotina: además de ser el principal alcaloide del tabaco (alrededor del 95% del contenido total de alcaloides[35]), es el principal responsable de su efecto adictivo[39].

Las razones farmacológicas para el consumo de la nicotina son las sensaciones placenteras que produce, como la mejora del estado de ánimo (por la evitación de los síntomas de abstinencia) y del funcionamiento físico o mental[35]. Una vez inhalada al fumar, la nicotina es rápidamente absorbida en el epitelio del tracto respiratorio, la mucosa bucal o incluso la piel. La nicotina llega rápidamente al cerebro, donde se une a receptores colinérgicos nicotínicos, liberando diversos neurotransmisores como la dopamina, serotonina, noradrenalina y acetilcolina. La dopamina produce una experiencia placentera y es un elemento clave en los efectos reforzadores de la nicotina. Las neuronas dopaminérgicas en el área tegmentaria ventral del mesencéfalo y en el núcleo *accumbens* son cruciales en la recompensa inducida por la droga; ambas regiones tienen un rol en las percepciones de placer y recompensa. Otros neurotransmisores que pueden estar implicados en la adicción a la nicotina son las hipocretinas, que son neuropéptidos producidos en el hipotálamo lateral que regulan los efectos estimulantes de la nicotina en los centros de recompensa en el cerebro[35].

Con la exposición repetida a la nicotina se desarrolla la neuroadaptación o tolerancia a algunos de sus efectos, lo que provoca un aumento de las conexiones de los receptores colinérgicos nicotínicos, probablemente en respuesta a la desensibilización de los receptores mediada por la nicotina. Se cree que esta desensibilización tiene un rol en la tolerancia y la dependencia: en los fumadores crónicos, las ansias por fumar y los síntomas de abstinencia comenzarían cuando los receptores previamente desensibilizados se vuelven receptivos durante los períodos

de abstinencia, como por ejemplo durante el sueño nocturno. La unión de la nicotina con estos receptores durante el consumo alivia las ansias de fumar y los síntomas de abstinencia. El consumo regular de cigarrillos mantiene una saturación casi completa de los receptores nicotínicos. Al mantener niveles suficientes de nicotina en la sangre para prevenir los síntomas de abstinencia también se derivan efectos de recompensa de los refuerzos condicionados asociados al consumo, tal como el gusto y la sensación del humo. La abstinencia de nicotina causa ansiedad y estrés, que son poderosos incentivos para volver a consumir tabaco.

Efectos psicoactivos de la nicotina: La nicotina induce placer y reduce el estrés y la ansiedad; ayuda a modular los niveles de excitación y a controlar el ánimo. Fumar mejora la concentración, el tiempo de reacción y el desempeño de ciertas tareas; aunque el alivio de los síntomas de abstinencia es probablemente la razón principal de este mejor desempeño y del estado de ánimo elevado[39].

Síndrome de abstinencia a la nicotina: En cuanto los niveles de nicotina disminuyen, los fumadores dependientes comienzan a experimentar los síntomas de abstinencia, entre ellos irritabilidad, ansiedad, dificultad de concentración, somnolencia, fatiga, hambre, aumento de peso, impaciencia y cansancio. La urgencia por retomar el consumo es recurrente y persiste incluso mucho después que los síntomas de abstinencia hayan desaparecido[35]. Estos síntomas tienden a manifestarse en las primeras 24 horas, alcanzan un pico en el primer par de semanas, y desaparecen generalmente dentro de los 30 días que siguen al abandono. Sin embargo, muchos fumadores reportan ansias de fumar esporádicas meses e incluso años después de haber abandonado el consumo[37]. No todos los fumadores la padecen; existe variabilidad en la intensidad y duración de los síntomas[23]. Los fumadores de hasta 5 cigarrillos diarios y los fumadores ocasionales fuman principalmente por los efectos reforzantes de la nicotina y generalmente no presentan síntomas de abstinencia, o bien éstos son mínimos; aún así, muchos de ellos pueden tener dificultades para dejar de fumar[35]. Incluso es posible que algunos puedan tener un nivel alto de dependencia, aunque la farmacodinámica de la

nicotina en ellos es diferente de la de aquéllos que son grandes fumadores[35]. En cuanto se reanuda el consumo y el organismo vuelve a tener los niveles de nicotina adecuados los síntomas de abstinencia desaparecen, lo que refuerza el consumo de tabaco.

Efectos biológicos de la nicotina: Una vez la nicotina es distribuida por los diferentes tejidos y órganos, puede afectar a todos los aparatos y sistemas. Afecta al sistema nervioso central, provocando efectos estimulantes y a la vez de relajación fisiológica; mejora algunas funciones cognitivas, tales como la atención y la evaluación de estímulos; produce efectos cardiovasculares, aumentando la frecuencia cardíaca y la presión sanguínea inmediatamente después de fumar, e incrementa el riesgo de padecer enfermedades cardiovasculares; también produce vasoconstricción periférica. Mientras que pequeñas dosis de nicotina pueden mejorar la respiración, en dosis altas puede causar insuficiencia respiratoria. Los efectos gastrointestinales de la nicotina son complejos, implicando un incremento en las secreciones y motilidad reducida por un corto período de tiempo; además produce cambios en la tasa metabólica responsable de un menor peso corporal. Finalmente, puede producir complicaciones en el embarazo y un aumento de la morbimortalidad perinatal[39].

Metabolismo de la nicotina: La nicotina se metaboliza principalmente en el hígado. El metabolismo está influenciado por factores genéticos, pero también por la dieta, la edad, el sexo, la distribución de grasa corporal, el uso de preparados hormonales que contienen estrógenos, el embarazo, las enfermedades renales y por supuesto el consumo de tabaco en sí mismo. También se han observado diferencias raciales y étnicas[40].

La variabilidad individual en el metabolismo de la nicotina puede contribuir a la naturaleza adictiva de esta droga, puesto que quienes metabolizan lentamente la nicotina están expuestos a concentraciones elevadas de nicotina sin transformar durante más tiempo y pueden ser más susceptibles a sus propiedades aversivas y por

este motivo pueden fumar menos cigarrillos al día. En cambio, quienes la metabolizan rápidamente pueden ser menos susceptibles a la toxicidad de la nicotina, pero pueden necesitar fumar más cigarrillos al día para mantener niveles de nicotina suficientes para prevenir los síntomas de abstinencia[37]. Aún no se tiene un conocimiento definitivo sobre las diferencias individuales en el metabolismo de la nicotina y su influencia en el consumo de tabaco y la dependencia.

La eliminación de la nicotina y de la fracción alcaloide no metabolizada se excreta por el riñón y en menor cuantía por el sudor, saliva y leche materna[23], y puede estar afectada por factores genéticos o la insuficiencia renal[40]. La cuantificación de la nicotina y de sus metabolitos, principalmente la cotinina, se utiliza para estudiar la exposición al tabaco. Determinar la exposición a sustancias específicas en el tabaco y en el humo del tabaco es útil en estudios epidemiológicos que exploran las relaciones entre la exposición a sustancias tóxicas específicas y el desarrollo de enfermedades, en la evaluación de programas de tratamiento de dependencia al tabaco y en la evaluación de los riesgos de los productos del tabaco potencialmente menos dañinos[41].

1.6. Biomarcadores de exposición al tabaco

Un biomarcador permite cuantificar la exposición de los fumadores a los constituyentes del humo del tabaco. Existe considerable variabilidad individual en la manera en que los fumadores fuman, y por tanto, en la ingesta del humo; asimismo, el diseño de los cigarrillos también influye en la exposición a los tóxicos del tabaco. Por ello, para estudiar la exposición al tabaco y a sus componentes es más apropiado analizar las concentraciones químicas en los fluidos corporales. Se ha propuesto la utilización de diversos biomarcadores (tabla 1), algunos de los cuales se describen a continuación.

Nicotina: La nicotina es de fácil absorción en el organismo. El humo inhalado del tabaco lleva la nicotina a los pulmones, siendo rápidamente absorbida en el sistema circulatorio y distribuida a los tejidos del cuerpo. Si bien existe una considerable oscilación en los picos de concentración de nicotina entre cigarrillos, ésta se acumula sobre el curso de 6 a 9 horas de consumo regular, lo que implica una exposición continuada durante las 24 horas del día[35]. Así, la nicotina no es una droga a la que el fumador esté expuesto de manera intermitente ni ésta se elimina rápidamente del organismo. Los fumadores tienden a ingerir la misma cantidad de nicotina cada día para conseguir los efectos deseados, y ajustan la manera de fumar para compensar los posibles cambios que se producen en la disponibilidad de nicotina y así regulan su nivel corporal[35].

La nicotina puede ser medida en diversos fluidos biológicos como en sangre, saliva u orina, y también en otras matrices como cabello, uñas o dientes. Es altamente específica del uso del tabaco; aunque existen algunas fuentes alimenticias de nicotina, éstas son insignificantes comparadas con la nicotina proveniente del consumo de tabaco[42]. Las concentraciones de nicotina en sangre y en orina correlacionan bien con la ingesta de nicotina y pueden ser usadas para estimar la magnitud del consumo de tabaco; sin embargo, debido a su corta vida media, de 2 horas, los niveles de nicotina no son útiles para evaluar el consumo de tabaco en un período previo superior a 8-12 horas[42], siendo más apropiado utilizar otros biomarcadores. Sin embargo, la nicotina en cabello o en las uñas sí permiten la monitorización de la exposición a largo plazo, pues se acumula en estas matrices de manera secuencial.

Tabla 1. Biomarcadores de exposición al tabaco.

Biomarcador	Precursor	Matriz	Vida media	Específico del tabaco	Otras fuentes
Nicotina*	Nicotina	Sangre, orina, saliva, cabello	1–2 h	Sí	Productos sustitutivos de la nicotina
Cotinina*	Nicotina	Sangre, orina, saliva, cabello	16–18 h	Sí	Productos sustitutivos de la nicotina
Anatabina*	Anatabina	Orina	10–16 h	Sí	Ninguna
NNAL, NNAL-glucuronidas	NNK (TSNA)	Sangre, orina	6 sem.	Sí	Ninguna
CO exhalado	Monóxido de carbono	Aire espirado	2–6 h	No	Tráfico, formación en el organismo
Carboxihemoglobina	Monóxido de carbono	Sangre	4–6 h	No	Tráfico, formación en el organismo
1-Hidroxipireno y otros metabolitos de los hidrocarburos aromáticos policíclicos (PAH)	PAHs	Orina	20 h	No	Tráfico, carnes a la parrilla, ocupación, combustión de biomasa en los hogares
Metabolitos del ácido mercoptúrico	1,3-Butadieno	Orina	_	No	Tráfico, productos en combustión
Metabolitos del ácido mercoptúrico	Acrilaldehído	Orina	_	No	Tráfico, productos en combustión
Acetonitrilo	Acetonitrilo	Orina, sangre, aire espirado	32 h	No	Ninguna
S-Ácido fenilo-mercaptúrico	Benceno	Orina	9 h	No	Tráfico, productos en combustión
Tiocianato	Cianuro de hidrógeno	Suero, saliva, orina	7–14 días	No	Dieta

NNAL: 4-(metilnitrosamino)-1-(3-piridil)-1-butanol; NNAL-gluc: 4-(metilnitrosamino)-1-(3-piridil)-1-butanol glucuronida; NNK: 4-(metilnitrosamino)-1-(3-piridil)-1-butanona; TSNA: nitrosaminas específicas del tabaco; PAH: hidrocarburos aromáticos policíclicos
Fuente: Benowitz y cols.[40].

Otros alcaloides menores del tabaco: Entre ellos están la nornicotina, anatabina, anabasina, miosmina, etc. Son absorbidos sistémicamente y pueden ser medidos en la orina. Su medición permite cuantificar el consumo de tabaco cuando el fumador está utilizando terapia sustitutiva de la nicotina, y por tanto son útiles para evaluar la abstinencia al tabaco.

Tiocianato: Su larga vida media, de aproximadamente dos semanas, le convierten en un buen biomarcador del consumo habitual de tabaco, aunque su principal

desventaja es el solapamiento observado en las distribuciones de sus niveles en fumadores y no fumadores[43]. La exposición industrial a cianidas pueden elevar los niveles de tiocianato en el organismo.

Nitrosaminas: Las nitrosaminas específicas del tabaco (TSNA en sus siglas en inglés) son formadas de la nicotina y otros alcaloides del tabaco durante el curado y combustión del tabaco, y son potentes cancerígenos en humanos y en animales[44]. Las TSNAs también pueden formarse de la reacción de la nicotina en el ambiente con el ácido nitroso, entre cuyas fuentes de emisión en interiores están la combustión del tabaco y la combustión proveniente de aparatos sin ventilación[45]. Algunas nitrosaminas son el 4-(metilnitrosamino)-1-(3-piridil)-1-butanona (NNK), N'-nitrosonornicotina (NNN), 1-(N-metil-N-nitrosamino)-1-(3-piridinil)-4-butanal (NNA), 4-(metilnitrosamino)-1-(3-piridil)-1-butanol (NNAL), 4-(metilnitrosamino)-4-(3-piridil)-1-butanol (iso-NNAL), N-nitrosoanabasina (NAB), y N'nitrosoanatabina (NAT).

Monóxido de carbono (CO): Es un gas inodoro que se produce por la combustión de cualquier sustancia orgánica. Por su afinidad con la hemoglobina, disminuye el transporte de oxígeno a los tejidos del cuerpo y al cerebro. La concentración de CO en aire espirado después de retener la respiración correlaciona muy bien con las concentraciones de carboxihemoglobina en sangre, y puede ser medido de una manera fácil, rápida y económica. Sin embargo, se necesita probar su fiabilidad como indicador de consumo habitual de tabaco, específicamente por la corta vida media de la carboxihemoglobina, de unas 4 horas[43]. Además, los niveles de CO se elevan con la exposición a cualquier producto en combustión, lo que le hace poco específico del consumo de tabaco. Fumar un paquete de cigarrillos puede equivaler a tener un nivel de CO en sangre de 20 partes por millón (ppm). El nivel de carboxihemoglobina en sangre se incrementa en promedio un 5% por paquete fumado al día, mientras que el nivel de saturación en el transcurso de 8 horas se eleva de un 7 a un 15%. Si bien los niveles de CO provenientes del consumo de tabaco no crean un problema urgente de salud, pueden ser causa de disnea y

aumento de la frecuencia cardíaca; con la exposición a largo plazo puede provocar un engrosamiento de las paredes arteriales y enfermedad cardíaca[39].

Cotinina: La nicotina es metabolizada aproximadamente en un 75% a cotinina[46]. Su vida media oscila entre unas 12 y 20 horas[47] y por ello ha sido ampliamente utilizada como un marcador específico de exposición al tabaco. Al igual que la nicotina, puede ser medida en los fluidos corporales como biomarcador de la nicotina inhalada[46]. Es fácilmente detectable en fumadores, y tiene una distribución de niveles completamente diferente de la de los no fumadores[48-50]. En ausencia de terapia sustitutiva de la nicotina, la cotinina es el mejor biomarcador de consumo de tabaco, aunque es indicativa del consumo actual y no del consumo a largo plazo[40]. Existe cierta variabilidad individual en la relación cuantitativa entre los niveles de cotinina y la ingesta de nicotina, debido a que diferentes personas convierten diferentes porcentajes de nicotina a cotinina (50 a 90%), y porque las personas también metabolizan la cotinina a diferente velocidad. Al igual que la nicotina, la cotinina puede ser detectada en dientes, cabello y uñas para evaluar la exposición a largo plazo.

1.7. Utilidad de la medición de la cotinina

Debido a que la nicotina es la principal sustancia adictiva del tabaco, los niveles de cotinina en los fluidos corporales, como indicadores de las dosis de nicotina ingerida, pueden ser de utilidad para caracterizar la adicción y predecir las tasas de cesación tabáquica. La identificación de los factores que afectan los niveles de cotinina en los fluidos corporales puede otorgar información útil para determinar la dosis adecuada para la terapia sustitutiva de la nicotina. Además, la ingesta de nicotina puede ser considerada un *proxy* de la exposición al alquitrán y a otras sustancias tóxicas y cancerígenas en el humo del tabaco, pudiendo de este modo ser predictivo de los efectos adversos del tabaquismo para la salud[51].

Se sabe muy poco sobre la dosificación de la nicotina en fumadores en todo el mundo. Considerando que la cotinina es el principal metabolito de la nicotina, su medición en los fluidos corporales puede otorgar una caracterización de la dosis de nicotina recibida por la población de fumadores[46]. Diversos estudios han mostrado diferencias considerables en las concentraciones medias de cotinina en sangre y saliva de fumadores en diferentes poblaciones. Por ejemplo, en una muestra de fumadores de Nuevo México las concentraciones medias de cotinina en saliva variaban entre 100 y 200 ng/ml según el sexo y el origen (hispano o no) de los participantes[52]. Otro estudio realizado en Estados Unidos mostraba diferentes concentraciones medias de cotinina en saliva y sangre en fumadores de diferentes grupos étnicos, incluyendo hispanos, negros y blancos[53]. Estas diferencias pueden reflejar diferencias en el consumo de tabaco, en la conducta del consumo, en el tipo de cigarrillos fumados y/o en el metabolismo de la nicotina en dichos grupos de fumadores. Estas mismas diferencias podrían estar relacionadas con las diferencias en el abandono del tabaco observadas en diferentes poblaciones. Por otra parte, aún no está claro el rol que cumplen la conducta tabáquica y las características de los productos derivados del tabaco en la modificación de las concentraciones de cotinina en el organismo.

La utilización de biomarcadores tales como la cotinina permite validar tanto el consumo autodeclarado como la abstinencia. Las concentraciones de cotinina también pueden predecir el resultado del tratamiento; se ha descrito que los fumadores con mayores niveles de cotinina suelen tener peores resultados durante el tratamiento de deshabituación[54,55]. Por otra parte, la definición de la adicción está realizada casi exclusivamente a partir de criterios sintomáticos o conductuales, y se suele ignorar en tal definición la ingesta de drogas, y por inferencia, los biomarcadores de su ingesta[42]. El nivel de consumo de tabaco tiende a ser estable en la mayoría de fumadores, y los biomarcadores están relacionados con el nivel de ingesta de nicotina. Si bien existe considerable variabilidad interindividual en la relación entre los niveles de cotinina y la ingesta diaria de nicotina del tabaco, se ha observado que los niveles de cotinina predicen mejor la ingesta de nicotina que el

consumo diario de cigarrillos[42,54]. Así, la dependencia a la nicotina y su gravedad pueden ser definidas en términos conductuales y en términos de un biomarcador. Debido a que el nivel de consumo y la gravedad de la adicción parecen estar relacionados, los biomarcadores podrían ser indicativos del nivel de dependencia, de la necesidad de medicación, o ambos[42].

1.8. Medición de la dependencia a la nicotina

La dependencia a la nicotina es un constructo difícil de medir, particularmente debido al desacuerdo que existe en relación a lo que ésta representa. Se ha intentado distinguir entre dependencia a la nicotina y dependencia al tabaco, siendo la primera una dimensión de la segunda[37]. La dependencia al tabaco refleja tanto una dependencia fisiológica a la nicotina como una dependencia psicosocial al consumo: las personas consumen tabaco en respuesta a los síntomas de abstinencia a la nicotina, a aspectos psicológicos y a aspectos sociales o contextuales. Las recaídas que siguen a la cesación son más probables que ocurran en algunas situaciones específicas: durante la noche, cuando hay un fácil acceso a los cigarrillos, cuando otros están fumando, después de comer o beber o frente a situaciones afectivas o anímicas negativas[37].

Por otra parte, se suele hablar indistintamente de adicción o de dependencia. El Informe del *Surgeon General* de 1988[39] considera ambos términos como sinónimos, referidos al uso compulsivo de una droga psicoactiva y asociados con tolerancia (necesidad de consumir progresivamente más droga) y dependencia física (síntomas de abstinencia que aparecen al interrumpir el uso de la droga). West[56] señala que la 'adicción' se refiere a un control deficitario de la conducta, mientras que la 'dependencia física' se refiere a un estado de adaptación fisiológica a una droga que necesita ser ingerida para prevenir los síntomas de abstinencia. También refiere la 'dependencia psicológica' como el estado en el cual una persona siente la 'necesidad' de algo; como tal, es sutilmente diferente de la adicción, que es un

síndrome que implica conductas y cogniciones. Adicción y dependencia son términos que se usan a menudo indistintamente, y en propias palabras de West, es difícil llegar a un consenso en su definición y distinción para lograr una definición formal. Por ello, estos términos se han utilizado indistintamente en la literatura, así como en este trabajo.

Así pues, la dependencia viene determinada no sólo por la ingesta de nicotina, sino también por aspectos psicológicos y ambientales asociados al consumo que influyen en la iniciación y en los patrones de consumo[39]. Una vez que el fumador es adicto a la nicotina le suele resultar difícil dejar de fumar. En Estados Unidos, de los 19 millones de adultos que intentaron dejar de fumar en 2005, sólo un 4-7% lo consiguió sin ayuda[57]. El riesgo de dependencia aumenta cuando el consumo comienza a temprana edad, pero también es altamente prevalente en personas con enfermedades mentales o con trastornos de abuso de drogas. Las mujeres también constituyen un grupo vulnerable a desarrollar adicción: por un lado, su consumo está más influenciado por factores condicionantes y afectos negativos, a diferencia de los hombres, entre quienes es más probable fumar en respuesta a factores farmacológicos; y por otro lado, se sabe que las mujeres metabolizan la nicotina más rápidamente que los hombres, contribuyendo a su mayor susceptibilidad a la adicción a la nicotina[35].

La evaluación de la dependencia es crucial en la planificación de una intervención orientada a la cesación tabáquica. La cuantificación de la dependencia es importante porque los fumadores que tienen una dependencia elevada probablemente necesitarán una terapia más intensiva[58]. Existen diversos instrumentos para su evaluación en cualquiera de sus aspectos, con diferentes niveles de complejidad y validez. A continuación se mencionarán los más utilizados (tabla 2).

Tabla 2. Principales instrumentos autoadministrables para evaluar la dependencia.

Instrumento	Nº ítems	Adaptación española	Referencia
Test de Fagerström	6	Sí	Becoña y cols.[59]
Heavy Smoking Index	2	Sí	Becoña y cols.[59]
Escala del Síndrome de Dependencia de la Nicotina (NDSS-T)	19	Sí	Becoña y cols.[60]
Escala del Síndrome de Dependencia de la Nicotina (NDSS-S)	6	Sí	Becoña y cols.[61]
Escala de Dependencia a los Cigarrillos (CDS-12)	12	No	-
Escala de Dependencia a los Cigarrillos (CDS-5)	5	En preparación	Fernández[62]

DSM-IV-TR: La Asociación Americana de Psiquiatría, en su Manual Estadístico y Diagnóstico de las Enfermedades Mentales, DSM-IV-TR[63], describe la dependencia de sustancias como un patrón desadaptativo de consumo de la sustancia que conlleva un deterioro o malestar clínicamente significativo, expresado por la presencia de tres o más de los siguientes ítems en algún momento de un período continuado de 12 meses: a) tolerancia a la sustancia; b) síntomas de abstinencia; c) consumo en mayores cantidades o durante más tiempo de lo que inicialmente se pretendía; d) deseo persistente o esfuerzos infructuosos de controlar o interrumpir el consumo; e) inversión importante de tiempo en actividades relacionadas con la obtención, el consumo, o la recuperación de los efectos de la sustancia; f) reducción de las actividades sociales, laborales o recreativas a causa del consumo; g) uso continuo de la sustancia a pesar de tener conciencia de tener problemas psicológicos o físicos recidivantes o persistentes aparentemente causados o exacerbados por el consumo de la sustancia. Se especifica además si existe o no dependencia fisiológica, valorada por la presencia de signos de tolerancia y/o abstinencia. La evaluación de la dependencia se realiza mediante una entrevista clínica estructurada llevada a cabo por un experto (médico, psicólogo, psiquiatra).

ICD-10: La Organización Mundial de la Salud, en la última revisión de su Clasificación Internacional de Enfermedades (ICD-10)[64], define el síndrome de dependencia como un conjunto de fenómenos comportamentales, cognitivos y

fisiológicos que se desarrollan tras el consumo reiterado de una sustancia. Su diagnóstico requiere la presencia simultánea de tres o más de las siguientes manifestaciones durante al menos un mes, o bien haberse presentado repetidas veces y simultáneamente en un período de 12 meses: a) deseo intenso de consumir la droga; b) dificultades para controlar su consumo; c) persistencia en el consumo a pesar de las consecuencias dañinas; d) mayor prioridad dada al consumo que a otras actividades y obligaciones; e) aumento de la tolerancia; f) un cuadro de abstinencia física. Como en el caso anterior; estos criterios deben ser evaluados por una persona experta en una entrevista clínica en profundidad.

Test de Fagerström. Sin lugar a dudas, el instrumento más utilizado en la práctica clínica de deshabituación tabáquica en todo el mundo es el test de Fagerström para la dependencia a la nicotina, FTND[65], versión revisada de su antecesor, el *Fagerström Tolerance Questionnaire*, FTQ[66]. Se caracteriza por su brevedad y fácil aplicación. Este test autoadministrable mide la dependencia física a la nicotina y consta de 6 preguntas, cuya puntuación varía entre 0 y 10, indicando una mayor dependencia cuanto mayor es la puntuación obtenida. El test de Fagerström tiene una validez demostrada, y guarda una buena relación con diversas medidas biológicas de consumo[65]. Su utilización es apropiada no sólo en un contexto clínico, sino también en estudios epidemiológicos, ya sea para la planificación de intervenciones comunitarias o para el estudio de la dinámica de la epidemia del tabaquismo en la población[13]. Este test también ha sido validado en una población española[59] (tabla 3).

Heavy Smoking Index: Desde una perspectiva clínica, la dependencia a la nicotina también puede ser medida con tan sólo dos ítems del test de Fagerström: el que evalúa el tiempo transcurrido hasta fumar el primer cigarrillo después de despertarse y el que evalúa la tasa de consumo diario de cigarrillos. Ambos ítems conforman el *Heavy Smoking Index* (HSI)[67]. Las personas que fuman su primer cigarrillo dentro de los 30 minutos después de despertarse y las que fuman en promedio más de 20 cigarrillos al día son más dependientes a la nicotina.

Tabla 3. Versión española del test de Fagerström (adaptación de Becoña y cols.[59]).

Ítem	Opciones de respuesta	Puntuación
1. ¿Cuánto tarda después de despertarse en fumar su primer cigarrillo?	Menos de 5 minutos 6-30 minutos 31-60 minutos Después de 60 minutos	3 2 1 0
2. ¿Encuentra difícil abstenerse de fumar en sitios donde está prohibido, tales como iglesia, biblioteca, cine, etc.?	Sí No	1 0
3. ¿A qué cigarrillo odiaría más renunciar?	El primero de la mañana Cualquier otro	1 0
4. ¿Cuántos cigarrillos fuma al día?	≤10 cigarrillos 11-20 cigarrillos 21-30 cigarrillos ≥31 cigarrillos	0 1 2 3
5. ¿Fuma más frecuentemente durante las primeras horas después de despertarse que durante el resto del día?	Sí No	1 0
6. ¿Fuma cuando está tan enfermo que pasa en la cama la mayor parte del día?	Sí No	1 0

Escala del Síndrome de Dependencia de la Nicotina, NDSS[68]. Sus criterios diagnósticos son similares a los del DSM-IV-TR. Es un cuestionario autoadministrable de 19 ítems. Constituye una evaluación multidimensional de la dependencia: permite evaluar un factor general de dependencia a la nicotina o bien cinco aspectos de la misma: impulso (*drive*), prioridad, tolerancia, continuidad y estereotipia. De esta forma, se puede obtener una puntuación única que capture la severidad general de la dependencia (NDSS-T), recomendada para estudiar las diferencias individuales en la dependencia y los efectos de tratamientos diferenciales, o bien se puede puntuar individualmente las 5 subescalas, recomendado para evaluar la dependencia a la nicotina de una manera más compleja y diferenciada. Se ha demostrado su validez discriminante y sus puntuaciones correlacionan con otros marcadores de dependencia a la nicotina. Recientemente esta escala ha sido adaptada a una población española[60] y se ha propuesto una versión breve de la misma (NDSS-S, tabla 4), con una buena fiabilidad[61].

Tabla 4. Versión abreviada de la Escala del Síndrome de Dependencia de la Nicotina (NDSS-S) de Becoña y cols.[61]

Ítem	Opciones de respuesta	Puntuación
1. Tiendo a evitar los restaurantes donde no se permite fumar, incluso aunque me guste su comida	No es cierto Algo cierto Moderadamente cierto Muy cierto Totalmente cierto	1 2 3 4 5
2. Comparado con cuando empecé a fumar, necesito fumar mucho más ahora para conseguir el mismo efecto	Igual al anterior	Igual al anterior
3. Tras pasar un tiempo sin fumar, necesito hacerlo para no sentirme mal	Igual al anterior	Igual al anterior
4. Cuando realmente deseo un cigarrillo, parece que estoy bajo el control de alguna fuerza desconocida	Igual al anterior	Igual al anterior
5. Siempre que estoy sin fumar durante algunas horas, siento unas ganas muy fuertes de hacerlo	Igual al anterior	Igual al anterior
6. Después de estar un tiempo sin fumar, necesito hacerlo para aliviar las sensaciones de inquietud e irritabilidad	Igual al anterior	Igual al anterior

Escala de Dependencia a los Cigarrillos (CDS). Esta escala autoadministrable ha sido desarrollada en Suiza[69] a partir de encuestas a fumadores y ex-fumadores a través de Internet y por correo electrónico acerca de qué signos ellos creían que eran indicativos de dependencia a los cigarrillos. Mediante la clasificación de las respuestas de acuerdo a su contenido, la revisión de la literatura y la evaluación de diversas propiedades psicométricas se obtuvo una batería de 12 preguntas (CDS-12) que otorga una medida continua de la dependencia. Cubre los principales criterios de dependencia establecidos en el DSM-IV y en el ICD-10 e incluye los dos ítems principales del test de Fagerström (el HSI). Se ha propuesto una versión abreviada de 5 preguntas, el CDS-5 (tabla 5). Es un instrumento en pleno desarrollo, cuyas propiedades han sido probadas en otros contextos[70,71] y que está en proceso de adaptación a una población española[62].

Tabla 5. Versión abreviada de la Escala de Dependencia a los Cigarrillos (CDS-5) de Etter y cols.[62,69]

Ítem	Opciones de respuesta	Puntuación
1. Indique con un número entre 0 y 100 cuál es su grado de dependencia a los cigarrillos. 0 = No soy en absoluto dependiente de los cigarrillos 100 = Soy extremadamente dependiente de los cigarrillos	Grado de dependencia autopercibida	0-20 = 1 21-40 = 2 41-60 = 3 61-80 = 4 81-100 = 5
2. ¿Cuántos cigarrillos fuma usted de media al día?	Cigarrillos/día	0-5 = 1 6-10 = 2 11-20 = 3 21-29 = 4 30 y más = 5
3. Habitualmente, ¿cuánto tiempo (en minutos) tarda usted en fumarse el primer cigarrillo tras despertarse?	Minutos	0-5 = 5 6-15 = 4 16-30 = 3 31-60 = 4 >60 = 5
4. Para usted, dejar de fumar definitivamente sería:	Imposible Muy difícil Bastante difícil Bastante fácil Muy fácil	5 4 3 2 1
5. ¿Hasta qué ponto está de acuerdo con la siguiente frase: "Después de algunas horas sin fumar, siento la necesidad irresistible de fumar"?	Totalmente en desacuerdo Más bien en desacuerdo Ni de acuerdo ni en desacuerdo Más bien de acuerdo Totalmente de acuerdo	1 2 3 4 5

1.9. Los estadios del cambio de Prochaska y DiClemente

Conocer el nivel de dependencia a la nicotina por parte de un fumador es indispensable para poder orientar el tratamiento de deshabituación. Sin embargo, el que logre dejar de fumar depende no sólo de su grado de dependencia a la nicotina, sino también de su motivación para hacerlo[72]. Si bien la mayoría de los fumadores desean dejar de fumar y realizan algún intento por hacerlo, sólo un 3 a un 5% de ellos lo consigue[37]. Muchos fumadores se quedan atrapados entre los intentos de abandono y las recaídas, evidenciando de esta manera la naturaleza adictiva de la nicotina.

En este sentido, un marco referencial desarrollado en el contexto de las conductas adictivas en general y frecuentemente utilizado en deshabituación tabáquica es el modelo transteórico del cambio de Prochaska y DiClemente[73,74], que permite evaluar este grado de motivación al cambio, entendido como el "grado de preparación" del fumador para dejar de fumar (*readiness to quit*). El modelo transteórico es un modelo integral de cambio conductual basado en el proceso de toma de decisiones. En dicho modelo se establece que la modificación de una conducta adictiva implica un proceso de cambio progresivo a través de una serie de etapas o estadios a través de los cuales las personas avanzan y retroceden muchas veces antes de dejar definitivamente la conducta adictiva[74]. Cada estadio es definido por las intenciones y la conducta relacionada con la conducta problema de interés. Estos estadios son el de precontemplación, contemplación, preparación, acción y mantenimiento.

Precontemplación: Es el estadio en el cual no hay una intención de cambio conductual en un futuro inmediato. Muchas personas en este estadio no son conscientes de sus problemas, o bien los minimizan, siendo las personas de su entorno inmediato quienes les presionan a realizar algún cambio, por ejemplo, buscar ayuda profesional; pero una vez la presión desaparece, es común que vuelvan a su conducta habitual. Los precontempladores no tienen intención de cambiar la conducta problema en un futuro cercano, dentro de los próximos seis meses.

Contemplación: Es el estadio en el cual las personas son conscientes de que tienen un problema y están pensando seriamente en superarlo, pero aún no han adquirido un compromiso para pasar a la acción; de hecho, pueden permanecer mucho tiempo atascados en este estadio. Un aspecto importante de este estadio es el peso de los pros y contras del problema y de su solución. Los contempladores están considerando seriamente cambiar la conducta adictiva en los próximos seis meses.

Preparación: Es un estadio que combina criterios de intención y conductuales. Las personas en este estadio están intentando pasar a la acción en el próximo mes y han tomado medidas no exitosas durante el último año para dejar de fumar. Realizan pequeños cambios conductuales, tal como reducir algo el consumo de cigarrillos. Si bien han hecho algunas reducciones en sus conductas problemáticas, aún no han alcanzado un criterio para la acción efectiva. Las personas en esta fase pretenden, sin embargo, tomar tal acción en un futuro muy cercano, dentro de los siguientes treinta días.

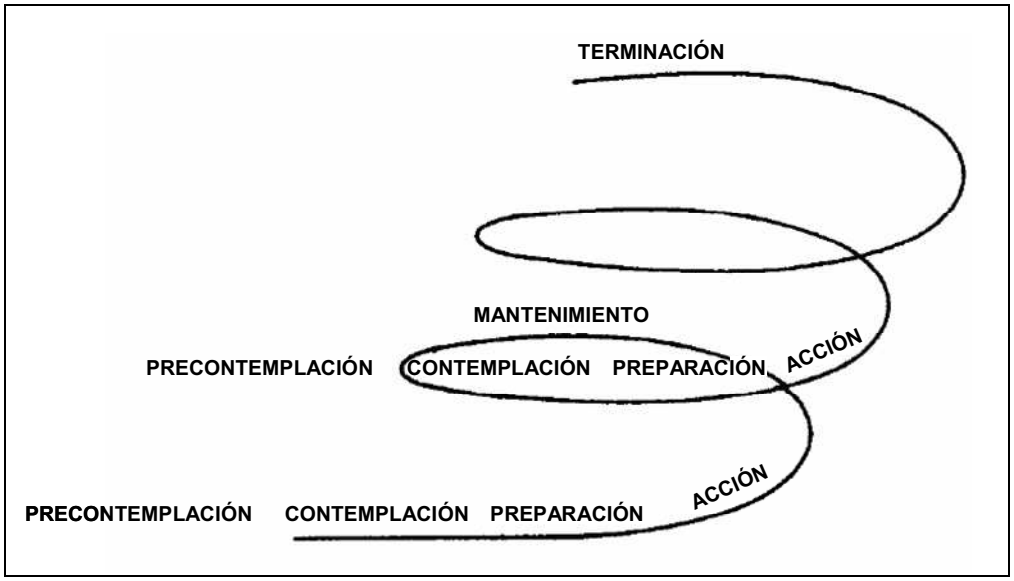
Acción: Es el estadio en el cual las personas modifican su conducta, experiencias, o ambiente para superar sus problemas. La acción implica cambios conductuales evidentes y requiere un compromiso considerable de tiempo y energía. Las personas a menudo igualan erróneamente acción con cambio, con lo cual pasan por alto el trabajo necesario que les prepara a la acción y los esfuerzos necesarios para mantener los cambios que siguen a la acción. Las personas en la fase de acción han alterado exitosamente la conducta adictiva por un período entre un día y seis meses, lo que significa alcanzar un criterio particular, en nuestro caso, la abstinencia.

Mantenimiento: Es el estadio en el cual las personas trabajan para consolidar las ganancias obtenidas durante la acción y para prevenir la recaída. El mantenimiento no es un estadio estático, sino que representa un cambio continuo a largo plazo. Este estadio se extiende desde los seis meses de la acción inicial hasta un período indeterminado en el futuro. Se considera que alguien está en el estadio de mantenimiento cuando es capaz de permanecer libre de la conducta adictiva por más de seis meses y es capaz de dedicarse consistentemente a una nueva conducta incompatible con la conducta adictiva.

La mayoría de las personas que emprenden la acción para modificar sus adicciones no mantienen de manera exitosa sus logros en su primer intento, siendo necesarios tres a cuatro intentos de acción antes de poder permanecer en la fase de mantenimiento a largo plazo[74]. La recaída y "reciclado" a través de los estadios es

muy frecuente en el camino hacia la modificación o eliminación de las conductas adictivas. La figura 5 representa el modelo cuyo patrón en espiral ilustra cómo la mayoría de las personas se mueven a través de los estadios del cambio y cómo muchas veces recaen. Durante la recaída, las personas retroceden a un estadio anterior, situación que en ocasiones se acompaña de sentimientos de vergüenza y culpabilidad. Estas personas se desmoralizan y se resisten a pensar en el cambio de conducta. Como resultado, vuelven al estadio de precontemplación, pudiendo permanecer allí por mucho tiempo.

Figura 5. Modelo en espiral de los estadios del cambio de Prochaska y DiClemente.



Fuente: Prochaska y cols.[74].

El estudio de los estadios del cambio en un contexto clínico aporta elementos adicionales en la comprensión de la conducta tabáquica y otorga orientaciones para las intervenciones[75]. Pero también tiene aplicaciones prácticas importantes a nivel poblacional, pues se ha demostrado que la distribución de los fumadores según los estadios del cambio puede diferir en distintas poblaciones[76]. En España también se han estudiado los estadios del cambio para caracterizar a los fumadores de una población concreta[75].

1.10. Justificación de la investigación

En España, la mayoría de estudios sobre consumo de tabaco, dependencia a la nicotina y estadios del cambio, ejes principales de la presente investigación, han sido realizados preferentemente en un contexto clínico de deshabituación tabáquica o bien en colectivos específicos (personal universitario, pacientes de centros asistenciales, personas con patologías específicas, adolescentes, etc.), mientras que son escasos los que han sido desarrollados en población general. La realización de estudios en población general como los propuestos en esta investigación permitirá describir y caracterizar un componente esencial de la epidemia del tabaquismo en nuestro país, como es la adicción de las personas fumadoras y sus intenciones de cambio.

Por otra parte, el estudio de las características del consumo de tabaco conjuntamente con la utilización de un biomarcador objetivo del consumo de cigarrillos, tal como la cotinina en saliva, permite un conocimiento más detallado de diversos factores asociados al consumo. Estudios de este tipo no se han realizado en población general española, por cuanto puede abrir una prometedora línea de investigación.

Por lo anteriormente expuesto, la *Unitat de Control del Tabaquisme* del Institut Català d'Oncologia se propuso realizar una serie de estudios sobre los determinantes del consumo de tabaco y su relación con el grado de adicción y la preparación de los fumadores para dejar de fumar a nivel poblacional[77,78].

2. HIPÓTESIS DE TRABAJO Y OBJETIVOS

2.1. Hipótesis de trabajo

1. El consumo de tabaco, tal y como se deriva del número de cigarrillos fumados, será el principal determinante de las concentraciones de cotinina en saliva: las concentraciones de cotinina en saliva incrementarán cuanto mayor sea el consumo de tabaco.

2. Las concentraciones de cotinina en saliva serán mayores cuanto menor sea el tiempo transcurrido desde que el fumador se despierta hasta que fuma el primer cigarrillo del día.

3. Los fumadores más dependientes, de acuerdo al test de Fagerström para la dependencia a la nicotina, tendrán concentraciones de cotinina en saliva más altas que los fumadores menos dependientes.

4. Los fumadores muy dependientes según el test de Fagerström y con altas concentraciones de cotinina estarán menos preparados para dejar de fumar que los fumadores menos dependientes.

2.2. Objetivos de la investigación

1. Caracterizar la distribución de las concentraciones de cotinina en saliva en fumadores y los factores que la determinan.

2. Estudiar la posible asociación entre el tiempo transcurrido hasta el primer cigarrillo fumado después de despertarse y la concentración de cotinina en saliva.

3. Analizar la relación entre la dependencia a la nicotina, medida con el test de Fagerström, y las concentraciones de cotinina en saliva en fumadores.

4. Estudiar la preparación para dejar de fumar por parte de los fumadores (estadios del cambio de Prochaska y DiClemente) de acuerdo a su perfil de dependencia y niveles de cotinina en saliva.

3. BREVE DESCRIPCIÓN DE LOS DATOS

Los datos analizados en esta investigación se derivan de dos estudios independientes. El primero de ellos es el estudio titulado *"Determinantes de los niveles de cotinina en saliva en una muestra representativa de la población general"* (estudio DCOT)[77]. Se trata de un estudio transversal realizado en una muestra representativa de la población general de Barcelona (n=1245) entre abril de 2004 y diciembre de 2005, consistente en la realización de entrevistas cara a cara mediante un cuestionario sobre tabaquismo activo y pasivo y la recolección de muestras de saliva para la determinación de la cotinina. El estudio DCOT obtuvo la aprobación del Comité Ético de Investigación Clínica (CEIC) de la Ciudad Sanitaria y Universitaria de Bellvitge en lo referente al protocolo del estudio y el consentimiento informado. La participación de las personas fue requerida mediante una carta firmada por el investigador principal, enviada de manera previa al contacto personal y nuevamente solicitada mediante el consentimiento informado.

El segundo estudio, titulado *"Prevalence of exposure to environmental tobacco smoke in European countries"* (EuroSurvey)[78], fue llevado a cabo entre junio y julio de 2006. Con un diseño también transversal, tenía como objetivo principal estudiar la prevalencia de exposición al humo ambiental del tabaco. Se entrevistó telefónicamente a una muestra representativa de la población española ≥18 años (n=2522). El cuestionario incluyó preguntas sobre consumo de tabaco y exposición pasiva. En este estudio, por tratarse tan sólo de una encuesta telefónica que no recogía datos personales de identificación, no requirió la aprobación del CEIC. Se solicitó a los participantes su consentimiento oral de participación antes de proceder a la entrevista.

4. OBJETIVOS Y RESULTADOS DE LOS ARTÍCULOS

De los objetivos propuestos para esta investigación se derivaron 6 trabajos, 4 de ellos publicados como artículos originales, uno recientemente aceptado para su publicación, y una carta al Editor con presentación de datos empíricos originales.

1. **Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study**. Este artículo original responde al objetivo nº 1 de esta tesis y fue publicado en 2009 en la revista *BMC Public Health*, clasificada en el lugar 41/140 (cuartil 2) de la categoría *Public, environmental & occupational health* en los *Journal Citation Reports (JCR) – Science Edition* de 2010. Esta revista tiene un factor de impacto de 2,364.

Resumen y principales resultados: El objetivo de este estudio fue describir y caracterizar los determinantes de la concentración de cotinina en saliva en fumadores adultos (>16 años). La muestra de estudio proviene del estudio DCOT, y estuvo conformada por 211 fumadores diarios residentes en Barcelona que fumaban únicamente cigarrillos. Tenían una edad media de 42 años, consumían una mediana de 15 cigarrillos en las últimas 24 horas (RI: 8-20 cigarrillos) y un 19,4% había fumado más de 20 cigarrillos, observándose un mayor consumo en los hombres ($p<0,05$). La concentración mediana de cotinina fue de 146,5 ng/ml (RI: 86,8-220,5 ng/ml), y difería significativamente por sexo: los hombres tenían concentraciones más altas de cotinina que las mujeres (172,6 y 120,7 ng/ml, respectivamente; $p<0,05$), con independencia de los cigarrillos fumados. Para evaluar los determinantes de las concentraciones de cotinina se utilizaron modelos de regresión lineal. Los principales resultados indicaron que la concentración de cotinina en saliva se asoció significativamente con el número de cigarrillos fumados en las últimas 24 horas (R^2=0.339). La inclusión de un componente cuadrático para el número de cigarrillos fumados mejoró el ajuste de los datos (R^2=0.386), observándose una tendencia creciente de la concentración de cotinina conforme

aumentaba el consumo de cigarrillos y que se estabilizaba aproximadamente a los 20 cigarrillos fumados. No hubo otras variables que se asociaran de manera significativa con la concentración de cotinina.

2. **Association between time to first cigarette after waking up and salivary cotinine concentration**. Este artículo original responde al objetivo nº 2 de esta tesis y fue publicado en 2011 en la revista *Nicotine & Tobacco Research*, clasificada en el lugar 31/140 (cuartil 1) de la categoría *Public, environmental & occupational health* en los *JCR–Science Edition* de 2010 y en el lugar 10/114 (cuartil 1) de la misma categoría en los *JCR–Social Sciences Edition* del mismo año. Esta revista tiene un factor de impacto de 2,801.

Resumen y principales resultados: Este estudio evaluó la posible asociación entre el tiempo transcurrido hasta fumar el primer cigarrillo después de despertarse y las concentraciones de cotinina en saliva. Los datos provienen del estudio DCOT, y la muestra de estudio la constituyeron 210 fumadores diarios >16 años. Los resultados mostraron que la mayoría de los fumadores fumaba su primer cigarrillo entre 6 y 30 minutos después de despertarse (el 35,7% de los fumadores) y después de 60 minutos de haberse despertado (el 34,8% de los fumadores). Se encontraron asociaciones significativas entre la concentración de cotinina en saliva y el tiempo hasta fumar el primer cigarrillo (β=57,0 ng/ml), entre el consumo de cigarrillos y el tiempo hasta fumar el primer cigarrillo (β=5,4 ng/ml), y entre las concentraciones de cotinina en saliva y el consumo de cigarrillos (β=6,5 ng/ml). Se observó una tendencia decreciente en la concentración de cotinina en saliva conforme aumentaba el tiempo transcurrido hasta fumar el primer cigarrillo del día. Luego de ajustar por consumo de cigarrillos y por sexo, se observaron diferencias significativas en la concentración media de cotinina en saliva en las categorías de la variable tiempo hasta fumar el primer cigarrillo: ≤5 min: 219,2 ng/ml; 6-30 min: 175,8 ng/ml; 31-60 min: 168,5 ng/ml; >60 min: 137,2 ng/ml). La comparación entre los grupos 6-30 min y 31-60 min fue la única que no fue significativa. El análisis estratificado de la concentración de cotinina según el tiempo hasta el primer cigarrillo (menos o más

de 30 minutos) permitió observar que los cambios en la concentración de cotinina de acuerdo al número de cigarrillos fumados son similares en los fumadores menos dependientes (tiempo hasta el primer cigarrillo >30 min) y en los más dependientes (tiempo hasta el primer cigarrillo ≤30 min); sin embargo, éstos últimos tenían mayores concentraciones de cotinina en saliva.

3. **Nicotine dependence and salivary cotinine concentration in daily smokers: a cross-sectional study**. Este manuscrito responde al objetivo nº 3 de esta tesis y acaba de ser aceptado para su publicación en la revista *European Journal of Cancer Prevention*, clasificada en el lugar 90/184 (cuartil 2) de la categoría *Oncology* en los *JCR–Science Edition* de 2010. Esta revista tiene un factor de impacto de 2,536.

Resumen y principales resultados: El objetivo de este estudio fue analizar la relación entre la dependencia a la nicotina y la concentración de cotinina en saliva en una muestra de fumadores diarios. La muestra de estudio proviene del estudio DCOT, y estuvo conformada por 196 fumadores diarios >16 años residentes en la ciudad de Barcelona, quienes fumaban únicamente cigarrillos. Su consumo medio era de 17 cigarrillos por día. La dependencia a la nicotina fue medida con el test de Fagerström (FTND). Los resultados indicaron una puntuación media en el FTND de 3,27 (IC 95%: 2,92-3,61). El 17,3% de los fumadores tenía una dependencia alta a la nicotina (FTND≥6). La media geométrica (MG) de la concentración de cotinina fue 113,65 ng/ml (IC 95%: 97,74-132,15 ng/ml), con una diferencia significativa entre hombres (MG: 141,94 ng/ml; IC 95%: 115,50-174,42 ng/ml) y mujeres (MG: 91,82 ng/ml; IC 95%: 74,09-113,78 ng/ml). Se observaron diferencias estadísticamente significativas en la concentración de cotinina según nivel educacional, con valores más altos en fumadores de menor nivel educacional, y por tipo de tabaco, con valores más altos en el grupo de fumadores de tabaco negro. La concentración de cotinina según los niveles de dependencia del FTND fueron 87,45 ng/ml, 159,12 ng/ml y 246,28 ng/ml en los grupos con dependencia baja, media y alta, respectivamente ($p<0,001$). La concentración de cotinina en saliva estaba asociada con las puntuaciones en el FTND (ρ de Spearman: 0,628): la concentración media de cotinina aumentaba a mayor puntuación individual de cada

ítem del FTND. El modelo de regresión lineal múltiple que incluía la suma de las puntuaciones en los ítems 2, 3 y 6, las puntuaciones individuales en los ítems 1, 4 y 5 y el sexo, explicaba el 41,4% de la varianza de los datos. El tiempo que transcurre hasta fumar el primer cigarrillo después de levantarse (ítem 1), el número de cigarrillos fumados diariamente (ítem 4) y si se fuma más durante las primeras horas del día (ítem 5) estaban significativamente relacionados con la concentración de cotinina en saliva.

4. **Stages of change, smoking characteristics, and cotinine concentration in smokers: Setting priorities for smoking cessation**. Este artículo original responde al objetivo nº 4 de esta tesis y fue publicado en 2011 en la revista *Preventive Medicine*, clasificada en el lugar 20/151 (cuartil 1) de la categoría *Medicine, general & internal*, y en el lugar 20/140 (cuartil 1) de la categoría *Public, environmental & occupational health* en los *JCR–Science Edition* de 2010. Esta revista tiene un factor de impacto de 3,299.

Resumen y principales resultados: El objetivo de este estudio fue describir la distribución de los fumadores diarios y su concentración de cotinina en saliva de acuerdo a su preparación para dejar de fumar y a algunas características del consumo. La muestra de estudio proviene del estudio DCOT, y estuvo conformada por 278 fumadores diarios >16 años, cuya edad promedio era de 43,5 años (la mayoría de ellos tenía entre 25 y 44 años). Se describió la prevalencia de fumadores según los estadios del cambio y algunas características individuales (sexo, edad, nivel educativo, índice de masa corporal) y de consumo (edad de inicio del consumo, tipo de cigarrillos, tipo de tabaco, uso de filtros, frecuencia y profundidad de la inhalación, consumo diario de cigarrillos, tiempo transcurrido hasta fumar el primer cigarrillo del día, dependencia a la nicotina). Se utilizaron medianas y rangos intercuartílicos (RI) para describir la concentración de cotinina según los estadios del cambio, consumo diario de tabaco y dependencia a la nicotina medida con el FTND. Los resultados indicaron que el 67,6% de los fumadores estaban en el estadio de precontemplación, el 21,6% estaba en contemplación, y el 10,8% estaba

en preparación, sin diferencias entre hombres y mujeres. El consumo medio fue de 17 cigarrillos diarios; según los estadios del cambio, el consumo medio fue de 16,3 cigarrillos en los precontempladores, de 19,4 cigarrillos en los contempladores y de 16,0 cigarrillos en los fumadores en fase de preparación (p=0,164). La concentración mediana de cotinina fue 151,3 ng/ml (RI: 83,2-227,8 ng/ml), sin diferencias según los estadios del cambio. Sin embargo, dentro de cada estadio la concentración de cotinina aumentaba significativamente a menor tiempo transcurrido hasta el primer cigarrillo del día y conforme aumentaba el consumo de cigarrillos y la dependencia a la nicotina, aunque sólo lo hizo significativamente en los grupos de fumadores precontempladores y contempladores. La puntuación media en el FTND fue 3,2 (desviación estándar de 2,4), sin diferencias significativas a través de los estadios del cambio. Las concentraciones de cotinina eran más altas cuanto mayor era el consumo de cigarrillos y cuanto mayor era la puntuación en el FTND.

5. **Dependencia a la nicotina y motivación para dejar de fumar en la población española**. Este artículo original responde a los objetivos nº 3 y 4 de esta tesis y fue publicado en 2011 en la revista *Adicciones*, clasificada en el lugar 11/14 (cuartil 4) de la categoría *Substance abuse* en los *JCR–Science Edition* de 2010 y en el lugar 16/29 (cuartil 3) de la misma categoría en los *JCR–Social Sciences Edition* del mismo año. Esta revista tiene un factor de impacto de 1,127.

Resumen y principales resultados: El objetivo de este estudio fue describir la dependencia a la nicotina y la preparación para dejar de fumar en la población española fumadora ≥18 años. Los datos provienen del estudio EuroSurvey; la muestra la conformaron 568 fumadores diarios y ocasionales (22,5% de los participantes). Se evaluó la dependencia a la nicotina mediante el FTND y la preparación para dejar de fumar de acuerdo a los estadios del cambio del modelo transteórico de Prochaska y DiClemente. Los resultados indicaron que la mayoría de los fumadores (56,5%) comenzaron a fumar entre los 15 y 18 años; el 36,1% fumaba entre 10 y 19 cigarrillos por día (media de 14,4 cigarrillos). El 74,1% de los

fumadores tenía una baja dependencia a la nicotina (puntuaciones entre 0 y 4), mientras que la puntuación media fue 2,8, sin diferencias según los estadios del cambio. Los fumadores más dependientes a la nicotina (FTND≥6) tenían mayoritariamente estudios primarios, comenzaron a fumar a edad más temprana y fumaban más cigarrillos al día. El 64,3% de los fumadores estaba en el estadio de precontemplación, el 25,4% en el de contemplación y el 10,4% en el estadio de preparación, sin diferencias por sexo. La proporción de fumadores que tenía una dependencia alta fue ligeramente superior en el estadio de preparación (22,0%) que en los estadios de precontemplación (14,5%) y contemplación (15,3%), aunque estas diferencias no fueron significativas.

6. **A comparison of the Fagerström test for nicotine dependence and smoking prevalence across countries: updated data from Spain**. Esta Carta al Editor, en la que se presentan resultados empíricos originales, complementa y apoya el tercer objetivo de esta tesis y fue publicada el 2009 en la revista *Addiction*, clasificada en el lugar 24/126 (cuartil 1) en la categoría *Psychiatry* y en el lugar 2/14 (cuartil 1) en la categoría *Substance abuse* en los *JCR–Science Edition* de 2010, y en el lugar 12/107 (cuartil 1) y 1/29 (cuartil 1) de las mismas categorías, respectivamente, en los *JCR–Social Sciences Edition* de 2010. Esta revista tiene un factor de impacto de 4,145.

Resumen: La carta se origina a partir del artículo de Fagerström y Furberg publicado en la revista Addiction[79], en que comparan la puntuación en el FTND y la prevalencia de tabaquismo en diversos países para comprobar si se cumple la hipótesis del "hardening", que indica que los fumadores que quedan en las poblaciones son los más dependientes a la nicotina[80,81]. El objetivo de la carta fue aportar datos actualizados sobre prevalencia de tabaquismo y dependencia a la nicotina a nivel de todo el estado español. Los datos provienen del estudio EuroSurvey, y de ellos se deriva que en el año 2006 el 23,4% de los españoles adultos eran fumadores (el 27,0% de los hombres y el 20,1% de las mujeres; $p<0,05$) y la puntuación media en el FTND era 2,8 (3,0 los hombres y 2,5 las

mujeres; $p<0,05$). Este diferente nivel de dependencia según sexo se debe principalmente a la diferencia en el número medio de cigarrillos fumados al día por los hombres (15,7) y las mujeres (12,8, $p<0,05$). Comparado con los datos españoles del estudio de Fagerström y Furberg, los datos provenientes del estudio EuroSurvey indican un decremento en la prevalencia de tabaquismo en los diez años que separan ambos estudios, pero no un incremento de la dependencia a la nicotina, lo cual cuestionaría la generalización de la teoría del "hardening".

5. PUBLICACIONES

1. **Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study.**
   Marcela Fu, Esteve Fernández, Jose M. Martínez-Sánchez, José A. Pascual, Anna Schiaffino, Antoni Agudo, Carles Ariza, Josep M. Borràs, and Jonathan M. Samet, for the DCOT Study investigators.
   BMC Public Health 2009; 9: 320.

2. **Association between time to first cigarette after waking up and salivary cotinine concentration.**
   Marcela Fu, Jose M. Martínez-Sánchez, Antoni Agudo, José A. Pascual, Josep M. Borràs, Jonathan M. Samet, and Esteve Fernández, for the DCOT Study Investigators.
   Nicotine & Tobacco Research 2011; 13(3): 168-172.

3. **Nicotine dependence and salivary cotinine concentration in daily smokers.**
   Marcela Fu, Jose M. Martínez-Sánchez, Antoni Agudo, José A. Pascual, Carles Ariza, Albert Moncada, and Esteve Fernández, for the DCOT Study Investigators.
   European Journal of Cancer Prevention 2011 (aceptado para su publicación).

4. **Stages of change, smoking characteristics, and cotinine concentrations in smokers: Setting priorities for smoking cessation.**
   Marcela Fu, Esteve Fernández, José A. Pascual, Jose M. Martínez-Sánchez, Antoni Agudo, Albert Moncada, Manel Nebot, and Josep M. Borràs, for the DCOT Study Investigators.
   Preventive Medicine 2011; 52(2): 139-145.

5. **Dependencia a la nicotina y preparación para dejar de fumar en la población española.**
   Marcela Fu, Jose M. Martínez-Sánchez, María J. López, Manel Nebot, Antònia Raich y Esteve Fernández, en nombre del ETS EuroSurvey Working Group.
   Adicciones 2011; 23(2): 103-109.

6. **A comparison of the Fagerström test for nicotine dependence and smoking prevalence across countries: updated data from Spain.**
   Marcela Fu, Jose M. Martínez-Sánchez, Mónica Pérez-Ríos, María J. López, and Esteve Fernández.
   Addiction 2009;104(2): 326-327.

A continuación se presentan estas publicaciones.

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Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study

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Published: 3 September 2009

BMC Public Health 2009, **9**:320 doi:10.1186/1471-2458-9-320

Received: 18 May 2009
Accepted: 3 September 2009

This article is available from: http://www.biomedcentral.com/1471-2458/9/320

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Abstract

Background: Characterizing and comparing the determinant of cotinine concentrations in different populations should facilitate a better understanding of smoking patterns and addiction. This study describes and characterizes determinants of salivary cotinine concentration in a sample of Spanish adult daily smoker men and women.

Methods: A cross-sectional study was carried out between March 2004 and December 2005 in a representative sample of 1245 people from the general population of Barcelona, Spain. A standard questionnaire was used to gather information on active tobacco smoking and passive exposure, and a saliva specimen was obtained to determine salivary cotinine concentration. Two hundred and eleven adult smokers (>16 years old) with complete data were included in the analysis. Determinants of cotinine concentrations were assessed using linear regression models.

Results: Salivary cotinine concentration was associated with the reported number of cigarettes smoked in the previous 24 hours ($R^2 = 0.339$; $p < 0.05$). The inclusion of a quadratic component for number of cigarettes smoked in the regression analyses resulted in an improvement of the fit ($R^2 = 0.386$; $p < 0.05$). Cotinine concentration differed significantly by sex, with men having higher levels.

Conclusion: This study shows that salivary cotinine concentration is significantly associated with the number of cigarettes smoked and sex, but not with other smoking-related variables.

Background

Nicotine, the main alkaloid of tobacco, is responsible for its addictive effect. It is readily absorbed from tobacco smoke, and its concentration rises over 6-8 hours during the day in regular smokers [1]. About 70 to 80% of nicotine is metabolized to cotinine [2]. As the primary metabolite of nicotine, cotinine has been widely used as a specific biomarker of tobacco exposure because its half-life in the body (12-20 hours) is longer than that of nicotine (3-4 hours) [1,2]. Cotinine in biological materials is suitable for assessment of doses over short periods of time (from 1 to 10 days, in urine, plasma, or saliva) or longer periods (weeks or months, in hair or nails). Consequently cotinine concentration is feasibly used as a biomarker in epidemiological studies [3-5].

Cotinine measurements have been used to describe and compare patterns of tobacco consumption in smokers in different countries to establish if addiction and smoking patterns vary across populations [6-8]. These studies show that the number of cigarettes smoked is the main determinant of salivary cotinine concentrations [9]. These studies have been conducted in selected samples from a variety of countries at different stages of the tobacco epidemic, such as China, Mexico, Brazil, and Poland [9,10]. However, there is scant information about the relation between cotinine measurements and smoking patterns in samples from the general population.

Spain is currently in an advanced stage of the tobacco epidemic [10,11]. Data from the 2006 Spanish National Health Interview Survey show prevalence rates of daily smokers of 31.6% and 21.5% in adult men and women, respectively [12]. In men, a steady increase in smoking occurred during the first half of the twentieth century, reaching a peak prevalence rate of 59.1% in the nineteen-seventies. This peak was followed by a decade of stabilization and a continued decrease of smoking until the present. Uptake of smoking in women was delayed, with a prevalence rate of 5% through the nineteen-seventies. This was followed by a substantial increase throughout the next two decades (22.5% by 1995), which only recently stopped [11,13,14].

An understanding of cotinine concentration and smoking patterns at the population level is potentially useful to design suitable strategies for cessation. The aim of this study is to describe and characterize the distribution of salivary cotinine concentration in a representative sample of adult (>16 years old) daily smokers in Barcelona, Spain.

Methods

Study design and subjects

We conducted a cross-sectional study among the general population of Barcelona, Spain, between March 2004 and December 2005. A representative random sample by age, sex, and district was drawn from the official 2001 population census of Barcelona, a reliable source of population-based information. To detect a difference in cotinine concentration in smokers of 50 ng/ml (with a mean value of 500 ng/ml and a standard deviation of 200 ng/ml), with an alpha of 5% and a beta of 10% (statistical power of 90%), we estimated that a sample size of 337 smokers would be needed. Considering a 27% prevalence of smoking from the 2001 Health Survey of Barcelona, we estimated a needed sample size of 1560 people, taking into account smokers and non-smokers. In cases of non-response, substitution by persons of the same sex within the 5-year age group and residing in the same district was allowed according to protocol.

Smoking status, secondhand smoke exposure as well as demographic information were obtained by questionnaire, and a saliva specimen was collected to determine cotinine concentration. The research and ethics committee of the Bellvitge University Hospital approved the study protocol, and informed consent was obtained from all participants. The procedure was as follows: a personal letter was sent to eligible participants, and trained interviewers contacted the subjects (or a proxy for children) at home and informed them about the study. Participants signed the consent form, answered a questionnaire, and provided a saliva specimen at home. The study ended in December 2005 with a new Spanish law banning smoking in public places and enclosed workplaces coming into effect in January 2006 [15]. We expected changes in smoking behavior after this date (number of cigarettes smoked by smokers and passive exposure levels in nonsmokers) and hence 315 selected participants were not approached. By the end of the study, 1245 subjects had been interviewed (participation rate of 79.8% from the initial sample drawn). The study design allowed replacement of the index person by another person of the same sex, 5-year age group, and district of residence. In 49.3% of cases the first selected index person was interviewed; 24.4% of first substitutes were interviewed; and 26.3% of second or subsequent substitutes were interviewed. The final sample interviewed included 285 daily smokers (at least 1 cigarette per day), 62 occasional (non-daily) smokers, 354 ex-smokers, 525 never-smokers, and 19 people were less than 17 years of age. The present report is based on adults who were daily smokers.

Measures

Questionnaire

We obtained information on demographics, and levels of secondhand smoke exposure at home, work or study centre, and during leisure time. Detailed information was also collected on self-reported smoking for smokers: number of cigarettes smoked daily, number of cigarettes smoked during the previous 24 and 48 hours, duration of

smoking, brand of cigarettes smoked most often, brands of cigarettes smoked during the survey day and in the previous day, use of cigarettes with filter tips, depth and frequency of inhalation, use of other tobacco products, and use of nicotine gum or patches.

Body mass index

We measured participants' weights and heights using a standardized protocol (with an electronic portable scale and a tape measure). Body mass index (BMI) was computed as weight/squared height (kg/m^2) and stratified using standard categories of BMI (underweight: <18.50, normal: 18.50-24.99, overweight: 25.00-29.99, and obese: ≥30.00 kg/m^2).

Saliva specimen

A standardized protocol for saliva collection was used. Participants were asked to rinse their mouths and then suck a lemon-flavored candy (Smint®) to stimulate saliva production. They were asked first to spit out a small amount of saliva, and then to spit about 8 ml into a polypropylene test tube. The specimens were kept at 4 °C and then frozen at -20 °C in 3 ml aliquots for transport in dry ice to the Bioanalysis Research Group of the Municipal Institute for Medical Research (IMIM-Hospital del Mar). Cotinine concentration in nanograms per milliliter (ng/ml) was determined by gas chromatography, with detection by mass spectrometry (GC/MS) [16,17]. With this technique, cotinine concentration can be quantified as low as 1 ng/ml (limit of detection: 0.3 ng/ml; quantification error <15%).

Data analyses

Sample exclusions

Of the 285 current adult daily smokers, 7 were excluded from the analysis either because they did not provide a saliva specimen or that cotinine determination was not possible (i.e., insufficient sample). We included only cigarette smokers, hence 53 people who smoked other tobacco products (mainly cigars and roll tobacco) were excluded, as were 2 subjects who used nicotine gum or nicotine patch for cessation. Additionally, 12 people were excluded because their cotinine concentrations were too high in relation to the self-reported consumption, that is, over 35 ng/ml per one cigarette smoked. This level of cotinine represents the maximum level of absorption per one cigarette smoked, assuming that the typical cotinine concentration of 12 ng/ml per cigarette is equivalent to the usual absorption of 1 mg of nicotine per cigarette, and that a cigarette smoker can absorb up to 3 mg of nicotine per cigarette with very intense smoking [9]. The final sample for analysis consisted of 211 current daily smokers.

Variables

The outcome variable was salivary cotinine concentration (ng/ml). Potential modifiers of the relation between cotinine concentration and the number of cigarettes smoked in the last 24 hours included individual characteristics (sex, age, educational level, BMI), type of tobacco (use of regular or non-regular cigarettes [light, ultralight, mentholated, low nicotine yield], use of blond or black tobacco, and use of filter tips), and smoking behavior (frequency and depth of smoke inhalation).

Statistical analyses

Medians and 25th and 75th percentiles (interquartile range, IQR) of salivary cotinine concentration were computed according to the different strata of the potential modifiers. Median cotinine concentrations across the different variables were compared using non-parametric test for medians. Simple linear regression was used to derive the average increase in cotinine level (ng/ml) per one cigarette smoked, adjusting for the remaining variables. We analyzed the relation between number of cigarettes smoked in the previous 24 hours and salivary cotinine concentration using multiple linear regressions according to the strata of the potential modifiers of interest. Since the distributions of cotinine concentration and of the number of cigarettes were skewed, we first used log transformation, but the fit of the models did not improve. Following previous studies [9,18], we included a quadratic term for number of cigarettes to improve the models' fit. We assessed the improvement of fit between the adjusted and simple model with the *F* test statistic [19]. All models were tested for the applicability of conditions of linear regression (model specification, normality of errors, homoscedasticity, absence of multicollinearity, absence of outliers and lack of self-correlation). All analyses were performed using SPSS v13.0 (SPSS Inc., Chicago, IL).

Results

Among the 211 current daily smokers (104 men and 107 women), the median age was 42.0 years (IQR 31.0-53.0). The sample was uniformly distributed across educational levels. The majority of participants (56%) were of normal weight and 19.4% had smoked more than 20 cigarettes in the last 24 hours. The median number of cigarettes smoked according to selected sociodemographic and smoking characteristics is shown in Table 1. The median number of cigarettes smoked in the last 24 hours was 15.0 (IQR 8.0-20.0), with significantly higher consumption in men compared to women ($p < 0.05$). Differences in cigarette consumption were also found by type of tobacco: smokers of black tobacco had smoked more cigarettes in the last 24 hours (median: 20 cigarettes) than smokers of blond tobacco (median: 12 cigarettes, $p < 0.05$).

Median cotinine concentrations by individual characteristics and smoking parameters are shown in Table 2. The overall median cotinine concentration was 146.5 ng/ml (IQR 86.8-220.5). Median cotinine concentration differed significantly by sex (172.6 ng/ml for men and 120.7 ng/

Table 1: Median number of cigarettes smoked in the last 24 hours and interquartile ranges in adult daily smokers, according to individual characteristics, type of tobacco, and smoking characteristics.

	n	*median (IQR*)*	*p*-value†
Total	211	15.0 (8.0, 20.0)	-
Individual characteristics			
Sex			0.002
Men	104	20.0 (10.0, 25.0)	
women	107	10.0 (6.0, 20.0)	
Age (years)			0.073
17-44	120	12.5 (8.3, 20.0)	
45-64	79	19.0 (10.0, 25.0)	
≥ 65	12	8.5 (4.8, 18.0)	
Educational level			0.162
Less than primary and primary	68	16.5 (10.0, 20.0)	
secondary	74	14.5 (8.8, 20.0)	
university	68	11.5 (6.0, 20.0)	
Body mass index (kg/m²)‡			0.705
underweight	4	10.0 (7.0, 17.5)	
normal	116	14.0 (8.0, 20.0)	
overweight	66	15.0 (8.0, 20.8)	
obese	21	20.0 (8.5, 30.0)	
Type of tobacco			
Type of cigarettes			0.040
regular	148	15.0 (8.5, 20.0)	
non-regular (light, ultralight, etc.)	63	10.0 (8.0, 20.0)	
Type of tobacco			0.003
blond	171	12.0 (8.0, 20.0)	
black	40	20.0 (10.5, 28.8)	
Use of filter tip			0.207
with filter	209	15.0 (8.0, 20.0)	
without filter	2	7.0 (4.0, 10.0)	
Smoking characteristics			
Frequency of inhalation			0.014
all the time	21	20.0 (10.5, 20.0)	
half the time	150	11.0 (7.0, 20.0)	
seldom	39	20.0 (12.0, 30.0)	
Depth of inhalation			0.739
light	22	16.0 (10.0, 22.5)	
moderate	78	12.0 (7.9, 20.0)	
deep	108	15.0 (8.0, 20.0)	

Barcelona (Spain), 2004-2005.
* *IQR*: interquartile range
† non-parametric test for medians
‡ underweight: <18.50 kg/m2; normal: 18.50-24.99 kg/m2; overweight: 25.00-29.99 kg/m2; obese: _30.00 kg/m2

ml for women, $p < 0.001$) regardless of the number of cigarettes smoked. Significant differences in cotinine concentrations were not found by age, educational level, or BMI (Table 2).

As shown in Table 2, we found no statistically significant differences in the salivary cotinine concentration by type of cigarettes, use of filter, frequency, or depth of inhalation. Median cotinine concentration was higher among smokers of black tobacco (180.2 ng/ml) than among smokers of blond tobacco (137.0 ng/ml; $p = 0.043$). This association was confounded by the higher median consumption by smokers of black tobacco (Table 1), and by the predominance of men (70%) among users of black tobacco. There was no association between the type of tobacco smoked and cotinine concentration within strata of number of cigarettes smoked (1-9, 10-19, and = 20 cigarettes in the last 24 hours) or of sex (data not shown).

Coefficients (β) derived from simple linear regression estimate the average increase in cotinine concentration per one cigarette smoked during the previous 24 hours (Table 3). The increase in cotinine concentration per one cigarette smoked was 5.3 ng/ml in men and 7.7 ng/ml in

Table 2: Median cotinine concentrations (ng/ml) and interquartile ranges in adult daily smokers, according to individual characteristics, type of tobacco, and smoking characteristics.

	n	*median* (*IQR**)	*p*-value†
Total	211	146.5 (86.8, 220.5)	-
Individual characteristics			
Sex			
men	104	172.6 (115.3, 255.4)	< 0.001
women	107	120.7 (69.6, 208.8)	
Age (years)			
17-44	120	127.1 (82.8, 297.1)	0.090
45-64	79	171.1 (103.9, 239.4)	
≥ 65	12	135.8 (54.6, 215.7)	
Educational level			
less than primary and primary	68	173.9 (106.1, 295.8)	0.194
secondary	74	134.4 (86.5, 216.2)	
university	68	137.7 (67.4, 194.7)	
Body mass index (kg/m²)‡			
underweight	4	132.3 (72.4, 281.8)	0.151
normal	116	127.9 (85.1, 219.5)	
overweight	66	155.3 (88.7, 223.3)	
obese	21	166.6 (91.2, 224.2)	
Type of tobacco			
Type of cigarettes			
regular	148	149.5 (96.6, 229.8)	0.313
non-regular (light, ultralight, etc.)	63	128.4 (74.7, 214.8)	
Type of tobacco			
blond	171	137.0 (84.5, 219.6)	0.043
black	40	180.2 (128.6, 259.5)	
Use of filter tip			
with filter	209	146.9 (89.7, 220.5)	0.157
without filter	2	41.9 (12.7, 71.0)	
Smoking characteristics			
Frequency of inhalation			
all the time	21	166.6 (101.5, 207.1)	0.473
half the time	150	137.1 (83.1, 220.2)	
seldom	39	177.3 (108.6, 248.8)	
Depth of inhalation			
light	22	151.3 (80.6, 306.9)	0.957
moderate	78	142.8 (98.8, 220.2)	
deep	108	146.7 (84.8, 213.7)	

Barcelona (Spain), 2004-2005.
* *IQR*: interquartile range
† non-parametric test for medians
‡ underweight: <18.50 kg/m2; normal: 18.50-24.99 kg/m2; overweight: 25.00-29.99 kg/m2; obese: _30.00 kg/m2

women. No consistent trend was found in cotinine concentration by age; the greatest increase was observed in participants <45 years (β = 7.0; 95% CI, 5.2 - 8.8 ng/ml). Cotinine level increase per one cigarette smoked was greater among subjects who were at normal weight (8.2 ng/ml) and overweight (6.5 ng/ml) than in those who were obese (1.9 ng/ml). By type of tobacco, the greatest increase in cotinine concentration per one cigarette smoked was found in those smoking non-regular cigarettes (8.4 ng/ml) and in smokers of blond tobacco (6.9 ng/ml). Consistent trends were not found by use of filter tip, frequency, or depth of inhalation.

The distribution of salivary cotinine concentration in relation to the number of cigarettes smoked during the 24 hours prior to saliva collection is shown in Fig 1. In the simple unadjusted linear model the number of cigarettes smoked in the last 24 hours was a predictor of cotinine concentrations (R^2 = 0.339; solid line). A significant improvement of the fit was obtained with a quadratic model, in which the number of cigarettes smoked accounted for almost 39% (adjusted R^2) of the variance, and the exposure-response relationship leveled-off near 20 cigarettes (Fig. 1; dashed line). [see Additional file 1]

Table 3: Average increase in cotinine concentration (ng/ml) in adult daily smokers per one cigarette smoked in the previous 24 hours, according to individual characteristics, type of tobacco, and smoking characteristics. Barcelona (Spain), 2004-2005.

	n	β*	95% CI†	R^2
Total	211	6.4	5.2, 7.7	0.338
Individual characteristics				
Sex				
men	104	5.3	3.5, 7.2	0.244
women	107	7.7	5.9, 9.5	0.412
Age (years)				
17-44	120	7.0	5.2, 8.8	0.329
45-64	79	5.8	3.9, 7.8	0.329
≥ 65	12	6.1	-0.2, 12.5	0.316
Educational level				
less than primary and primary	68	5.4	2.9, 7.8	0.226
secondary	74	6.5	4.6, 8.4	0.392
university	68	7.5	5.4, 9.6	0.435
Body mass index (kg/m²)‡				
underweight	4	--§	--§	--§
normal	116	8.2	6.5, 9.9	0.439
overweight	66	6.5	4.3, 8.7	0.350
obese	21	1.9	-0.8, 4.8	0.102
Type of tobacco				
Type of cigarettes				
regular	148	5.8	4.4, 7.2	0.321
non-regular (light, ultralight, etc.)	63	8.4	5.7, 11.1	0.395
Type of tobacco				
blond	171	6.9	5.5, 8.3	0.356
black	40	5.1	2.1, 8.0	0.244
Use of filter tip				
with filter	209	6.3	5.1, 7.6	0.333
without filter	2	--§	--§	--§
Smoking characteristics				
Frequency of inhalation				
all the time	21	5.9	2.3, 9.5	0.384
half the time	150	8.4	6.8, 9.9	0.439
seldom	39	3.3	0.6, 6.0	0.147
Depth of inhalation				
light	22	7.9	2.8, 13.0	0.348
moderate	78	4.9	2.7, 7.0	0.217
deep	108	6.8	5.2, 8.3	0.416

Barcelona (Spain), 2004-2005.
* estimates from simple linear regression
† 95% confidence interval of _
‡ underweight: <18.50 kg/m2; normal: 18.50-24.99 kg/m2; overweight: 25.00-29.99 kg/m2; obese: _30.00 kg/m2
§not computed for insufficient observations

Due to differences found in cotinine concentrations between men and women, we analyzed these groups separately (Table 4). We observed an increment of 15.7 and 11.2 ng/ml in cotinine concentration per one cigarette smoked at a consumption of 1 cigarette per day in the quadratic model for men and for women, respectively. Further adjustment for age, educational level, and BMI in the quadratic model showed the best fit of the data with a similar increase in the cotinine concentration by cigarettes smoked (Table 4). Adjustment for other potential confounders identified in the bivariate analysis did not improve the model fit and hence these variables were not included in the final models (data not shown). Fig 2 shows the regression lines from linear and quadratic models for men and women. We verified the final models for error specification, normality, homoscedasticity, multicollinearity, outliers and self-correlation, and all diagnostics showed that the chosen models fulfilled the assumption [see Additional file 1]

Discussion

This is the first study on smoking behavior in a Spanish adult population using both a questionnaire and a biomarker of tobacco exposure. Salivary cotinine concen-

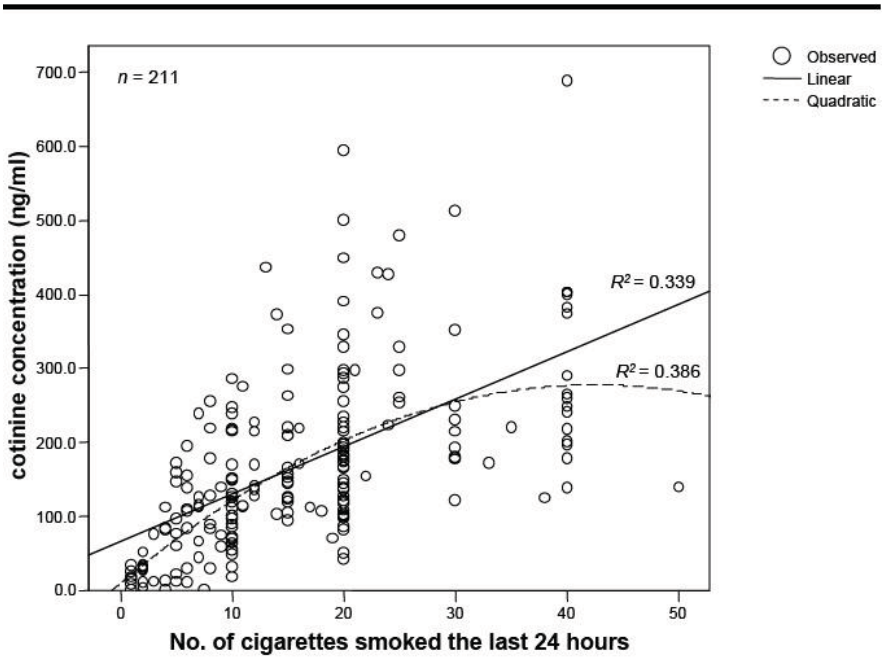

Figure 1
The distribution of salivary cotinine concentration in relation to the number of cigarettes smoked during the 24 hours prior to saliva collection.

tration was associated with the number of cigarettes smoked in the last 24 hours. This relation was better explained with a quadratic function and in separate strata for men and women. The greater the number of cigarettes smoked, the greater the cotinine concentration in a linear scale up to 20 cigarettes per day, after which the association plateaus. A similar relation between salivary [6-9,20] or serum [21] cotinine concentrations and number of cigarettes smoked has been observed in other studies. Abrams et al. dichotomized tobacco consumption, and found that for smokers of less than 25 cigarettes per day, salivary cotinine concentration was highly correlated with tobacco consumption, while among heavier smokers the relation was not evident [22].

Other studies have found that cotinine concentration plateaus at different numbers of cigarettes: 25 cigarettes per day [23], 5 cigarettes per day [24], and 4 cigarettes per day in adolescent smokers [25]. The evidence suggests that cotinine concentration rises in a non-linear fashion with increasing number of cigarettes smoked, but the point where concentrations level off may vary across different populations. This finding suggests a difference in how people regulate their intake of nicotine to reach the desired dose [2], even for adolescents, who may be more susceptible to nicotine than adults and require only 4-5 cigarettes per day to satisfy their nicotine cravings [25].

We observed that cotinine concentrations differed by sex, regardless of the number of cigarettes smoked. Some studies reported similar findings of higher cotinine concentrations in men than in women [7,23,26,27], but other studies did not find differences by sex [6,28]. Association between urinary cotinine and cigarettes smoked according to sex was found in a study in the USA: urinary cotinine concentrations in men increased up to 34 cigarettes per day and then declined, while no flattening was observed in women [29]. The differences we observed by sex could reflect not only differences in tobacco consumption by sex, i.e., men usually smoke more cigarettes than women, but also a difference in the metabolism of nicotine between men and women [30,31].

Our data showed a higher cotinine concentration in smokers of black tobacco that did not persist with control for the number of cigarettes smoked. Whereas uptake of carcinogens is higher among black tobacco smokers [32-34], differences in nicotine uptake by type of tobacco smoked have not been reported [35]. In our study, use of filter, frequency, and depth of inhalation were not related to cotinine concentrations. An explanation of these results could be that smokers tend to maintain the same intake level of nicotine by drawing in more smoke per cigarette when they try to smoke fewer cigarettes. Benowitz et al. reported that among people who reduced from 37 to 5

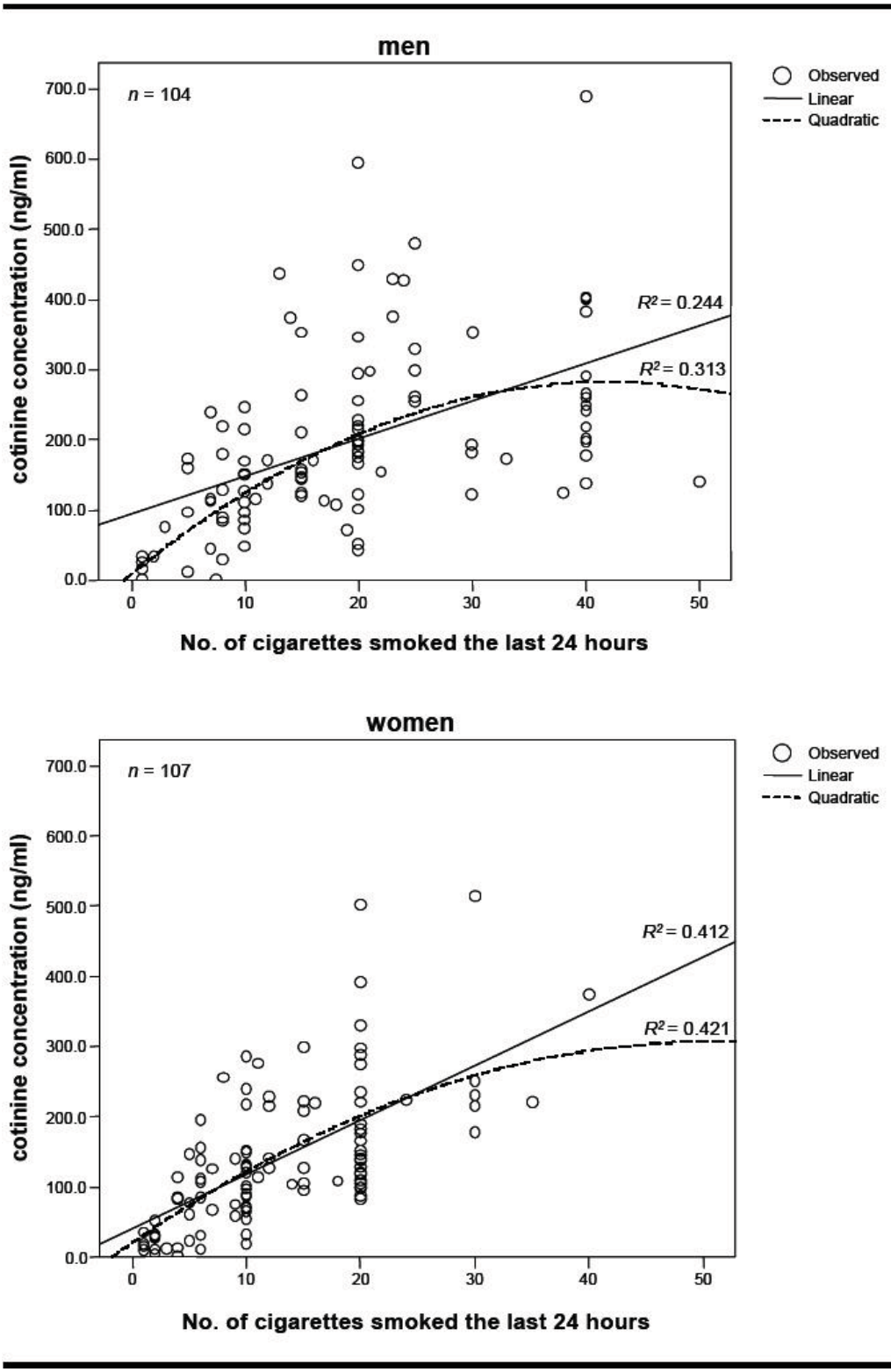

Figure 2
The regression lines from linear and quadratic models for men and women.

Table 4: Average increase in cotinine concentration (ng/ml) in adult daily smokers per one cigarette smoked in the previous 24 hours by type of regression model.

Estimation of model	β*	95% *CI*	R^2	*p*-value†
Men (n = 103)				
simple linear model	5.3	3.5, 7.2	0.244	----
quadratic model	15.7	9.0, 22.3	0.313	< 0.05
quadratic model adjusted for covariates†	14.8	8.1, 21.5	0.353	< 0.05
Women (n = 104)				
simple linear model	7.7	5.9, 9.5	0.412	----
quadratic model	11.2	5.7, 16.7	0.421	0.188
quadratic model adjusted for covariates‡	11.3	5.8, 16.7	0.458	0.078

Barcelona (Spain), 2004-2005.
β for the simple variable "number of cigarettes smoked in previous 24 hours" (for one cigarette smoked)
p-value for the change of fit between the adjusted models and the simple linear model adjusted for age, educational level, and body mass index

cigarettes per day on average, the intake of tobacco toxins per cigarette increased roughly threefold [36]. This could also explain how cotinine concentrations level-off in smokers of more than 20 cigarettes per day, when a certain intake of nicotine is achieved [8,9].

The role of age in cotinine concentrations is still not clear, since our results, as well as previous studies [7,37], indicated no association between cotinine concentrations and age, while others have found a significant association [6,18,29,38]. Some studies have modeled the relation between cotinine concentrations and cigarette consumption by taking into account several of these variables. The fit of the multivariate model improved once age, BMI, educational level, and a quadratic term for cotinine were included.

Study limitations and strengths

To our knowledge, this is one of the few studies in which information about tobacco exposure was obtained in a representative random sample of the general population with a simultaneous use of a questionnaire and a biological marker. In the USA, the National Health and Nutrition Examination Survey (NHANES) provides population-based national estimates of smoking prevalence using both standard questionnaire and serum cotinine concentration [39]. Most previous studies were based on selective samples from existing observational studies [6,8,18,25,37] or smoking cessation trials [21,22,29]. Other factors affecting validity also need to be considered. Although the use of self-reported data from questionnaires could be a source of bias, self-reports on smoking are accurate and have acceptable validity [40,41]. Cotinine is a specific biomarker of tobacco exposure [1,2], and the laboratory methods are highly sensitive [17].

Some potential limitations deserve consideration. We found that the model fit could be affected by the measurement scale of the number of cigarettes. Smokers tend to round up the number of cigarettes smoked, particularly heavy smokers [42], and hence some information bias due to digit preference cannot be disregarded. While some loss of representativeness due to non-response might also be possible, the sample did not differ by sex, age, and district of residence from the Barcelona population. Moreover, the prevalence of smokers in the sample (28.6% of men and 18.2% of women) was similar to that derived from the 2006 Health Interview Survey of Barcelona (27.3% of men and 20.6% of women) [43]. The participation rate was almost complete because the study design allowed replacement of non-respondents by subjects in the same strata of sex, age, and district of residence.

Conclusion

Cotinine concentration differed by sex and increased up to consumption of 20 cigarettes per day and then flattened at higher levels of smoking. Further investigation may help to better understand the relationship between number of cigarettes smoked, age, sex, weight, subjects' levels nicotine or cotinine concentrations, and the degree of nicotine dependence that may have implications in smoking cessation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The DCOT investigators designed the study. JT, AS and MF co-ordinated participant recruitment, collected data and were responsible for data management. JAP was responsible for cotinine analyses. MF, JMMS, and EF performed statistical analyses. All authors participated in the interpretation of results. MF drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. All authors approved the final version of the manuscript. EF is the guarantor.

Additional material

Additional file 1

***Supplemental material**. Salivary cotinine concentration (ng/ml) in adult daily smokers in relation to the number of cigarettes smoked in the last 24 hours. Barcelona (Spain), 2004-2005, and Salivary cotinine concentration (ng/ml) in adult daily smokers in relation to the number of cigarettes smoked in the last 24 hours, in separate strata for men and women. Barcelona (Spain), 2004-2005.*

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Acknowledgements

This project was funded by the Instituto de Salud Carlos III (grants FIS PI020261 & PI081436) and the Thematic Network of Cooperative Research on Cancer (grant RD06/0020/0089), Government of Spain, and the Ministry of Universities and Research (grant 2009SGR192), Government of Catalonia. We also thank Chupa Chups Spain for providing the Smint® candies.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2458/9/320/prepub

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Nicotine & Tobacco Research, Volume 13, Number 3 (March 2011) *168–172*

Original Investigation

Association Between Time to First Cigarette After Waking Up and Salivary Cotinine Concentration

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Received September 9, 2010; accepted November 24, 2010

Abstract

Introduction: The time to first cigarette smoked after waking up appears to be a good predictor of plasma and urine cotinine levels; however, collection of blood and urine is difficult in population-based studies and may influence participation. We aimed to test whether time to first cigarette is associated with salivary cotinine.

Methods: We used data from a cross-sectional study on a representative sample of the general population of Barcelona, Spain. We gathered information on smoking by means of a questionnaire and collected saliva for cotinine analysis. Of 1,245 participants, 22.9% were daily smokers, and the final sample for analysis consisted of 210 daily smokers.

Results: There were significant associations between salivary cotinine and time to first cigarette, between cigarette consumption and time to first cigarette, and between salivary cotinine and cigarette consumption. Salivary cotinine had decreased as time to first cigarette increased. After adjusting for cigarette consumption and sex, there were significant differences in mean salivary cotinine according to time to first cigarette (≤5 min: 219.2 ng/ml; 6–30 min: 175.8 ng/ml; 31–60 min: 168.5 ng/ml; >60 min: 137.2 ng/ml). All paired comparisons were significant ($p < .001$) except in the 6- to 30-min group versus the 31- to 60-min group ($p = .701$).

Conclusions: After adjustment for the number of cigarettes smoked in the last 24 hr, time to first cigarette is associated with salivary cotinine concentration.

Introduction

Measurements of cotinine, the main metabolite of nicotine, have been widely used as a biomarker of nicotine intake (Rebagliato, 2002). Cotinine concentration in different biological fluids varies with the number of cigarettes smoked (Abrams, Follick, Biener, Carey, & Hitti, 1987; Blackford et al., 2006; Etter, Vu, & Perneger, 2000; Fu et al., 2009; Joseph et al., 2005; Olivieri et al., 2002) but is also influenced by other factors, such as smoking topography, cigarette characteristics, or individual factors (Caraballo et al., 1998; Fidler, Jarvis, Mindell, & West, 2008; Muscat, Stellman, Caraballo, & Richie, 2009; Patterson et al., 2003; Swan, Habina, Means, Jobe, & Esposito, 1993). The time to smoking the first cigarette after awakening has also been proposed as a predictor of cotinine levels (Muscat et al., 2009). This component of the Fagerström Test for Nicotine Dependence (FTND) has the strongest strength as a predictor of addiction to nicotine (Boyle et al., 2000; Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

We examined the time to smoking the first cigarette after waking up as a predictor of the concentration of cotinine in saliva, a sample more easily collected than blood or urine. Because

doi: 10.1093/ntr/ntq232
Advance Access published on January 10, 2011
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of the high correlations among cotinine concentrations in blood, urine, and saliva (Benowitz, 1996), we anticipated finding an association between time to first cigarette and salivary cotinine.

Methods

The data were collected in a cross-sectional study conducted during 2004–2005 on the general population of Barcelona, Spain, that had the aim of describing the determinants of salivary cotinine concentration in both smokers (Fu et al., 2009) and nonsmokers (Martínez-Sánchez, Fernández, et al., 2009). The research and ethics committee of the Bellvitge University Hospital approved the study protocol, including the informed consent. Detailed information about the study design, sampling, analytic procedures, and baseline characteristics have been described elsewhere (Fu et al., 2009; Martínez-Sánchez, Fernández, et al., 2009). In brief, a representative random sample by age, sex, and district of residence was drawn from the official 2001 population census, and replacement of the index person by another person of the same sex, 5-year age group, and district was allowed. We gathered information on smoking and secondhand smoke exposure from 1,245 people by means of a face-to-face interview (participation rate of 79.8%). For smokers, the questionnaire included the number of cigarettes smoked during the last 24 hr and the FTND to assess nicotine dependence (Heatherton et al., 1991). At the end of the interview, we collected 8 ml of saliva to determine cotinine concentration (in nanograms per milliliter). Samples were frozen at −20 °C in three aliquots and sent in dry ice to be analyzed by gas chromatography/mass spectrometry by the Bioanalysis Research Group of the Municipal Institute for Medical Research (Pascual et al., 2003). The sample included 285 daily smokers (at least 1 cigarette/day); of these, 75 were excluded from analysis: 7 had insufficient or no saliva specimen, 53 smoked only tobacco products other than cigarettes, 2 used nicotine replacement therapy, 12 had unreliably high cotinine concentration relative to their self-reported consumption, that is, more than 35 ng/ml per cigarette smoked (Blackford et al., 2006), and 1 smoker had incomplete data on time to first cigarette (Item 1 from the Fagerström test). Hence, the current analysis included information from 210 adult (aged >16 years) daily smokers. We used the Spearman correlation coefficient and linear regression to explore the paired associations between salivary cotinine concentration, cigarette consumption in the last 24 hr, and the score obtained in the time to first cigarette item from the Fagerström test. We also compared the mean salivary cotinine concentration in the four categories of the time to first cigarette variable (≤5, 6–30, 31–60, and >60 min) using analysis of variance (ANOVA) and the Wilcoxon test for independent samples, adjusting for cigarette consumption and sex. We also tested the effect modification of the association between number of cigarettes smoked in the last 24 hr and salivary cotinine by time to first cigarette: ≤30 min (high dependent phenotype) and >30 min (low dependent phenotype) using an interaction term in a linear regression model with a quadratic term for cigarette consumption.

Results

Most subjects smoked their first cigarette between 6–30 min (35.7%) and >60 min (34.8%) after waking up. There were no significant differences in the proportion of smokers in each category of the time to first cigarette variable by sex, except in ≤ 5-min category, where there was a greater proportion of male smokers (20.2%) compared with female smokers (10.4%). Salivary cotinine, cigarette consumption, and score of time to first cigarette item were moderately correlated (Table 1). There were significant linear associations between salivary cotinine concentration and the score of time to first cigarette item (β = 57.0 ng/ml), between cigarette consumption and the score of time to first cigarette item (β = 5.4 cigarettes/day), and between salivary cotinine and cigarette consumption (β = 6.5 ng/ml). ANOVA analysis indicated that there were differences in salivary cotinine concentration according to the time to first cigarette ($p < .001$) that remained after adjustment for cigarette consumption and sex (data not shown). Furthermore, salivary cotinine concentration had a decreasing trend as time to first cigarette increased (Table 2). There were also significant differences in mean values of salivary cotinine for each comparison of the different categories of the time to first cigarette variable, except in the 6- to 30-min group versus the 31- to 60-min group (Table 2). Figure 1 shows that the slopes were similar in high and low dependent smokers (p for interaction = .812). Nevertheless, 89% of smokers from the high dependent phenotype (smoking at ≤30 min after waking up) had a salivary cotinine concentration more than 100 ng/ml, whereas the corresponding proportion for low dependent phenotype smokers (smoking at >30 min after waking up) was 52%.

Table 1. Correlation Matrix of Cigarette Consumption, Salivary Cotinine, and the Score of Time to First Cigarette[a] Among 210 Spanish Daily Smokers (Barcelona, 2004–2005)

	Time to first cigarette	Cigarette consumption
Cigarette consumption	.506*	–
Salivary cotinine	.533*	.434*

[a]Item 1 of the Fagerström Test for Nicotine Dependence.
*$p < .001$

Discussion

The data show that the time to first cigarette smoked is associated with salivary cotinine concentration, regardless of the cigarettes smoked in the last 24 hr. The shorter the time to first cigarette, the higher the salivary cotinine concentration. These results are in agreement with the findings described by Heatherton, Kozlowski, Frecker, Rickert, and Robinson (1989) when validating the Heavy Smoking Index to measure nicotine dependence and are similar to the results obtained with plasma and urinary cotinine (Muscat et al., 2009). Factors such as smoking topography and nicotine metabolism could explain this finding as smokers regulate their smoking behavior to compensate for variations of nicotine levels in the body (Benowitz, 2008). Thus, smokers from the high dependent phenotype may smoke more intensely and deeply at the first few minutes of the day after overnight abstinence, resulting in higher cotinine concentration compared with low dependent smokers. The effect of these factors should be investigated in future studies, focusing

Table 2. Mean and 95% CI of Salivary Cotinine Concentration (nanograms per milliliter) by Time to First Cigarette in 210 Spanish Daily Smokers (Barcelona, 2004–2005), Adjusted for Cigarettes Per Day and Sex

Time to first cigarette (min)	*n*	Salivary cotinine (ng/ml)		Time to first cigarette (min)[a]			
		Mean	95% *CI*	≤5	6–30	31–60	>60
≤5	32	219.18	199.51–238.84	–	< .001	< .001	<.001
6–30	75	175.79	164.08–187.50	–	–	.701	<.001
31–60	30	168.54	155.55–181.53	–	–	–	<.001
>60	73	137.18	126.33–148.04	–	–	–	–

Note. [a]*p* values for the Wilcoxon test for independent samples.

on interindividual differences. It is known that cigarette consumption is the main determinant of cotinine concentration (Blackford et al., 2006; Fu et al., 2009), but individual differences in the way people smoke and in the nicotine metabolism make cigarette consumption an imprecise estimator of nicotine intake. Furthermore, the half-life of cotinine is about 16 hr, and its levels tend to build up throughout the day, remaining at near steady-state values, but the level of cotinine in the body in an individual is influenced by the daily exposure level and the rate of clearance (Benowitz, 1996).

Unlike Muscat et al. (2009), our data show that changes in cotinine concentration by number of cigarettes smoked is similar in high and low dependent smokers; nevertheless, cotinine concentration was higher among the most dependent smokers. This pattern seems to support the observed relation between salivary cotinine concentration and time to first cigarette, regardless of the number of cigarettes smoked. This finding is of particular interest, considering that the number of cigarettes smoked is a strong determinant of cotinine concentration.

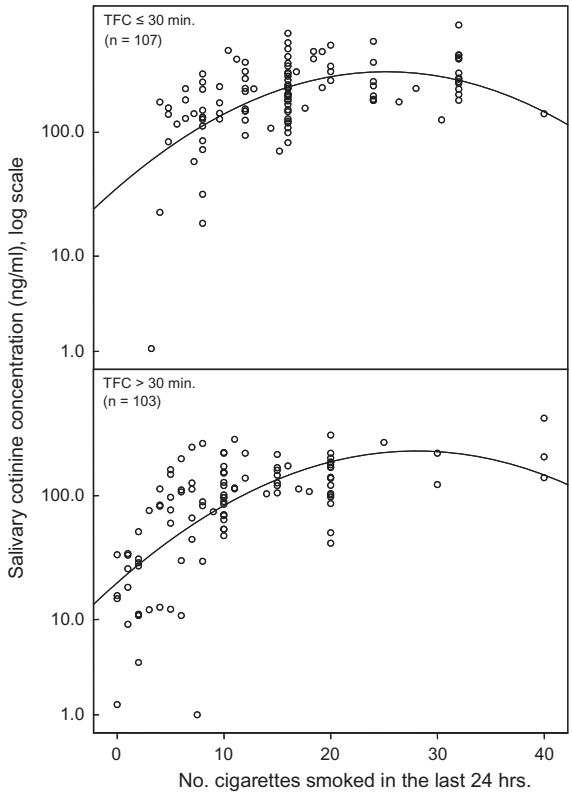

Figure 1. Relation between cigarette consumption and salivary cotinine concentration by time to first cigarette (TFC) in 210 Spanish daily smokers (Barcelona, Spain, 2004–2005).

Our results distinguished the differences in mean salivary cotinine values between each category of time to first cigarette better than mean plasma and urinary cotinine values (Muscat et al., 2009). The magnitude of the association between urine and blood cotinine concentrations could be affected by the differences in production and excretion of creatinine according to some individual characteristics, such as age, sex, or race (Muscat et al., 2009). Since the collection of saliva is easier than collection of urine and less invasive than collection of blood, we consider salivary cotinine as the biomarker of choice for indication of tobacco intake differences according to the time to first cigarette.

One possible limitation of our study is the use of the cigarettes smoked within the last 24 hr as an indicator of tobacco consumption instead of the mean number of cigarettes smoked daily as widely used in the literature (Centers for Disease Control and Prevention, 1994). However, salivary cotinine is a good marker of recent tobacco consumption, and the 24-hr recall period seems adequate (Blackford et al., 2006). Self-reported data from questionnaires could be a possible source of bias, although self-report on smoking are considered accurate with an acceptable validity (Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009; Patrick et al., 1994). Although we did not take into account in the analyses the time of the day the sample was collected, the half-life of cotinine (about 16 hr) and its ability to reflect exposure after 3–4 days assure a sensitive estimate of ongoing tobacco smoke exposure, and for this reason, it is considered as a biomarker for daily intake (Benowitz, Hukkanen, & Jacob, 2009). Other possible factor that limits the comparison with the data from Muscat et al. (2009) is the use of a different definition of smoker, in our case, anyone who smokes at least 1 cigarette/day (and not a minimum of 5 cigarettes/day for a minimum of 1 year). The relatively small sample size prevented us from further investigating potential interaction between time to first cigarette and other sociodemographic variables (e.g., sex, age, education, or social class) or other characteristics of smoking (frequency and depth of inhalation, type of cigarettes smoked, etc.), although we were able to observe

significant results for the main hypothesis of the study. On the other hand, we found that the optimal cutpoint to distinguish between smokers and nonsmokers in our population was 9.2 ng/ml (Martínez-Sánchez, Fu, 2009), and five smokers (2.4%) had salivary cotinine concentration under this value. Nevertheless, we excluded those smokers whose cotinine values were unreliable in relation to their self-reported consumption, that is, more than 35 ng/ml per cigarette smoked (Blackford et al., 2006). Other strengths of our study include the use of data from smokers in the general population with a high participation rate (79.8%). In addition, saliva specimens were collected in different moments of the day, in workdays and weekends over 20 months, minimizing possible errors due to day or time of the saliva collection or seasonality.

In conclusion, this study confirms that the time to first cigarette smoked is associated with salivary cotinine concentration, regardless of the number of cigarettes smoked. These indicators of nicotine dependence can be used in population-based studies of smoking behavior.

Funding

This study was supported by the Instituto de Salud Carlos III (grants FIS PI020261 and PI081436) and the Thematic Network of Cooperative Research on Cancer (grant RD06/0020/0089) from the Government of Spain and by the Ministry of Universities and Research (grant 2009SGR192) from the Government of Catalonia.

Declaration of Interests

None declared.

Acknowledgments

The authors want to thank Chupa Chups, Spain, for providing the Smint candies used to facilitate salivation.

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CE: Satish ED: Dheiran Op: csr CEJ 200518: LWW_CEJ_200518

Nicotine depedence and salivary cotinine concentration in daily smokers

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There is scant information on nicotine dependence in smokers not seeking cessation treatment. This study analyses the relationship between nicotine dependence, measured by the Fagerström Test for Nicotine Dependence (FTND), and salivary cotinine concentration in a sample of smokers from the general population. We conducted a cross-sectional study (2004–2005) of a representative sample of the general population of Barcelona, Spain (n=1245). The analysis included 196 daily smokers aged more than 16 years. Information on smoking was obtained by questionnaire and cotinine concentration was determined in saliva. Geometric means of cotinine concentration by every single FTND item were computed, and multivariate linear regression was used to explore the relationship among these variables. Participants smoked a mean of 17.0 cigarettes per day, and the mean FTND score was 3.27 (95% confidence interval: 2.92–3.61). Subjects (17.3%; 95% confidence interval: 12.0–22.5%) had high nicotine dependence. Cotinine concentration differed significantly by nicotine dependence levels. In a multiple linear regression model including the sum of the FTND items 2, 3, and 6, and the single FTND items 1, 4, and 5, adjusted for sex, the time to first cigarette after waking up (item 1), the number of cigarettes smoked daily (item 4), and smoking more in the first hours of the day (item 5) were significantly related to salivary cotinine concentration (R^2=0.414). Salivary cotinine levels were associated with nicotine dependence as measured by the FTND, especially with the items on daily tobacco consumption, time to first cigarette after waking up, and smoking more in the first hours of the day. *European Journal of Cancer Prevention* 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2011, **00**:000–000

Keywords: cotinine, cross-sectional study, dependence, epidemiology, smoking

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Received 16 March 2011 **Accepted** 15 June 2011

Introduction

It is well established that smoking is mainly sustained by dependence or addiction to nicotine (US Department of Health and Human Services, 1988). Quitting smoking is difficult once smokers are addicted to nicotine, and thus they may require additional help besides their willingness to quit. But dependence relies not only on nicotine intake, but also on genetic and environmental factors, including drug-associated stimuli and social pressure that influence initiation and patterns of use (US Department of Health and Human Services, 1988).

Assessing smokers' dependence is crucial not only to direct the treatment, but also for research purposes. Different approaches have been used to assess dependence, such as qualitative methods (questions addressed to know whether the smoker has some difficulty to refrain from smoking or to stop smoking), quantitative methods (by means of standardized questionnaires), or objective methods (such as measurement of biomarkers of nicotine intake; West, 2004). Diagnostic criteria for dependence from Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision and International Classification of Diseases-10th Revision are widely used for clinical purposes, and require a structured interview done by experts. The Fagerström Test for Nicotine Dependence (FTND; Heatherton *et al.*, 1991) is a self-administered tool widely used for clinical and epidemiological purposes (Gerstenkorn, 2000; Gallus and La Vecchia, 2004; Gallus *et al.*, 2005; Diaz *et al.*, 2005). It is a short six-item test reflecting a continuum of dependence, with a demonstrated validity and a good relation with biological measures of smoking (Heatherton *et al.*, 1991). A shorter version of this questionnaire, the Heavy Smoking Index (HSI), has also a demonstrated validity (Heatherton *et al.*, 1989; 1991; Benowitz, 1996).

0959-8278 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0b013e32834a7e59

The use of a biological marker of tobacco smoking such as cotinine to assess dependence, in addition to questionnaires, may provide a more comprehensive description on the complex patterns of tobacco consumption at both clinical setting and population level. Nicotine dependence at a population level has seldom been assessed (Fagerström and Furberg, 2008). The aim of this study was to analyse the relationship between nicotine dependence, measured by the FTND, and salivary cotinine concentration in adult daily smokers from the general population.

Methods

We conducted a cross-sectional study on the general population of Barcelona, Spain, between March 2004 and December 2005. A representative sample was drawn from the 2001 residents' register of Barcelona by simple random sampling. To detect a difference in smokers' cotinine concentration of 50 ng/ml (with a mean value of 500 ng/ml and a standard deviation of 200 ng/ml), with an α value of 5% and a β of 10% (statistical power of 90%), we estimated that a sample size of 337 smokers would be needed. Considering that the prevalence of smokers from the 2001 Health Survey of Barcelona was 27%, we estimated a sample size of 1560 people, taking into account smokers and nonsmokers. A letter was sent to eligible participants explaining the study, and trained interviewers contacted them at home. In case they were less than or equal to 16 years, a proxy was used to assist the interview. When a nonresponse occurred (refusal to participate or after seven unsuccessful attempts), it was replaced by an individual of the same sex, 5-year age group, and district, also selected at random from the population. The research and ethics committee of the Bellvitge University Hospital approved the study protocol. Participants gave the informed consent form, answered a questionnaire, and provided a saliva specimen to determine the cotinine concentration. The study was ended just before 1 January 2006, when the new Spanish smoking law came into effect (Fernandez, 2006). This law bans smoking in all enclosed public spaces and in all workplaces, with some exceptions in hospitality sector; hence, some changes in smoking behaviour could be expected because of the law. Therefore, 1245 people were interviewed and 315 people could not be approached before 31 December. From the 1245 participants, 285 were daily smokers (at least one cigarette per day), 62 were occasional (nondaily) smokers, 354 exsmokers, 525 never smokers, and 19 were less than or equal to 16 years, who were interviewed (either directly or using a proxy respondent) on second-hand smoke exposure only. We focused on adult people who were daily smokers.

Measures

Questionnaire

Besides sociodemographics and second-hand smoke exposure in different settings, detailed information on smoking habits was gathered from smokers: number of cigarettes smoked daily and during the previous 24 and 48 h, age at which they started smoking, brand of cigarettes usually smoked and those used in the last 24 and 48 h, use of cigarettes with filter tips, depth and frequency of inhalation, use of other tobacco products, and use of nicotine gum or patches. Nicotine dependence was assessed with the FTND. Questions included: time to the first cigarette smoked after waking up, difficulty to refrain from smoking where it is forbidden, cigarette that the smoker hates most to give up, number of cigarettes smoked per day, time of the day when smoking is more frequent, and smoke when ill. FTND score ranges from 0 to 10, with higher scores indicating more nicotine dependence.

Body mass index

We measured participants' weight and height with an electronic portable scale and a tape measure, and the body mass index (BMI) was calculated as weight/squared height, in kg/m^2. We used standard categories of BMI in analyses: underweight (< 18.50), normal (18.50–24.99), overweight (25.00–29.99), and obese (≥ 30.00).

Saliva specimen

After a standardized protocol, interviewers asked the participants to rinse their mouths and suck a lemon-flavoured candy (Smint) to stimulate salivation. They were asked first to spit out a small amount of saliva, and then to spit about 8 ml of saliva into a polypropylene test tube. The specimen was kept at 4° and then frozen at $-20^{\circ}C$ in 3 ml aliquots for transport in dry ice to the Bioanalysis Research Group of the Municipal Institute for Medical Research (IMIM-Hospital del Mar). Cotinine concentration in nanograms per millilitre was determined by gas chromatography/mass spectrometry, as done in other studies (Shin *et al.*, 2002), and quantified as low as 1 ng/ml (limit of detection: 0.3 ng/ml; quantification error $< 15\%$).

Strategy of analysis

Sample exclusions

From 285 daily smokers, seven were excluded from the analysis because of missing cotinine concentration data (due to scant sample, or saliva specimen not provided). As we focused on cigarette smokers only, we excluded 53 people who smoked other tobacco products (mainly cigars and roll tobacco) and two people who were using nicotine gums or nicotine patches for cessation. Twelve were excluded because their cotinine concentration were unreliable in relation to their self-reported consumption, that is, over 35 ng/ml per cigarette smoked (Blackford *et al.*, 2006), and 15 people were also excluded because they had incomplete information to obtain FTND score. Thus, the final sample for analysis consisted of 196 adult daily smokers.

Variables

The outcome variable was salivary cotinine concentration (ng/ml). We calculated the FTND score (0–10 points)

and classified the smokers according to nicotine dependence levels as described by Fagerstrom *et al.*, 1990: low = 0–4, medium = 5, and high = 6–10. Other variables concerning individual characteristics (sex, age, educational level, and BMI), type of tobacco [regular vs. nonregular (light, ultralight, etc.), blond vs. black], and smoking characteristics (frequency and depth of inhalation) were considered to adjust the relation between FTND scores and salivary cotinine concentration.

Statistical analyses

We calculated geometric means (GMs), geometric standard deviations, and 95% confidence intervals (CI) to describe FTND scores and salivary cotinine concentration by individual characteristics, type of tobacco, and smoking characteristics. As the distributions were nonnormally distributed, we analysed the salivary cotinine concentration and the FTND scores according to the variables of interest using the Wilcoxon test and the Kruskal–Wallis test to assess differences in each group. We also studied the distribution of cotinine concentration according to each single FTND item. We explored the correlation between salivary cotinine concentration and the overall FTND score using a scatterplot and Spearman's rank correlation. We used log-transformed salivary cotinine concentration to adjust multiple linear regression models including the overall FTND score, a single FTND item, and all single FTND items, adjusting for potential confounders. We chose the model with the best fit according to the partial *F*-test (indicating the significant variables to maintain in every step). We tested the final model for the applicability of conditions of linear regression. All analyses were conducted using SPSS, v15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

From all 196 daily smokers, 51% were women and approximately 60% were between 17 and 44 years. Participants were similarly distributed across educational levels. Most of them (58.0%) had a normal weight. The average cigarette consumption was 17.0 cigarettes per day.

The distribution of FTND scores was bimodal; 18.4% of participants had 0-point score, and 44.4% had scores

Table 1 Fagerström Test for Nicotine Dependence scores and salivary cotinine concentration (ng/ml) according to individual and tobacco consumption characteristics

			FTND score		Salivary cotinine concentration	
	n	%	Mean (SD)	*P* value	GM (SDG)	*P* value
Total	196	100.0	3.27 (2.43)	–	113.65 (2.92)	–
Individual characteristics						
Sex				0.047[a]		<0.001[a]
Men	96	49.0	3.66 (2.55)		141.94 (2.77)	
Women	100	51.0	2.89 (2.27)		91.82 (2.95)	
Age (years)				0.344[b]		0.180[b]
17–44	116	59.2	3.07 (2.32)		107.01 (2.89)	
45–64	69	35.2	3.62 (2.61)		128.04 (3.00)	
≥ 65	11	5.6	3.09 (2.47)		101.57 (2.74)	
Educational level				0.226[b]		0.024[b]
Less than primary and primary	62	31.6	3.63 (2.56)		141.85 (3.05)	
Secondary	69	35.2	3.35 (2.29)		109.85 (2.74)	
University	65	33.2	2.83 (2.42)		95.38 (2.91)	
Body mass index (kg/m^2; n=193)				0.849[b]		0.419[b]
Normal[c]	112	58.0	3.28 (2.36)		108.87 (2.75)	
Overweight	62	32.2	3.13 (2.49)		125.32 (2.87)	
Obese	19	9.8	3.32 (2.79)		97.94 (4.32)	
Type of tobacco						
Type of cigarettes				0.078[a]		0.162[a]
Regular	139	70.9	3.46 (2.44)		119.96 (2.89)	
Nonregular (light, ultralight, etc.)	57	29.1	2.79 (2.37)		99.63 (2.97)	
Type of tobacco				0.011[a]		0.042[a]
Blond	164	83.7	3.05 (2.30)		109.38 (2.83)	
Black	32	16.3	4.38 (2.79)		138.31 (3.35)	
Smoking characteristics						
Frequency of inhalation				0.187[b]		0.209[b]
All the time	18	9.2	3.33 (2.63)		109.28 (2.75)	
Half the time	142	72.4	3.08 (2.41)		108.75 (2.93)	
Seldom	36	18.4	3.94 (2.35)		137.94 (2.97)	
Depth of inhalation (n=194)				0.592[b]		0.678[b]
Light	20	10.3	3.50 (2.70)		150.74 (2.34)	
Moderate	76	39.2	3.00 (2.17)		115.13 (2.72)	
Deep	98	50.5	3.39 (2.58)		104.94 (3.19)	

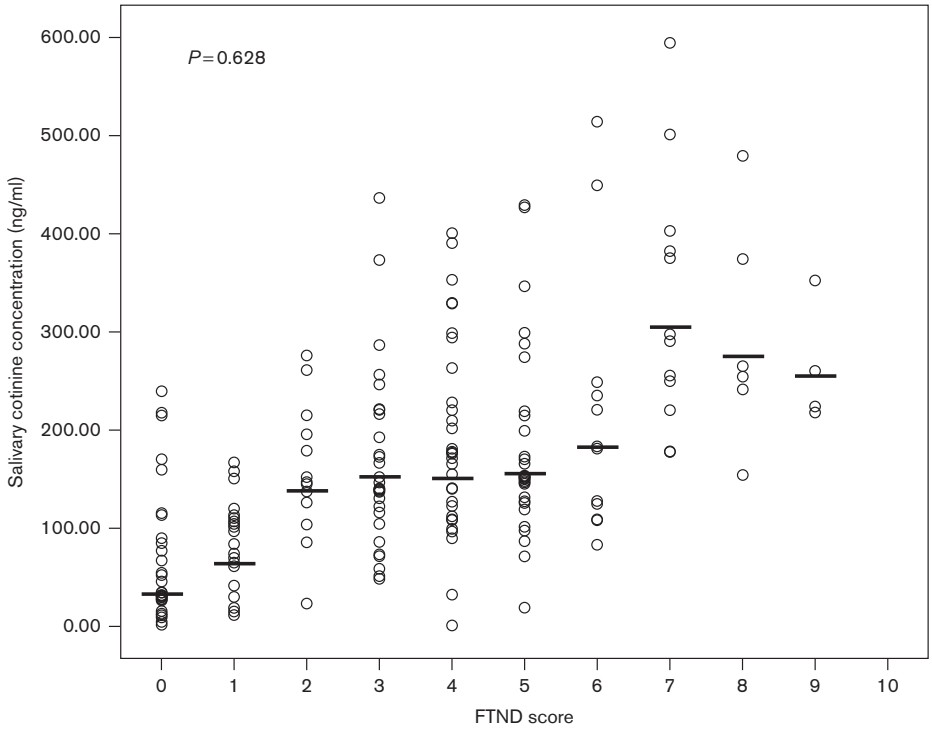
FTND, Fagerström Test for Nicotine Dependence; SD, standard deviation; GM, geometric mean; SDG, GM's standard deviation.
Barcelona (Spain), 2004–2005
[a]Wilcoxon test for two independent samples.
[b]Kruskal–Wallis test for several independent samples.
[c]It includes four cases that were underweight.

between 3 and 5. None of them scored the maximum 10 points. The FTND scores and salivary cotinine concentration according to individual characteristics, type of tobacco, and other smoking characteristics are shown in Table 1. The mean FTND score for all participants was 3.27 and differed by sex (3.66 for men and 2.89 for women; $P < 0.05$). No statistically significant differences in FTND scores by sex were found across different categories of tobacco consumption (data not shown). The highest scores were found in the 45–64 years age group, in the lowest educational level group, and in smokers who were obese, although these differences were nonstatistically significant. The FTND scores differed by the type of tobacco (3.05 in smokers of blond tobacco and 4.38 in smokers of black tobacco; $P < 0.05$). Other significant differences or consistent trends in cotinine concentration were not found.

The overall GM of salivary cotinine concentration was 113.65 ng/ml (95% CI: 97.74–132.15 ng/ml). There were significant differences by sex; men had a higher cotinine concentration (GM: 141.94 ng/ml; 95% CI: 115.50–174.42 ng/ml) than women (GM: 91.82 ng/ml; 95% CI: 74.09–113.78 ng/ml). We observed significant differences in salivary cotinine concentration by educational level, with the highest value at the lowest category, and by type of tobacco, with higher value in the black-tobacco group. Salivary cotinine concentration was correlated with FTND scores (Spearman's $P = 0.628$), as shown in Fig. 1. The GMs of cotinine concentration were 87.45, 159.12, and 246.29 ng/ml for people with low, medium, and high dependence, respectively ($P < 0.001$; Tables 2).

GMs of salivary cotinine concentration according to the single FTND items are shown in Table 2. All items except item 2 showed differences in salivary cotinine concentrations, with higher concentrations at higher single score. We performed multiple linear regressions to obtain the model that better explains salivary cotinine concentration. We first performed a linear regression model including the overall FTND score and then we included potential confounders (sex, age, educational level, BMI, type of cigarettes, type of tobacco, frequency, and depth of inhalation) and the only statistically significant variable was sex. Models including a single FTND item plus sex (one model per each item) were all significant except that including item 2. A model including all single items and sex indicated that the items 1, 4, and 5 were significantly associated with cotinine concentration. Finally, a model including the

Fig. 1



Distribution of salivary cotinine concentrations by Fagerström Test for Nicotine Dependence (FTND) scores. Barcelona (Spain), 2004–2005. Horizontal lines indicate geometric mean of salivary cotinine concentration by FTND scores.

Table 2 Salivary cotinine concentrations (ng/ml) according to Fagerström Test for Nicotine Dependence items

	n	%	GM	SDG	*P* value
All cases	196	100.0	113.65	2.92	–
Nicotine dependence levels					<0.001[a]
Low (0–4 points)	135	68.9	87.45	3.11	
Medium (5 points)	27	13.8	159.12	1.87	
High (6–10 points)	34	17.3	246.29	1.62	
FTND items:					
(1) Time to first cigarette					<0.001[a]
After 60 min (0 points)	72	36.7	56.03	3.21	
31–60 min (1 point)	28	14.3	134.29	1.55	
6–30 min (2 points)	66	33.7	178.98	1.85	
Within 5 min (3 points)	30	15.3	195.59	3.12	
(2) Difficult to refrain from smoking					0.054[b]
No (0 points)	179	91.3	108.75	3.01	
Yes (1 point)	17	8.7	180.92	1.53	
(3) Cigarette hating most to give up					<0.001[b]
All others (0 points)	109	55.6	88.40	3.11	
The first one in the morning (1 point)	87	44.4	155.71	2.45	
(4) Cigarettes per day					<0.001[a]
10 or less (0 points)	65	33.2	50.03	3.69	
11–20 (1 point)	82	41.8	146.94	1.88	
21–30 (2 points)	30	15.3	228.73	1.63	
31 or more (3 points)	19	9.7	205.99	1.65	
(5) Smoking more in the first hours of the day					<0.001[b]
No (0 points)	141	71.9	95.14	3.16	
Yes (1 point)	55	28.1	179.27	1.91	
(6) Smoking when ill					0.003[b]
No (0 points)	159	81.1	101.65	3.11	
Yes (1 point)	37	18.9	183.60	1.66	

Barcelona (Spain), 2004–2005.
FTND, Fagerström Test for Nicotine Dependence; GM, geometric mean; SDG, GM's standard deviation
[a]Kruskal–Wallis test for several independent samples.
[b]Wilcoxon test for two independent samples.

Table 3 Regression model of salivary cotinine concentration[a]

	β	SE	*P*	R^2
Model				0.414
Constant	1.767	0.100	<0.001	
Item 1 from FTND: time to first cigarette				
After 60 min (0 points)	Ref.	–	–	
31–60 min (1 point)	0.149	0.093	0.111	
6–30 min (2 points)	0.284	0.072	<0.001	
Within 5 min (3 points)	0.202	0.103	0.052	
Item 4 from FTND: cigarettes per day				
10 or less (0 points)	Ref.	–	–	
11–20 (1 point)	0.329	0.068	<0.001	
21–30 (2 points)	0.428	0.092	<0.001	
31 or more (3 points)	0.427	0.113	<0.001	
Item 5 from FTND: smoking more in the first hours of the day				
No (0 points)	Ref.	–	–	
Yes (1 point)	0.140	0.061	0.023	
Sum of partial scores of items 2, 3, and 6 from FTND	0.022	0.040	0.590	
Sex				
Men	Ref.	–	–	
Women	−0.105	0.054	0.052	

Barcelona (Spain), 2004–2005.
FTND, Fagerström Test for Nicotine Dependence; SE, standard error.
[a]Log-transformed salivary cotinine concentration.

sum of the scores in the items 2, 3, and 6, and the single significant items 1, 4, and 5 and sex accounted for 41.4% of variance (Table 3). We tested the final model for error specification, normality of errors, homoscedasticity, multicollinearity, outliers, and self-correlation, and all diagnostics indicated that the model fulfilled the assumptions.

Discussion

We found that the FTND scores and the salivary cotinine concentration were related. The best predictors of cotinine concentration were items 1, 4, and 5. This is in agreement with the previous evidence (Heatherton *et al.*, 1991); two of these items form the HSI, the FTND brief alternative to assess dependence.

We also found that FTND scores differed by sex, with men having higher scores, as in other studies (Fagerström *et al.*, 1996; Becoña and Vazquez, 1998; Gerstenkorn, 2000; Gallus *et al.*, 2005; Fagerström and Furberg, 2008). A previous study in a Spanish population found differences in FTND scores by sex and by age groups, and found that the FTND scores were affected by the cigarettes smoked daily (Becoña and Vazquez, 1998). When we compared the FTND scores by categories of tobacco consumption, the differences between men and women did not appear as significant. Factors related to sex (i.e., biological differences in the metabolism of men and women) or to sex (i.e., behavioural differences in the way women and men smoke) possibly influencing nicotine dependence should be further investigated (Benowitz *et al.*, 2006; Melikian *et al.*, 2007; Pauly, 2008). Genetic factors may also be playing a role in dependence. Although salivary or plasmatic cotinine have shown to be excellent markers of exposure, monitoring the metabolic ratio between the two nicotine metabolites, trans 3′-hydoxycotinine and cotinine, has been proposed as a marker of CYP2A6 activity, responsible for the metabolism of nicotine to cotinine, and therefore having a role in nicotine dependence (Dempsey *et al.*, 2004; Malaiyandi *et al.*, 2006). Some studies have related the ratio between these metabolites and the FTND or other questionnaires measuring dependence; but none of them have found a significant association (West *et al.*, 2011). Other metabolic routes (e.g. glucuronidation) have also been proposed as genetic determinants of nicotine fate (Lessov-Schlaggar *et al.*, 2009). However, the multiple genetic factors involved produce large variations of those metabolic ratios reducing its potential use as direct markers of a specific trait (Swan *et al.*, 2009).

When we described salivary cotinine concentration according to FTND scores, we observed a positive relation between these variables; the more the FTND scores, the more the cotinine concentration. GMs showed that salivary cotinine concentration levelled off at medium and high FTND scores. This shape is similar to the described quadratic relation (first linear and then flat) between the cotinine concentration and the number of cigarettes smoked (Caraballo *et al.*, 1998; Joseph *et al.*, 2005; Blackford *et al.*, 2006; Fu *et al.*, 2009). This similarity could be due to the fact that the tobacco consumption is a significant contributor to the FTND scores. It seems that more dependent smokers have higher tobacco consumption and have higher cotinine concentration than less dependent smokers. Nevertheless, tobacco consumption is generally not closely associated with dependence, especially in groups of smokers who are quitting (West *et al.*, 2011). Thus, in addition to the tobacco consumption, other factors might also have an effect on cotinine concentration and could explain the flat form of the relation in the highest strata of consumption and in the highest FTND scores. Although the first cigarettes of the day produce the most intense effects over physiological and behavioural responses (Henningfield and Benowitz, 2004), the last cigarettes of the day in heavy smokers would not be a meaningful contributor to cotinine concentration once smokers had reached the desired levels of nicotine in the body. In any case, the flat form of the distribution of salivary cotinine concentration in the highest FTND scores should be considered with caution, because the sample included few very high-dependent smokers.

The mean FTND score in our sample was 3.27, similar to those found in other population-based studies (Fagerström *et al.*, 1996; Gallus *et al.*, 2005; Joseph *et al.*, 2005; Blackford *et al.*, 2006; Fagerström and Furberg, 2008). As in another Spanish sample (de Leon *et al.*, 2002), our data showed that 17.3% of smokers had a high nicotine dependence. These figures are smaller than those found in Poland (46.3%; Gerstenkorn, 2000) and close to the 20% in Italy (Gallus and La Vecchia, 2004) and to the 18.5% in the Spanish data from the WHO Countrywide Integrated Noncommunicable Diseases Intervention Programme (Gerstenkorn, 2000), thus reflecting the different stages in the progression of the tobacco epidemic (Lopez *et al.*, 1994) in these populations.

Study limitations and strengths

This is the first study in Spain that assesses the relationship between nicotine dependence and a specific biomarker of tobacco consumption such as salivary cotinine. The methods used for cotinine analyses are highly sensible (Pascual *et al.*, 2003), and the questionnaire used has an acceptable validity (Fernandez *et al.*, 2007). Nevertheless, we cannot ignore some limitations in our study. The fit of models could be affected by the trend of the respondents to round off the tobacco consumption, specifically the heaviest smokers (Klesges *et al.*, 1995), and hence some information bias due to digit preference cannot be disregarded. This potential bias could be also affecting the shape of the relation between salivary cotinine and FTND scores, as tobacco consumption is an important contributor to the FTND score. Some loss of representativeness due to nonresponse might also be possible, on the other hand, the sampling strategy used (sampling with replacement) could result in a potential bias, if willingness to participate would be related to the outcomes investigated. Nevertheless, our sample did not differ by sex, age, district of residence, and smoking behaviour from the Barcelona population because the design allowed replacement according to those variables. The prevalence of daily smokers in our sample (28.6% of men and 18.2% of women) was similar to that derived from the 2006 Health Interview Survey of Barcelona (27.3% of men and 20.6% of women; Villalbí *et al.*, 2009).

In conclusion, our findings suggest that salivary cotinine is associated with nicotine dependence. Salivary cotinine concentration was best associated with the FTND items

related to daily tobacco consumption, time to first cigarette smoked after waking up, and smoking more in the first hours of the day. This study confirms the FTND and its simplified version (the 2-item HSI) as useful tools to assess nicotine dependence in both clinical settings and epidemiological studies. As changes in prevalence consumption are not expected in the European region in the very next years (Strong *et al.*, 2008), monitoring dependence at the population level is needed to describe potential changes in smokers.

Acknowledgements

This work was supported by the Instituto de Salud Carlos III, Government of Spain (grants FIS PI020261, FIS PI081436, and RTICC RD06/0020/0089); and the Ministry of Universities and Research, Government of Catalonia (grant 2009SGR192). The authors also thank Chupa Chups Spain for providing the Smint candies.

Conflicts of interest

None declared.

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Preventive Medicine 52 (2011) 139–145

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Stages of change, smoking characteristics, and cotinine concentrations in smokers: Setting priorities for smoking cessation

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ARTICLE INFO

Available online 14 December 2010

Keywords:
Stages of change
Transtheoretical model
Cotinine
Smoking

ABSTRACT

Objective. We assessed whether the salivary cotinine content of daily smokers varied with the readiness to quit and smoking characteristics.

Methods. This cross-sectional study was conducted in Barcelona, Spain ($n = 1245$) in 2004–2005. We administered a questionnaire to assess smoking behaviour and collected saliva to determine the cotinine content. We determined the distribution of 278 adult daily smokers across different stages of change and categorised them by individual and smoking characteristics. We used medians and interquartile ranges (IQR) to relate cotinine concentrations to different stages of change, tobacco consumption, and nicotine dependence based on the Fagerström Test for Nicotine Dependence (FTND).

Results. Around 68%, 22%, and 11% of smokers were in precontemplation, contemplation, and preparation stages, respectively. A mean of 17.0 cigarettes was smoked daily, with no differences among stages of change. The median cotinine concentration was 151.3 ng/ml (IQR: 83.2–227.8 ng/ml), with no differences among stages of change. The cigarette consumption scores, FTND, and time to first cigarette of the day were positively associated with cotinine concentration.

Conclusions. The cotinine concentration was similar among the stages of change, but varied within each stage according to the number of cigarettes smoked, time to first cigarette of the day, and nicotine dependence.

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Introduction

Tobacco smoking is the main cause of premature mortality in developed countries. Nicotine, the main alkaloid of tobacco, is mainly responsible for the addictive effect of tobacco. Many smokers cannot quit due to nicotine dependence. Nevertheless, success in quitting smoking depends on both the magnitude of the smoker's dependence on tobacco and on the strength of his/her motivation to quit (West, 2004).

The transtheoretical model is a conceptual framework widely used to study the process of quitting smoking. It is an integrative model of

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0091-7435/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.ypmed.2010.12.003

behavioural change based on the decision making process of the individual. It implies that the processes of change occur in 5 stages. Movement through these stages involves a progression/regression process that smokers undergo before they quit smoking (Prochaska et al., 1992).

The stages of change model has received some criticism (Etter and Perneger, 1999; West, 2005) and the evidence for the effectiveness of stage-based interventions on smoking cessation is controversial (Riemsma et al., 2003; Spencer et al., 2002). Nevertheless, descriptions of smokers by stages of change continue to be widely used in clinical settings, because they are useful in directing the treatment, studying different populations of smokers, analysing profiles of subjects by stage over time (Connors et al., 2004), and assessing priorities for individuals or groups within a population that are targets of different health education strategies (Jhun and Seo, 2006; Wewers et al., 2003).

Some studies classifying smokers by the stages of change have also used different biomarkers of tobacco consumption to validate self-reported consumption (de Granda-Orive et al., 2004; Prochaska and DiClemente, 1983), but few of them have related biomarkers to different smoker characteristics (Ahijevych and Parsley, 1999; Etter et al., 2000). Cotinine, the major metabolite of nicotine, can be related to nicotine dependence; thus, baseline cotinine levels may be useful for categorising smokers that enter smoking cessation programmes (Hall et al., 1984; Paoletti et al., 1996; Tønnesen et al., 1993). Although some studies have described cotinine concentrations in different populations of smokers, none have taken into account the stage of change of the smokers (Blackford et al., 2006; Fidler et al., 2008; Muscat et al., 2009).

In order to explore priorities for smoking cessation, we aimed to determine whether the salivary cotinine concentrations of daily smokers varied with their readiness to quit and with their smoking characteristics.

Methods

Study design

This cross-sectional study was conducted between April 2004 and December 2005 in Barcelona, Spain. The details of our procedures were described elsewhere (Fu et al., 2009; Martínez-Sánchez et al., 2009). In brief, we obtained a representative random sample from the 2001 official census of Barcelona. Trained interviewers contacted participants at home to administer a face-to-face paper-based questionnaire and, immediately afterwards, collected a saliva specimen for cotinine determination. At the end of the collection period, 1245 people were interviewed, and 285 were adult (age >16 years old) daily smokers (at least 1 cigarette per day [CPD]). The research and ethics committee of the University Hospital of Bellvitge approved the study, and all participants provided written informed consent.

Measures

Questionnaire

We gathered information on demographics, second-hand smoke exposure in different settings, and detailed information from smokers: average CPD, cigarette consumption during the last 24 and 48 h, brand of cigarettes smoked, age when they started smoking, type of cigarettes smoked (regular or non-regular: light, ultralight, …), type of tobacco smoked (blond, flue-cured; or black, air-cured), use of filter tips, frequency and depth of inhalation, and nicotine dependence based on the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). We collected information on the number of attempts to quit smoking and the readiness to quit according to the stages of change.

Body mass index (BMI)

BMI may affect cotinine absorption; therefore, we measured the weight and height according to a standardised protocol and calculated the BMI (kg/m^2). The BMIs were stratified into standard categories (World Health Organization, 1995).

Salivary cotinine

Participants were asked to provide a saliva specimen, and were offered a lemon-flavoured candy (Smint®) to stimulate salivation. The cotinine concentration (ng/ml) was determined by gas chromatography with mass spectrometric detection (GC/MS) (Pascual et al., 2003) in the Municipal Institute for Medical Research (IMIM-Hospital del Mar) (quantification limit: 1 ng/ml; detection limit: 0.3 ng/ml; quantification error <15%).

Data analysis

Of 285 daily smokers, 278 subjects with complete information were analysed. Most smoked manufactured cigarettes, but 21 subjects smoked other tobacco products (pipes, cigars, or rolled tobacco).

Variables

We classified salivary cotinine concentration by the stage of change based on the Prochaska and DiClemente algorithm. We considered three stages of change: the precontemplators, smokers that were not seriously considering quitting within the next 6 months; the contemplators, smokers that were seriously considering quitting within the next 6 months, but not within the next 30 days or smokers that had not attempted to quit for at least 24 hours in the past year, or both; and the preparation stage, smokers that were planning to quit within the next 30 days and had attempted to quit for at least 24 hours in the past year (DiClemente et al., 1991). In this study, we focused on current daily smokers; therefore, we did not consider the other two stages: action (those who had quit during the past 6 months) and maintenance (those who had quit for more than 6 months). Based on the FTND scores (range 0–10 points), we classified subjects according to their nicotine dependence (low = 0–4; medium = 5; high = 6–10) (Fagerström et al., 1990).

Statistical analysis

Individual and smoking characteristics were described in terms of prevalence rates or means and standard deviations (SD). Due to the skewed distribution of cotinine concentrations, we used medians and interquartile ranges (IQR) to relate it to the stages of change and smoking characteristics. The smoking characteristics included the age when smoking started, type of cigarettes, type of tobacco, use of filter tips, frequency and depth of inhalation, CPD, time to the first cigarette after waking up (TFC; item 1 from the FTND), and nicotine dependence. We stratified the data by individual and smoking characteristics. We used box-plots to represent the distributions of salivary cotinine concentrations across the stages of change, nicotine dependence, and CPD, where the length of the box indicates the IQR, the line included in the box represents the median, and whiskers represent the minimum and maximum non-atipic values; circles represent

Table 1
Distribution of 278 adult daily smokers across the stages of change according to individual characteristics. Barcelona (Spain), 2004–2005.

	n*	Stages of change		
		Precontemplation, *n* (%)	Contemplation, *n* (%)	Preparation, *n* (%)
Total	278	188 (67.6)	60 (21.6)	30 (10.8)
Sex				
Men	152	105 (69.1)	32 (21.0)	15 (9.9)
Women	126	83 (65.9)	28 (22.2)	15 (11.9)
Age				
17–24 years	24	18 (75.0)	5 (20.8)	1 (4.2)
25–44 years	128	77 (60.2)	30 (23.4)	21 (16.4)
45–64 years	101	71 (70.3)	23 (22.8)	7 (6.9)
≥65 years	25	22 (88.0)	2 (8.0)	1 (4.0)
Educational level				
Less than primary and primary	96	69 (71.9)	17 (17.7)	10 (10.4)
Secondary	95	65 (68.4)	19 (20.0)	11 (11.6)
University	86	53 (61.6)	24 (27.9)	9 (10.5)
Body mass index (kg/m^2)†				
Normal‡	156	110 (70.5)	30 (19.2)	16 (10.3)
Overweight	93	59 (63.4)	25 (26.9)	9 (9.7)
Obese	25	17 (68.0)	3 (12.0)	5 (20.0)

* The sum does not add up to the total in some cases, due to some missing values.
† Body mass index categories: normal: 18.50–24.99; overweight: 25.00–29.99; obese: ≥30.00 kg/m^2.
‡ This includes 5 cases that were underweight (body mass index <18.50 kg/m^2).

Table 2
Distribution of 278 adult daily smokers across stages of change, according to smoking characteristics. Barcelona (Spain), 2004–2005.

	n*	Stages of change			p-value
		Precontemplation, n (%)	Contemplation, n (%)	Preparation, n (%)	
Total, n (%)	278	188 (67.6)	60 (21.6)	30 (10.8)	–
Age that smoking started, n (%)					
<15 years	38	30 (78.9)	5 (13.2)	3 (7.9)	0.459+
15–17 years	114	72 (63.2)	26 (22.8)	16 (14.0)	
18–19 years	56	39 (69.6)	14 (25.0)	3 (5.4)	
≥20 years	70	47 (67.2)	15 (21.4)	8 (11.4)	
Type of cigarettes, n (%)					
Regular	204	144 (70.6)	40 (19.6)	20 (9.8)	0.188+
Non-regular (light, ultralight, etc.)	73	43 (58.9)	20 (27.4)	10 (13.7)	
Type of tobacco, n (%)					
Blond	213	143 (67.2)	48 (22.5)	22 (10.3)	0.766+
Black	63	43 (68.3)	12 (19.0)	8 (12.7)	
Use of filter tip, n (%)					
With filter	260	173 (66.5)	59 (22.7)	28 (10.8)	0.261+
Without filter	17	14 (82.3)	1 (5.9)	2 (11.8)	
Frequency of inhalation, n (%)					
All the time	32	23 (71.9)	6 (18.7)	3 (9.4)	0.742+
Half the time	189	131 (69.3)	40 (21.2)	18 (9.5)	
Seldom	56	34 (60.7)	14 (25.0)	8 (14.3)	
Depth of inhalation, n (%)					
Light	36	24 (66.7)	8 (22.2)	4 (11.1)	0.356+
Moderate	101	76 (75.3)	18 (17.8)	7 (6.9)	
Deep	138	87 (63.0)	33 (23.9)	18 (13.1)	
Cigarette consumption (CPD§)					
Overall CPD, mean (SD)	257	16.3 (11.6)	19.4 (11.6)	16.0 (10.1)	0.164†
Levels of consumption, n (%)					
1–10 CPD	90	64 (71.1)	16 (17.8)	10 (11.1)	0.170+
11–20 CPD	102	64 (62.8)	24 (23.5)	14 (13.7)	
21–30 CPD	40	31 (77.5)	7 (17.5)	2 (5.0)	
>30 CPD	25	13 (52.0)	10 (40.0)	2 (8.0)	
Time to first cigarette, n (%)					
>60 min	104	68 (65.4)	26 (25.0)	10 (9.6)	0.597+
31–60 min	41	29 (70.8)	6 (14.6)	6 (14.6)	
6–30 min	95	69 (72.6)	18 (19.0)	8 (8.4)	
≤5 min	37	22 (59.5)	10 (27.0)	5 (13.5)	
Nicotine dependence‡					
Overall FTND *score*, mean (SD)	237	3.11 (2.364)	3.48 (2.697)	3.16 (2.154)	0.748†
Levels of nicotine dependence, n (%)					
Low	165	111 (67.3)	34 (20.6)	20 (12.1)	0.402+
Medium	33	23 (69.7)	7 (21.2)	3 (9.1)	
High	39	24 (61.6)	13 (33.3)	2 (5.1)	

* The sum does not add up to the total in some cases, due to some missing values.
\+ Pearson χ^2 test.
† Kruskal–Wallis test.
§ CPD: cigarettes per day.
‡ As measured by the FTND: low: 0–4; medium: 5; high: 6–10.

outliers (values between 1.5 IQRs and 3 IQRs from the end of the box) and asterisks represent extreme values (values more than 3 IQRs from the end of the box). We used the Pearson χ^2 test to compare proportions and the Kruskal–Wallis test to compare medians and means. The type I error was set at 1% ($p<0.01$) to adjust for multiple comparisons.

Results

Among 278 daily smokers (152 men and 126 women), 67.6% were in precontemplation, 21.6% in contemplation, and 10.8% in preparation, with no differences in sex; 65.3 had completed secondary or university studies, and 56.1% had BMIs in the normal range. The average age was 43.5 years (46.0% aged 25–44 years). The distribution of smokers was similar across the strata of age, but the precontemplation stage had the highest proportion of older smokers (88.0%). The proportion of precontemplators varied inversely with the level of education, and the proportion of contemplators varied proportionately with the level of education (Table 1).

The mean cigarette consumption was 17.0 CPD (SD = 11.5), with no differences among different stages of change ($p=0.164$; Table 2). Most people smoked regular cigarettes, with a filter tip, and used blond tobacco. We observed that the precontemplators were more prone to smoking regular cigarettes, and the contemplators and those in preparation tended to use non-regular cigarettes. There was a slight positive trend in the proportion of precontemplators that inhaled all the time; conversely, the largest proportions of contemplators and those in preparation seldom inhaled. Heavy smokers (>20 CPD) were more likely to be in the precontemplation stage ($p=0.170$; Table 2). Concerning nicotine dependence, the overall mean FTND score was 3.2 (SD = 2.4), with no meaningful differences among stages of change. Most contemplators showed high nicotine dependence, and most smokers in the preparation stage had low dependence. In the preparation stage, half as many smokers showed high dependence (5.1%) compared to the number with low (12.1%) or medium (9.1%) dependence ($p=0.402$; Table 2).

The overall median cotinine concentration was 151.3 ng/ml (IQR: 83.2–227.8 ng/ml), with no statistical differences among stages of change (Table 3). The highest cotinine concentrations were found in precontemplators and contemplators aged 45–64 and in those in preparation aged ≥65 (Table 3). We found no other differences among groups in the other individual characteristics. Regarding smoking characteristics (Table 4), we found that smokers of black

Table 3
Median and interquartile ranges of salivary cotinine concentrations (ng/ml) in 278 adult daily smokers across stages of change according to individual characteristics. Barcelona (Spain), 2004–2005.

	n*	Stages of change			p-value+
		Precontemplation, n = 188	Contemplation, n = 60	Preparation, n = 30	
Total	278	152.5 (83.3; 245.1)	145.8 (86.1; 223.1)	147.5 (55.1; 207.3)	0.746
Sex					
Men	152	179.2 (106.5; 278.7)	149.4 (88.0; 234.9)	192.7 (97.2; 218.0)	0.475
Women	126	127.0 (60.6; 216.6)	135.6 (83.9; 223.1)	113.1 (44.6; 194.9)	0.487
Age (years)					
17–24	24	151.5 (104.5; 184.3)	34.2 (6.8; 99.8)	50.5 (50.5; 50.5)	0.024
25–44	128	138.4 (77.9; 254.6)	155.6 (102.2; 215.6)	139.4 (45.9; 198.8)	0.628
45–64	101	177.9 (94.5; 248.8)	172.4 (96.6; 373.8)	171.1 (118.4; 239.3)	0.785
≥65	25	129.6 (34.9; 234.9)	35.2 (34.1; 36.3)	206.8 (206.8; 206.8)	0.363
Educational level					
Less than primary and primary	96	179.2 (102.7; 289.8)	214.8 (91.2; 383.2)	200.2 (123.5; 272.8)	0.586
Secondary	95	137.1 (83.1; 223.5)	113.7 (94.5; 201.3)	118.4 (50.5; 202.7)	0.805
University	86	138.4 (64.7; 218.4)	136.3 (67.4; 208.8)	97.2 (34.9; 158.5)	0.415
Body mass index (kg/m²)†					
Normal‡	156	137.7 (84.1; 250.3)	118.8 (94.2; 196.8)	147.4 (48.0; 219.2)	0.763
Overweight	93	172.9 (77.2; 260.0)	152.2 (59.7; 236.1)	113.1 (50.6; 198.8)	0.409
Obese	25	166.6 (63.8; 218.8)	265.5 (154.4; 383.8)	161.6 (129.1; 234.2)	0.240

* The sum does not add up to the total in some cases, due to some missing values.
\+ Kruskal–Wallis test.
† Body mass index categories: normal: 18.50–24.99; overweight: 25.00–29.99; obese: ≥30.00 kg/m².
‡ This includes 5 cases that were underweight (body mass index <18.50 kg/m²).

Table 4
Median and interquartile ranges of salivary cotinine concentrations (ng/ml) of 278 adult daily smokers across stages of change according to smoking characteristics. Barcelona (Spain), 2004–2005.

	n*	Stages of change			p-value+
		Precontemplation, n = 188	Contemplation, n = 60	Preparation, n = 30	
Total	278	152.5 (83.3; 245.1)	145.8 (86.1; 223.1)	147.5 (55.1; 207.3)	0.746
Age that smoking started					
<15 years	38	192.5 (152.6; 287.3)	105.1 (53.7; 138.6)	139.7 (15.0; 275.6)	0.020
15–17 years	114	142.8 (82.7; 238;7)	174.3 (79.6; 219.3)	150.5 (56.6; 203.8)	0.829
18–19 years	56	148.8 (113.0; 227.8)	189.5 (105.3; 384.7)	202.7 (155.3; 594.6)	0.323
≥20 years	70	119.9 (45.2; 235.0)	107.0 (36.3; 167.0)	115.8 (47.6; 206.3)	0.918
Type of cigarettes					
Regular	204	156.3 (83.6; 258.9)	135.1 (86.1; 244.8)	158.5 (66.8; 200.8)	0.785
Non-regular (light, ultralight, etc.)	73	130.1 (82.6; 199.0)	164.6 (76.8; 220.1)	99.4 (46.0; 216.4)	0.881
Type of tobacco					
Blond	213	150.2 (89.6; 248.8)	124.2 (83.6; 217.1)	136.9 (49.0; 207.3)	0.392
Black	63	177.3 (64.8; 227.8)	153.3 (102.1; 272.2)	150.7 (77.3; 214.2)	0.789
Use of filter tip					
With filter	260	152.6 (86.5; 243.2)	146.5 (86.8; 223.8)	158.5 (77.4; 208.3)	0.851
Without filter	17	119.0 (37.7; 356.3)	71.0 (71.0; 71.0)	51.9 (47.2; 56.6)	0.668
Frequency of inhalation					
All the time	32	189.8 (87.5; 254.4)	153.4 (112.6; 198.3)	193.5 (171.1; 218.0)	0.781
Half the time	189	137.1 (76.5; 235.0)	153.3 (89.3; 244.8)	91.4 (44.0; 193.3)	0.175
Seldom	56	178.6 (117.2; 288.3)	96.2 (35.8; 221.5)	182.2 (139.5; 216.4)	0.155
Depth of inhalation					
Light	36	95.7 (51.3; 290.7)	224.2 (89.9; 381.3)	96.6 (61.1; 475.6)	0.487
Moderate	101	153.6 (99.7; 242.2)	100.7 (44.9; 157.0)	85.6 (44.6; 206.8)	0.035
Deep	138	165.6 (84.5; 239.4)	146.5 (100.9; 231.3)	166.4 (84.7; 204.2)	0.986
Cigarette consumption (CPD§)					
1–10 CPD	90	74.8 (30.8; 129.7)	57.5 (13.1; 207.2)	139.2 (41.5; 210.0)	0.505
11–20 CPD	102	168.4 (127.0; 250.2)	124.2 (99.3; 164.8)	158.5 (103.5; 225.5)	0.076
21–30 CPD	40	214.8 (172.9; 298.1)	223.8 (190.8; 426.9)	150.0 (97.2; 202.7)	0.415
>30 CPD	25	220.5 (150.1; 321.6)	245.6 (117.9; 376.0)	178.9 (139.7; 218.0)	0.782
Time to first cigarette					
>60 min	104	79.9 (33.1; 144.8)	101.5 (34;2; 171.4)	48.9 (37.2; 133.6)	0.579
31–60 min	41	165.7 (126.5; 226.8)	105.7 (77.2; 133.7)	118.3 (78.4; 164.0)	0.037
6–30 min	95	187.1 (127.7; 290.0)	174.3 (118.7; 255.8)	198.1 (164.7; 216.9)	0.765
≤5 min	37	237.5 (180.4; 292.5)	319.7 (206.5; 414.5)	206.8 (75.4; 406.3)	0.196
Nicotine dependence†					
Low	165	120.1 (56.4; 181.2)	111.5 (68.9; 178.3)	147.4 (46.1; 205.8)	0.872
Medium	33	172.9 (146.9; 281.2)	145.1 (86.8; 383.8)	118.4 (97.2; 161.6)	0.297
High	39	227.8 (178.7; 296.0)	249.6 (172.6; 392.8)	406.3 (218.0; 594.6)	0.529

* The sum does not add up to the total in some cases, due to some missing values.
\+ Kruskal–Wallis test.
§ CPD: cigarettes per day.
† As measured by the Fagerström Test for Nicotine Dependence: low: 0–4; medium: 5; high: 6–10.

tobacco had higher salivary cotinine concentrations than smokers of blond tobacco; also, concentrations were higher in the precontemplation than in the preparation stages. No clear trends emerged in the dependence variables among different stages of change. Nevertheless, we observed consistent trends in cotinine concentrations within every stage (Table 4); cotinine levels rose with the number of cigarettes smoked, with higher nicotine dependence, and with lower TFC. The median salivary cotinine concentration differed according to the stage of change and nicotine dependence. Cotinine concentrations significantly increased with increasing nicotine dependence among smokers in the precontemplation ($p<0.001$) and contemplation ($p=0.002$) stages, but not for smokers in the preparation stage ($p=0.132$; Fig. 1). Similarly, cotinine concentrations increased with the number of CPD only in the precontemplation ($p<0.001$) and contemplation ($p=0.004$) stages (Fig. 2).

Discussion

We found that the cotinine concentration was similar among the three stages of change; in contrast, cotinine concentration was directly related to CPD, nicotine dependence, and TFC within each stage. Cotinine levels rose with higher CPD, higher nicotine dependence, and lower TFC. These results indicate that the relationship between cotinine concentration and the stages of change is not simple; therefore, cotinine does not directly indicate progress through the stages of change. Previous studies showed divergent results, although they were based on selected samples of smokers (Ahijevych and Parsley, 1999; Etter et al., 2000), thus partly explaining the lack of effectiveness observed in the stage-based interventions for changing smoking behaviour (Bridle et al., 2005; Riemsma et al., 2003).

We observed no differences in TFC, age when smoking started, or CPD among different stages of change. This was consistent with previous findings from one study (Ahijevych and Parsley, 1999), but not from another (Fava et al., 1995). Our results showed that smokers with the highest CPD tended to be in the precontemplation stage, and smokers with lower CPD tended to be in preparation; this was similar

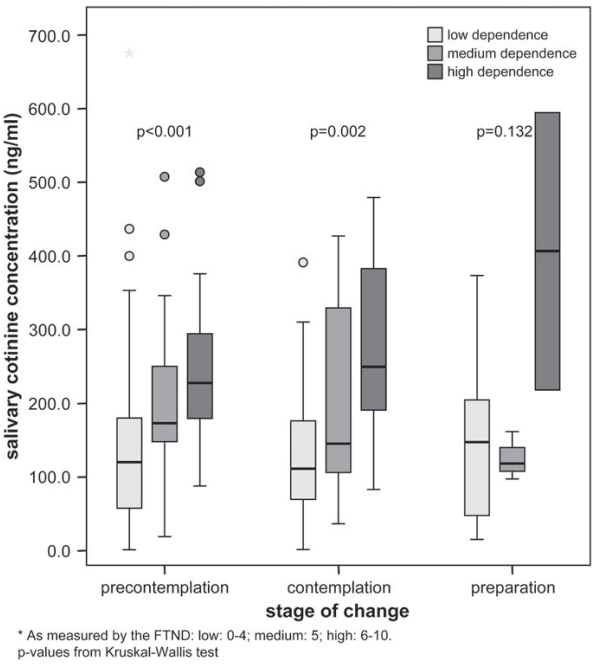

Fig. 1. Salivary cotinine concentrations (ng/ml) in 278 daily smokers across stages of change and nicotine dependence*. Barcelona (Spain), 2004–2005.

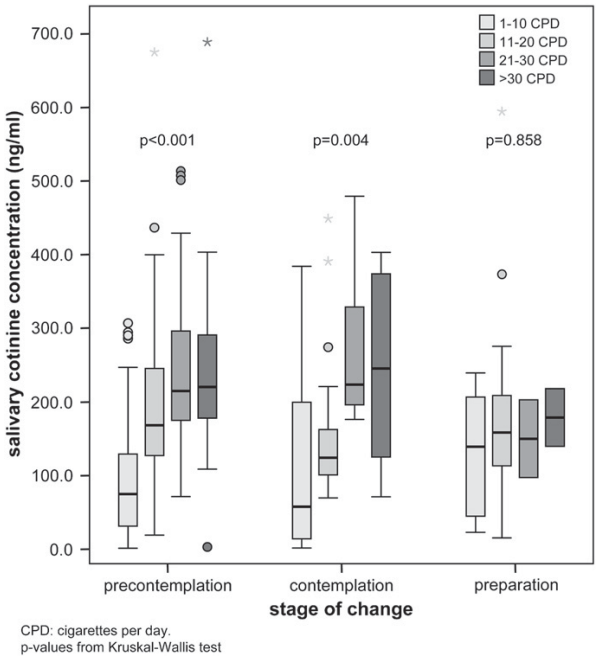

Fig. 2. Salivary cotinine concentrations (ng/ml) in 278 daily smokers across stages of change and levels of cigarette consumption. Barcelona (Spain), 2004–2005.

to other studies (DiClemente et al., 1991; Fava et al., 1995; John et al., 2003; Pallonen et al., 1992). Although, in our sample, nicotine dependence was similar among all stages, most smokers in the preparation stage had low dependence. Furthermore, these smokers tended to smoke non-regular cigarettes and seldom inhaled; this probably reflected a greater concern about smoking. These results appear to be consistent with the predictions of the transtheoretical model (Velicer et al., 1999).

In our sample, the distribution of smokers in different stages was very similar to those observed in some European studies (Becoña, 2000; Etter et al., 1997; Pallonen et al., 1992), but different from those in some American studies (Fava et al., 1995; Velicer et al., 1995). This may reflect differences in the progress of the tobacco epidemic in different populations (Lopez et al., 1994). In our data, the sex distribution of smokers was equivalent within each stage because Spain is now at stage IV of the tobacco epidemic, and sex differences in smoking have narrowed (Borràs et al., 2000; Fernández et al., 2003). Accordingly, other studies that were conducted in populations in the advanced stages of the tobacco epidemic found no differences in the sex distributions of smokers by stages of change (DiClemente et al., 1991; Velicer et al., 1995; Yang et al., 2001). Hence, different distributions of smokers across the stages of change may reflect differences in the progress of the tobacco epidemic.

In our study, 68% of smokers were precontemplators, or smokers not willing to quit. Smoking-control programmes should orientate interventions according to smoker characteristics; they should aim to increase the awareness of the benefits of smoking cessation. Interventions at the population level should take into account the distribution of smokers among the stages of change, because smokers in different stages require different approach strategies. Most smokers started smoking before they were 17 years old; thus, there is a need to prevent the initiation of tobacco consumption and nicotine addiction in youths. Restrictions in advertising and tobacco sales to young people (aged <18) that are promoted by the Spanish tobacco law (Fernández, 2006) are important steps in preventing initiation; however, there is a need for more comprehensive educational

campaigns that address this specific group of potential smokers, as recommended by the World Health Organization Framework Convention in Tobacco Control (World Health Organization, 2003).

Study limitations and strengths

Our study included a wide range of smokers from the general population; thus, our sample was less homogeneous than studies with volunteers that are generally conducted in a clinical setting; the latter samples usually biased to be in the in the preparation stage, women, and highly educated (Bovet et al., 2002; Curry et al., 1990; Velicer et al., 1995). Another strength of this study was the use of cotinine as a biomarker for tobacco consumption (Benowitz, 1996). To our knowledge, few investigations have related cotinine concentration to the stages of change (Ahijevych and Parsley, 1999; Etter et al., 2000). However, some limitations cannot be disregarded. The use of questionnaires could be a source of information bias, although self-reported smoking has been considered accurate and sufficiently valid (Gorber et al., 2009; Patrick et al., 1994). Also, we may have lost some representativeness due to non-responders; nevertheless, our sample did not differ from the entire Barcelona population in terms of sex, age, residence, and smoking behaviour (Villalbí et al., 2009). The participation rate was nearly complete, because the study design allowed the replacement of non-responders according to the strata of sex, age, and district of residence.

Conclusion

This study showed that salivary cotinine concentrations were similar among smokers in different stages of change. However, cotinine levels varied within the precontemplation and contemplation stages according to the levels of tobacco consumption and nicotine dependence. Population-based strategies of cessation should consider interventions that address smokers in precontemplation, because they had the largest proportion of smokers with moderate cigarette consumption, low nicotine dependence, and low salivary cotinine concentrations. Also, from a high-risk prevention perspective (Chaiton et al., 2008; Rose, 2001), specific attention should be paid to older smokers, with low education, and high nicotine dependence within every stage; those groups had relatively high cotinine concentrations. Measurement of baseline cotinine concentration might facilitate the characterisation of smokers motivated to quit and thus, might benefit from individually tailored nicotine replacement therapy. Before introducing this approach into clinical practice, we need further evidence from cessation trials that take into account baseline cotinine concentrations. Finally, future studies should consider the distribution of smokers in different stages of change in the population in both cross-sectional and longitudinal studies. This would facilitate assessments of smokers as they transition through the stages of change and provide a measure of the impact of public health interventions.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

Role of the funding source

This project was funded by the Instituto de Salud Carlos III (grants FIS PI020261 and PI081436) and the Thematic Network of Cooperative Research on Cancer (grant RD06/0020/0089) of the Government of Spain, and the Ministry of Universities and Research (grant 2009SGR192) of the Government of Catalonia.

The sponsors had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

Acknowledgments

We want to thank Chupa Chups, Spain for providing the Smint® candies.

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Dependencia a la nicotina y preparación para dejar de fumar en la población española

Nicotine dependence and readiness to quit smoking in the Spanish population

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recibido: Septiembre 2010
aceptado: Diciembre 2010

RESUMEN

Objetivo: Describir la dependencia a la nicotina y la preparación para dejar de fumar en la población fumadora.
Métodos: Estudio transversal de una muestra representativa de la población española ≥18 años. La información se obtuvo mediante entrevistas telefónicas realizadas en junio y julio de 2006. Se estudió la dependencia a la nicotina mediante el test de Fagerström (FTND) y la preparación para dejar de fumar de acuerdo a los estadios del cambio del modelo transteórico en una muestra de fumadores de cigarrillos.
Resultados: El 22,5% de los participantes (IC 95%: 20,9-24,2%) fumaba cigarrillos. Su consumo medio fue de 14,4 cigarrillos diarios (desviación estándar 9,15) y su puntuación media en el FTND fue de 2,8, sin diferencias según los estadios del cambio. El 64,3% (IC 95%: 60,3-68,2%) de los fumadores estaba en el estadio de precontemplación, el 25,4% (IC 95%: 21,8-28,9%) en el de contemplación y el 10,4% (IC 95%: 7,9-12,9%) en el estadio de preparación, sin diferencias por sexo. Los fumadores más dependientes a la nicotina (FTND≥6) tenían mayoritariamente estudios primarios, comenzaron a fumar a edad más temprana y fumaban más cigarrillos al día.
Conclusiones: Los fumadores presentan mayoritariamente un bajo nivel de dependencia a la nicotina y se encuentran en fase de precontemplación. Los programas de deshabituación deberían ir dirigidos a reducir el nivel de dependencia, ayudar a los fumadores a avanzar a través de los estadios del cambio y, consecuentemente, disminuir la prevalencia de fumadores en la población.

Palabras clave: tabaquismo, dependencia a la nicotina, estadios del cambio, modelo transteórico, prevalencia, epidemiología

ABSTRACT

Objective: To describe the nicotine dependence and readiness to quit smoking in the smoker population.
Methods: Cross-sectional study on a representative sample of the Spanish population of ≥18 years old. We gathered information by means of telephone interviews conducted between June and July of 2006. We studied the nicotine dependence with the Fagerström Test for Nicotine Dependence (FTND) and the readiness to quit according to the stages of change from the Transtheoretical Model in a sample of cigarette smokers.
Results: 22.5% of participants (95% CI: 20.9-24.2%) smokers cigarettes. They smoked an average of 14.4 cigarettes per day (standard deviation 9.15) and the mean FTND score was 2.8, with no differences by the stages of change. 64.3% (95% CI: 60.3-68.2%) of smokers were in the precontemplation stage, 25.4% (95% CI: 21.8-28.9%) in contemplation, and 10.4% (95% CI: 7.9-12.9%) in preparation, with no differences by sex. The most nicotine dependent smokers (FTND≥6) had mainly primary studies, started to smoke at earlier ages, and smoked more cigarettes per day.
Conclusions: Most Spanish smokers have low nicotine dependence and are in precontemplation stage. Smoking cessation programmes should be addressed to reduce dependence, help smokers to progress through the stages of change, and, consequently, reduce the prevalence of smokers in the population.

Keywords: smoking, nicotine dependence, stages of change, transtheoretical model, prevalence, epidemiology

INTRODUCCIÓN

El consumo de tabaco aumenta el riesgo de padecer enfermedades respiratorias agudas y crónicas, así como enfermedades cardiovasculares, cáncer y alteraciones de la función reproductiva[1]. Informar a los fumadores acerca de los efectos nocivos del tabaquismo para la salud y estimularlos a abandonar el consumo son objetivos fundamentales en la práctica clínica en particular y de la salud pública en general. Para poder desarrollar programas de prevención e intervención orientados a cumplir estos objetivos resulta de gran interés conocer el nivel de dependencia a la nicotina y la preparación de los fumadores para dejar de fumar.

Existe una serie de instrumentos para evaluar la dependencia a la nicotina. Uno de los más utilizados en el ámbito clínico es el test de Fagerström de dependencia a la nicotina[2,3], debido a su brevedad y sencillez de aplicación. Por otra parte, para evaluar la preparación para dejar de fumar en el contexto de la deshabituación tabáquica se ha utilizado ampliamente el modelo transteórico de Prochaska y DiClemente[4], que es un modelo integrado de cambio conductual basado en el proceso de toma de decisiones realizado por un individuo. Según este modelo, el proceso de cambio tiene lugar a través de 5 etapas o estadios, en cuyo camino el fumador avanza progresivamente hasta dejar el hábito de fumar.

En España existen algunos estudios que han descrito la dependencia a la nicotina o la preparación para dejar de fumar[3,5-11]. Sin embargo, la mayoría de ellos se han realizado en un contexto clínico o de cesación tabáquica[7-9,11] y ninguno de los estudios realizados a nivel poblacional incluyó una muestra representativa de la población adulta española[3,5,6,10]. El estudio de la dependencia y la preparación para dejar de fumar a nivel poblacional puede ser útil para desarrollar y evaluar políticas públicas dirigidas a disminuir el consumo y fomentar la cesación tabáquica. El objetivo del presente trabajo es describir la dependencia a la nicotina y la preparación para dejar de fumar (estadios del cambio) en la población adulta española.

MÉTODOS

Los datos provienen de un estudio multicéntrico de diseño transversal con el objetivo de describir la prevalencia y algunas características del consumo de tabaco (como la dependencia a la nicotina y los estadios del cambio) y la exposición al humo ambiental del tabaco en la población general de 6 países europeos[12]. Este trabajo está centrado en los datos de España[13], cuya muestra teórica de 2.500 personas se obtuvo de forma proporcional por comunidad autónoma, tamaño del municipio de residencia, sexo y grupos de edad. El muestreo contempló la sustitución de las no-respuestas a partir de los mismos estratos. Los participantes fueron seleccionados en dos fases: en la primera de ellas se escogieron hogares de manera aleatoria a partir de un directorio telefónico, y en la segunda fase se seleccionó a la persona del hogar que respondería a la encuesta, de acuerdo a los estratos establecidos en el muestreo. Después de otorgar el consentimiento oral, los participantes fueron encuestados telefónicamente por entrevistadores entrenados durante junio y julio de 2006. La muestra final, representativa de la población adulta española ≥18 años, estuvo conformada por 2.538 personas y se obtuvieron 2.522 encuestas válidas (1.221 hombres y 1.301 mujeres). El 23,4% eran fumadores (22,0% fumadores diarios y 1,4% fumadores ocasionales), el 27,3% eran exfumadores y el 49,2% de los participantes no había fumado nunca.

Variables

Se definió como fumadores a aquellas personas que declararon fumar cigarrillos diaria u ocasionalmente en el momento de realizar la entrevista (n=568). No fueron incluidas en el análisis aquellas personas que sólo fumaban puros o cigarros, puritos, pipas o tabaco de liar (n=23, que representaban menos del 1% de la prevalencia total de consumo de tabaco).

Dependencia a la nicotina. Para evaluar la dependencia a la nicotina se utilizó el test de Fagerström[3]. Las preguntas incluyen: tiempo transcurrido desde que el individuo se despierta hasta que fuma el primer cigarrillo del día (0-3 puntos); dificultad para abstenerse de fumar en lugares donde está prohibido hacerlo (0-1 punto); cigarrillo del día al que le cuesta más renunciar (0-1 punto); número de cigarrillos fumados por día (0-3 puntos); momento del día en que fuma más frecuentemente (0-1 punto); y si fuma aun estando enfermo (0-1 punto). Se describieron los niveles de dependencia a la nicotina como baja (0-4 puntos), media (5 puntos) y alta (6-10 puntos)[2].

Estadios del cambio: Se consideraron los estadios del cambio del modelo transteórico de Prochaska y DiClemente[4,14] correspondientes a la fase fumadora: *precontemplación*, en el que los fumadores no se plantean dejar de fumar en un futuro cercano; *contemplación*, en el que los fumadores consideran seriamente dejar de fumar durante los próximos 6 meses; y *preparación*, que describe a los fumadores que desean dejar de fumar en el transcurso del próximo mes y han realizado al menos un intento no exitoso de dejar de fumar en el último año.

Análisis estadístico

Se calculó la distribución de las variables estudiadas mediante proporciones y sus intervalos de confianza del 95% (IC 95%) según sexo, grupos de edad (18-39, 40-59 y ≥60 años), nivel de estudios (primaria o menos que primaria, secundaria y universitaria), edad de inicio del consumo (<15, 15-18 y ≥19 años) y número de cigarrillos fumados diariamente (<10, 10-19 y ≥20 cigarrillos). Se describió gráficamente la distribución de los fumadores de acuerdo a sus puntuaciones en el test de Fagerström. Los análisis fueron realizados con los programas SPSS 15.0 y Excel.

RESULTADOS

De los 568 participantes que declararon fumar cigarrillos en el momento de la entrevista (22,5% de la muestra), el 54,4% eran hombres, el 57,0% tenía entre 18-39 años y el 44,5% tenía estudios secundarios. La mayoría de los fumadores (56,5%) comenzaron a fumar entre los 15 y 18 años. El 36,1% fumaba entre 10 y 19 cigarrillos por día (media de 14,4 cigarrillos; desviación estándar de 9,2).

La mayoría de los fumadores tenía una baja dependencia a la nicotina (Figura 1): el 74,1% obtuvo puntuaciones en el test de Fagerström entre 0 y 4. La puntuación media en el test fue de 2,80 (2,97 los hombres y 2,58 las mujeres). En la Tabla 1 se presenta la distribución de los fumadores según su nivel de dependencia a la nicotina, de acuerdo a las variables sociodemográficas y algunas características del consumo. La distribución de los fumadores según sexo a través de los niveles de dependencia era homogénea. Se puede constatar un mayor porcentaje de fumadores con dependencia media y alta entre 40-59 años comparados con los otros grupos de edad. La mayor prevalencia de fumadores con dependencia alta a la nicotina se observó en el grupo con estudios primarios (22,6%) y en los que habían comenzado a fumar antes de los 15 años (35,6%). La mayoría de los fumadores de menos de 10 cigarrillos diarios tenía una baja dependencia a la nicotina, mientras que la proporción de fumadores con dependencia media y alta aumentaba con el consumo de cigarrillos (Tabla 1).

En cuanto a la distribución de los fumadores según los estadios del cambio, el 64,3% de los fumadores estaban en el estadio de precontemplación, el 25,4% en el de contemplación, y el 10,4% en el estadio de preparación, sin diferencias según sexo (Tabla 2). Los fumadores ≥60 años estaban más preparados para dejar de fumar que los fumadores más jóvenes. Aquéllos que comenzaron a fumar antes de los 18 años se encontraban mayoritariamente en el

Figura 1. Distribución de 568 fumadores españoles según sus puntuaciones en el test de Fagerström, 2006.

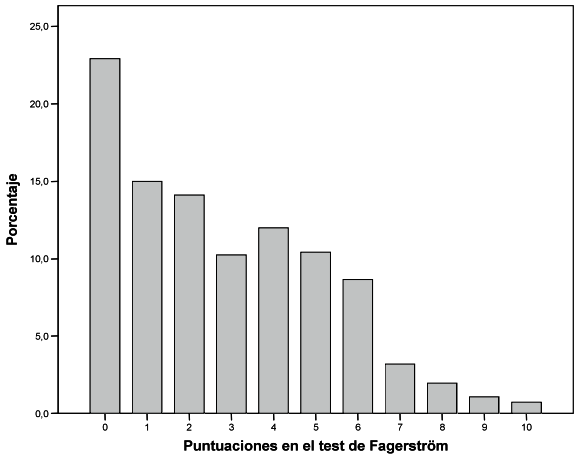

Tabla 1. Prevalencia (%) e intervalo de confianza del 95% (IC 95%) de los niveles de dependencia a la nicotina en 568 fumadores españoles según variables sociodemográficas y algunas características del consumo de tabaco, 2006.

		Dependencia a la nicotina*					
		baja		media		alta	
	n	%	IC 95%	%	IC 95%	%	IC 95%
Total	568	74,1	70,5 - 77,7	10,4	7,9 - 12,9	15,5	12,5 - 18,5
Sexo							
hombres	309	73,5	68,5 - 78,4	10,4	7,0 - 13,8	16,2	12,1 - 20,3
mujeres	259	74,9	69,6 - 80,2	10,4	6,7 - 14,1	14,7	10,4 - 19,0
Edad							
18-39 años	324	79,6	75,2 - 84,0	8,3	5,3 - 11,3	12,0	8,5 - 15,6
40-59 años	207	65,7	59,2 - 72,2	13,5	8,9 - 18,2	20,8	15,2 - 26,3
≥60 años	37	73,0	57,0 - 84,6	10,8	4,3 - 24,7	16,2	7,7 - 31,1
Estudios							
primarios y menos	195	65,1	58,4 - 71,8	12,3	7,7 - 16,9	22,6	16,7 - 28,4
secundarios	253	79,4	74,5 - 84,4	9,9	6,2 - 13,6	10,7	6,9 - 14,5
universitarios	119	77,3	69,8 - 84,8	8,4	3,4 - 13,4	14,3	8,0 - 20,6
Edad de inicio del consumo							
<15 años	87	52,9	42,4 - 63,4	11,5	4,8 - 18,2	35,6	25,6 - 45,7
15-18 años	321	77,9	73,3 - 82,4	10,3	7,0 - 13,6	11,8	8,3 - 15,4
≥19 años	160	78,1	71,7 - 84,5	10,0	5,4 - 14,6	11,9	6,9 - 16,9
Número de cigarrillos							
<10 cigarrillos/día	183	99,5	97,0 - 99,9	0,5	0,1 - 3,0	0,0	0,0 - 2,1
10-19 cigarrillos/día	205	82,9	77,8 - 88,1	10,7	6,5 - 15,0	6,3	3,0 - 9,7
≥20 cigarrillos/día	180	38,3	31,2 - 45,4	20,0	14,2 - 25,8	41,7	34,5 - 48,9

*Según la puntuación en el test de Fagerström: baja: 0-4 puntos; media: 5 puntos; alta: 6-10 puntos.

Tabla 2. Prevalencia (%) e intervalo de confianza del 95% (IC 95%) de los estadios del cambio en 568 fumadores españoles según variables sociodemográficas y algunas características del consumo de tabaco, 2006.

		Estadios del cambio					
		precontemplación		contemplación		preparación	
	n	%	IC 95%	%	IC 95%	%	IC 95%
Total	568	64,3	60,3 - 68,2	25,4	21,8 - 28,9	10,4	7,9 - 12,9
Sexo							
hombres	309	66,0	60,7 - 71,3	22,7	18,0 - 27,3	11,3	7,8 - 14,9
mujeres	259	62,2	56,3 - 68,1	28,6	23,1 - 34,1	9,3	5,7 - 12,8
Edad							
18-39 años	324	65,1	59,9 - 70,3	24,4	19,7 - 29,1	10,5	7,2 - 13,8
40-59 años	207	63,3	56,7 - 69,9	28,0	21,9 - 34,1	8,7	4,9 - 12,5
≥60 años	37	62,2	46,5 - 77,8	18,9	6,3 - 31,5	18,9	6,3 - 31,5
Estudios							
primarios y menos	195	65,1	58,4 - 71,8	26,2	20,0 - 32,3	8,7	4,8 - 12,7
secundarios	253	63,6	57,7 - 69,6	24,9	19,6 - 30,2	11,5	7,5 - 15,4
universitarios	119	64,7	56,1 - 73,3	24,4	16,7 - 32,1	10,9	5,3 - 16,5
Edad de inicio del consumo							
<15 años	87	67,8	58,0 - 77,6	17,2	9,3 - 25,2	14,9	7,5 - 22,4
15-18 años	321	67,6	62,5 - 72,7	23,4	18,7 - 28,0	9,0	5,9 - 12,2
≥19 años	160	55,6	47,9 - 63,3	33,8	26,4 - 41,1	10,6	5,9 - 15,4
Número de cigarrillos							
<10 cigarrillos/día	183	65,0	58,1 - 71,9	23,5	17,4 - 29,6	11,5	6,9 - 16,1
10-19 cigarrillos/día	205	61,5	54,8 - 68,1	29,3	23,0 - 35,5	9,3	5,3 - 13,2
≥20 cigarrillos/día	180	66,7	59,8 - 73,6	22,8	16,7 - 28,9	10,6	6,1 - 15,0

*Según la puntuación en el test de Fagerström: baja: 0-4 puntos; media: 5 puntos; alta: 6-10 puntos.

Tabla 3. Prevalencia (%) e intervalo de confianza del 95% (IC 95%) de los estadios del cambio según los niveles de dependencia a la nicotina en 568 fumadores españoles, 2006.

		Dependencia a la nicotina*					
		baja		media		alta	
Estadios del cambio	n	%	IC 95%	%	IC 95%	%	IC 95%
precontemplación	365	75,1	70,6 - 79,5	10,4	7,3 - 13,5	14,5	10,9 - 18,1
contemplación	144	74,3	67,2 - 81,4	10,4	5,4 - 15,4	15,3	9,4 - 21,2
preparación	59	67,8	55,9 - 79,7	10,2	2,5 - 17,9	22,0	11,5 - 32,6

*Según la puntuación en el test de Fagerström: baja: 0-4 puntos; media: 5 puntos; alta: 6-10 puntos.

estadio de precontemplación, mientras que no se observó un patrón claro en los fumadores en fase de preparación.

En la Tabla 3 se muestra la distribución conjunta de la dependencia a la nicotina y los estadios de cambio de los fumadores. La proporción de fumadores que tenía una dependencia alta fue ligeramente superior en el estadio de preparación (22,0%) que en los estadios de precontemplación (14,5%) y contemplación (15,3%), si bien estas diferencias no fueron estadísticamente significativas.

DISCUSIÓN

Los resultados de este trabajo indican que la mayoría de los fumadores españoles se encuentran en el estadio de precontemplación y tienen una baja dependencia a la nicotina. Los fumadores más dependientes a la nicotina eran aquéllos con estudios primarios, los que iniciaron el consumo de tabaco a temprana edad, y quienes tenían un mayor consumo de cigarrillos. No se observaron diferencias en la distribución de los fumadores según los estadios del cambio y las variables sociodemográficas estudiadas, al igual que en otras poblaciones[15-17].

Este estudio es el primero que dispone de datos de fumadores a nivel nacional que describen de manera conjunta su nivel de dependencia y su distribución según los estadios del cambio. El trabajo más amplio publicado hasta ahora era el derivado del estudio IBERPOC, llevado a cabo durante 1996-1997 en 7 poblaciones de España (Oviedo, Burgos, Cáceres, Madrid, Sevilla, Manlleu y Bilbao) en población adulta entre 40 y 69 años[5]. En dicho estudio, los 1.059 fumadores entrevistados (26% de los participantes) tenían una puntuación media de 3,4 en el test de Fagerström (3,7 los hombres y 2,6 las mujeres) y aproximadamente el

39% de ellos estaba en el estadio de precontemplación, el 58% en contemplación y aproximadamente el 4% en fase de preparación para dejar de fumar[5]. Las diferencias que se observan entre estas cifras y las obtenidas en nuestro estudio podrían explicarse por el propio desarrollo de la epidemia del tabaquismo en el período transcurrido entre ambos estudios (10 años), que bien pudiera condicionar un cambio real de la distribución de los fumadores según los estadios del cambio. En estos 10 años, la prevalencia de exfumadores ha aumentado, seguramente a expensas de fumadores en fase contemplativa, por lo que la proporción de precontempladores puede haber aumentado, tal y como muestran los resultados de nuestro estudio. No podemos excluir que parte de las diferencias observadas tengan su origen en diferencias metodológicas entre nuestro estudio y el estudio IBERPOC[18], tales como la procedencia de la muestra (obtenida de 7 poblaciones españolas), la forma de contacto con los participantes (por correo o por teléfono), la inclusión de pruebas funcionales respiratorias que podría condicionar la participación, y el acotado grupo de edad estudiado. Al restringir los datos de nuestro estudio a los fumadores entre 40 y 69 años, se observa el mismo valor medio en el test de Fagerström que en el estudio IBERPOC, pero no se observan cambios sustanciales en la distribución de los fumadores según los estadios del cambio respecto a toda la muestra ≥18 años (63,4%, 27,2% y 9,5% para las fases de precontemplación, contemplación y preparación, respectivamente).

Otros estudios españoles realizados en los últimos 15 años en diferentes poblaciones describen puntuaciones entre 2,3 y 3,8 en el test de Fagerström[6,10,19,20] y una distribución de fumadores de acuerdo a los estadios del cambio de aproximadamente entre 40 y 69% en precontemplación, 25 y 46% en contemplación y 6 y 14% en preparación[6,19,21,22]. A pesar de existir cierta variabilidad, se puede constatar que la preparación para dejar de fumar en la población es distinta a la que se observa en el contexto clínico de deshabituación tabáquica, que oscila entre 32 y 66%, 5 y 26% y 7,6 y 20% para las fases de precontemplación, contemplación y preparación, respectivamente[8,9,11]. Además, se observan mayores puntuaciones en el test de Fagerström en los fumadores en deshabituación tabáquica, con independencia de que presenten o no alguna patología[7,8]. Esto podría explicarse porque aquéllos que son más dependientes a la nicotina pueden tener la percepción de menor autocontrol frente al consumo de tabaco y por ello buscan activamente la ayuda para dejar de fumar.

Debido a que gran parte de los estudios realizados a nivel poblacional indican que la mayoría de los fumadores se encuentran en fase de precontemplación[6,21,23] y tienen una baja dependencia a la nicotina[5,6,10], las intervenciones a este nivel deberían orientar sus esfuerzos a intentar que los fumadores se muevan hacia fases más avanzadas de los estadios del cambio. Así, se debería intentar motivar a aquellos fumadores que no desean dejar de fumar, y propiciar que los fumadores con una dependencia baja a la nicotina sean capaces de dejar el consumo. Los factores que han sido descritos como los más influyentes en la intención futura de dejar el consumo son: la preocupación por los efectos de la exposición pasiva en los niños, familiares y amigos de los fumadores; la preocupación por el papel modélico de los fumadores entre los niños y jóvenes; y el consejo médico[24]. De esta forma, las actividades de control del tabaquismo a nivel poblacional deberían incluir como mínimo estos aspectos[25,26].

La descripción de los fumadores de acuerdo al modelo transteórico y al grado de dependencia a la nicotina es útil en la planificación y evaluación de intervenciones poblacionales, así como en el tratamiento individualizado del tabaquismo, pues ayuda a comprender el grado y la naturaleza de la adicción. Estudios derivados de intervenciones clínicas en deshabituación tabáquica han identificado entre los factores que se asocian a la abstinencia el tener bajos niveles de dependencia a la nicotina[27-30] y encontrarse en estadios del cambio avanzados[28-31], si bien otros estudios señalan que el test de Fagerström[32] o los estadios del cambio[33] no predicen tan claramente la conducta tabáquica. A pesar de ello, se debe tener en cuenta que estos trabajos están realizados en un contexto clínico especializado, en el que es más frecuente que los sujetos estén motivados para dejar de fumar.

Una de las limitaciones de este estudio deriva del uso de un cuestionario, que recoge información autodeclarada del consumo sin un marcador objetivo del mismo, y por tanto está sujeta a un posible sesgo de información que puede afectar a la validez interna del estudio. Sin embargo, la validez de la autodeclaración del consumo de tabaco es muy elevada[34,35]. Otro posible sesgo de información puede generarse debido a la tendencia de los participantes a redondear al alza el consumo de cigarrillos, especialmente entre los grandes fumadores[36]. Otra limitación se deriva del hecho de haber utilizado un directorio de teléfonos fijos para la obtención de la muestra de estudio, considerando que en los últimos años el uso del teléfono móvil se ha ido extendiendo en la población, pudiendo incluso en algunos casos llegar a sustituir el uso del teléfono fijo, lo cual podría afectar a la representatividad geográfica de la muestra. Además, por tratarse de una encuesta telefónica, puede existir un sesgo de información debido a la deseabilidad social, reforzada por la reciente implantación de la Ley 28/2005 en el momento del trabajo de campo. Todo lo anterior podría explicar el hecho que la prevalencia de consumo en nuestro estudio sea ligeramente menor comparada con la obtenida en la Encuesta Nacional de Salud de España del año 2006[37], aunque similar a la de la encuesta del Centro de Investigaciones Sociológicas del año 2006[38].

Por otra parte, la principal fortaleza de este estudio reside en el hecho de disponer de datos provenientes de una muestra representativa de la población general española. Asimismo, los cuestionarios utilizados en este estudio para caracterizar la dependencia y la preparación para dejar de fumar han sido validados y ampliamente utilizados en la literatura internacional[39]. Obtener esta información a nivel poblacional es sencillo y factible, y disponer de ella de manera periódica ayudaría a planificar programas de salud pública orientados a disminuir la prevalencia de fumadores en el estadio de precontemplación y aumentar la de estadios

más avanzados. Se ha demostrado que la intención de dejar de fumar puede cambiar a través del tiempo, a veces espontáneamente e incluso en cortos períodos de tiempo[40], con lo cual intervenciones eficaces podrían acelerar este movimiento deseado.

En conclusión, este trabajo indica que la mayoría de los fumadores españoles se encuentra en fase de precontemplación y tiene una baja dependencia a la nicotina. Existe cierta relación entre la preparación para dejar de fumar y la dependencia a la nicotina, dado que los fumadores menos dependientes se concentran en la fase de precontemplación y los más dependientes en la fase de preparación. Los programas de deshabituación deberían ir dirigidos a reducir el nivel de dependencia, ayudar a los fumadores a avanzar a través de los estadios del cambio, y, consecuentemente, disminuir la prevalencia de fumadores en la población.

AGRADECIMIENTOS

Este estudio ha sido parcialmente financiado con fondos de la Comisión Europea (proyecto de la European Network for Smoking Prevention, ref. 2004323), el Instituto de Salud Carlos III del Ministerio de Sanidad (Red Temática de Investigación en Cáncer, ref. RD06/0020/0089), y el Department d'Universitats i Recerca de la Generalitat de Catalunya (ref. 2009 SGR 192).

CONFLICTOS DE INTERESES

Los autores declaran que no tienen conflictos de intereses.

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Addiction

Letter to the Editor

The journal publishes both invited and unsolicited letters. It is at the editor's discretion whether such letters are sent out through peer review.

A COMPARISON OF THE FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE AND SMOKING PREVALENCE ACROSS COUNTRIES: UPDATED DATA FROM SPAIN

We read with interest the paper by Fagerström & Furberg published recently in *Addiction* [1]. The authors' hypothesis is appealing: smokers remaining in populations where the prevalence of smoking has decreased are hardening. The data indicate an inverse relationship between smoking prevalence and nicotine dependence, assessed by the Fagerström Test for Nicotine Dependence (FTND) [2].

The data presented by Fagerström & Furberg derive from population-based cross-sectional studies conducted in different European countries and the United States during the last two decades. With regard to the Spanish data, the study used by Fagerström & Furberg was from a cross-sectional survey conducted in 1997 in Galicia [3,4], a region in the North West of Spain with approximately 7.5% of the Spanish population.

Since 1997, however, the prevalence of smoking has decreased in Spain [5,6]. We present recent prevalence rates and nicotine dependence levels in the whole Spanish population to address further the 'hardening hypothesis'. These data were not available to Fagerström & Furberg at the time they conducted their study.

We conducted a cross-sectional survey of a representative sample of the Spanish population aged ≥ 18 years to assess active and passive smoking at the population level. The sample was representative in terms of sex, age, municipality and region, and substitution by people of the same strata was allowed. Hence, we obtained valid responses from 2522 participants (1221 men and 1301 women). Data were collected in June and July 2006 by trained interviewers with a structured questionnaire using a computer-assisted telephone interview. As well as basic socio-demographic data, the questionnaire gathered information on smoking habits, including the FTND for current smokers, on perceived exposure to second-hand smoke for non-smokers, and about knowledge and attitudes of both active and passive smoking. Details of the methods and results on exposure to second-hand smoke are available elsewhere [7].

Results indicate that 23.4% of Spanish adults were daily cigarette smokers (27.0% of men, 20.1% of women, $P < 0.05$). The mean FTND score was 2.8 (3.0 in men and 2.5 in women, $P < 0.05$). This different level of dependence according to sex is due mainly to the difference in the mean number of cigarettes smoked per day by men (15.7) and women (12.8, $P < 0.05$). Overall, smokers reported smoking 14.4 cigarettes daily. The data indicate a decrease in smoking prevalence but not an increase in nicotine dependence, as also observed in Italy [8]. Apparently, the reduction of the prevalence without a substantial change in dependence would go against the generalization of the hardening hypothesis.

In addition to ecological studies including different countries as the unit of analysis [1], trends of smoking prevalence and FTND scores across time within countries should be analysed in repeated and comparable cross-sectional surveys to understand further the dynamics and determinants of nicotine dependence at the population level.

Declarations of interest

None.

Acknowledgements

This study was funded partly by the European Commission (European Network for Smoking Prevention, ref. 2004323) from the Instituto de Salud Carlos III, Government of Spain (Thematic Research Network in Cancer RD06/0020/0089) and from the Department of Universities and Research, Government of Catalonia (SGR 200500646). The funding sources had no involvement in the study design, collection, analysis or interpretation of data, and were not involved in the decision to submit this letter for publication.

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6. DISCUSIÓN CONJUNTA

Los resultados derivados de esta tesis indican que el principal determinante de la concentración de cotinina en saliva fue el consumo diario de cigarrillos (hipótesis 1). La asociación entre ambas variables queda mejor explicada con una función cuadrática para el número de cigarrillos y separadamente para hombres y mujeres. Esto quiere decir que el aumento de la concentración de cotinina es lineal conforme aumenta el consumo de cigarrillos (hipótesis 1) hasta llegar aproximadamente a las 20 unidades, punto en el cual la concentración de cotinina se estabiliza. Esta forma de la asociación entre la concentración de cotinina y el consumo de cigarrillos también ha sido descrita en otros estudios que utilizaban muestras de saliva[82] y sangre[9], aunque el punto en el cual la concentración de cotinina se estabiliza puede variar en diferentes poblaciones de fumadores[53,83,84]. Un posible factor explicativo de estas variaciones son las diferencias individuales en el metabolismo de la nicotina: se ha demostrado que los fumadores regulan su ingesta de nicotina para alcanzar los niveles deseados de nicotina en el organismo[46]; así por ejemplo, los adolescentes pueden requerir menos cigarrillos que los adultos para satisfacer sus ansias de nicotina[84].

Además del consumo de cigarrillos, otros factores pueden tener un efecto en la concentración de cotinina y pueden explicar la forma aplanada de la relación en los niveles más altos de consumo: a medida que se fuman más cigarrillos conforme avanza el día la tolerancia a los efectos de la nicotina se incrementa, pero disminuye durante la noche a causa de la privación de nicotina durante las horas de sueño; de esta forma, los primeros cigarrillos del día producen los efectos más intensos a nivel conductual y fisiológico[85], mientras que los últimos cigarrillos del día en los grandes fumadores no deberían contribuir significativamente a la concentración de cotinina, ya que la cantidad de cigarrillos fumados no es tan importante una vez que el fumador ha alcanzado los niveles deseados de nicotina en el cuerpo.

En cuanto a las diferencias encontradas por sexo en las concentraciones de cotinina en saliva, los resultados en la literatura son heterogéneos[86-89]. Estas diferencias podrían reflejar no sólo diferencias en el consumo de cigarrillos por sexo (usualmente los hombres fuman más cigarrillos que las mujeres), sino también diferencias en el metabolismo de la nicotina entre hombres y mujeres[85,90].

Por otra parte, encontramos que los fumadores con un alto consumo de cigarrillos tenían mayores puntuaciones en el test de Fagerström. Esto se explica en parte porque el consumo de cigarrillos contribuye de manera importante a la puntuación final del test de Fagerström. Consecuentemente, encontramos que la concentración de cotinina en saliva aumentaba a mayor puntuación global del test de Fagerström y a mayor puntuación individual de cada uno de los ítems del test (hipótesis 3); sin embargo, al igual como ocurría con el consumo de cigarrillos, en las puntuaciones más altas del test la concentración de cotinina se estabilizaba. Esto puede tener relación con el peso que tiene el consumo diario de cigarrillos en la puntuación global del test. La forma cuadrática de la concentración de cotinina en función de las puntuaciones parece indicar que los fumadores que son más dependientes consumen más cigarrillos y tienen concentraciones de cotinina en saliva más altas que los fumadores que son menos dependientes.

De todos los ítems del test de Fagerström, los mejores predictores de la concentración de cotinina en saliva fueron los ítems 1 (tiempo transcurrido hasta fumar el primer cigarrillo), 4 (consumo diario de cigarrillos) y 5 (momento del día en que se fuma más), siendo los dos primeros los ítems que más aportan a la puntuación global del test. Esto es coherente con los hallazgos de Heatherton y cols. que les llevaron a proponer la utilización de estos dos ítems como una versión abreviada del test de Fagerström para medir la "carga" del consumo (Heavy Smoking Index). Bajo el supuesto de que la carga de tabaquismo puede estar relacionada con la dependencia al tabaco, la utilización de estas dos preguntas permite clasificar de manera sencilla a los fumadores en los

tratamientos basados en el nivel de dependencia de los fumadores[67]. También encontramos que los hombres tenían mayores puntuaciones en el test de Fagerström y mayores concentraciones de cotinina en saliva que las mujeres, hallazgo que es concordante con los encontrados en otros estudios[59,79,91,92]. Estas diferencias permanecen incluso después de controlar por el consumo de cigarrillos, lo que parece indicar que los factores implicados en la dependencia a la nicotina también tienen que ver con diferencias biológicas en el metabolismo entre hombres y mujeres e incluso con diferencias conductuales relativas a la manera en que hombres y mujeres fuman, siendo este último aspecto de mayor relevancia en éstas últimas.

El estudio que relaciona específicamente el tiempo hasta el primer cigarrillo y las concentraciones de cotinina en saliva evidencia que la asociación existente entre ambas variables es independiente de los cigarrillos fumados en las últimas 24 horas: aunque la forma de la relación entre las concentraciones de cotinina y el número de cigarrillos es similar en los grupos de fumadores menos dependientes y más dependientes, las concentraciones de cotinina en saliva eran mayores en estos últimos (hipótesis 2). Esto permite suponer que los fumadores más dependientes pueden fumar más intensamente y más profundamente en los primeros minutos del día luego del período de abstinencia durante las horas de sueño, lo que resulta en una mayor concentración de cotinina en las primeras horas del día comparados con los fumadores menos dependientes. Si bien el consumo de cigarrillos es el principal determinante de la concentración de cotinina, las diferencias individuales en la manera de fumar y en el metabolismo de la nicotina hacen que el consumo de cigarrillos no sea un estimador muy preciso de ingesta de nicotina. Además, aunque los niveles de cotinina en el organismo tienden a acumularse a través del día y sus valores permanecen prácticamente constantes, estos niveles están también influenciados por la tasa de eliminación de los metabolitos[46]. Se ha observado que el tiempo hasta fumar el primer cigarrillo es mejor predictor de la cotinina que el consumo diario de cigarrillos, mientras que éste último es mejor predictor de los niveles de nicotina

que el primero; por lo que se ha planteado que el tiempo hasta fumar el primer cigarrillo podría reflejar niveles bioquímicos duraderos, mientras que el consumo diario de cigarrillos se relacionaría más bien con niveles recientes[67].

En cuanto a las puntuaciones obtenidas en el test de Fagerström, la puntuación en el estudio poblacional en Barcelona (DCOT) fue 3,27, similar a otros estudios poblacionales en otros países[9,79,82,92,93] y españoles[94], pero superior al 2,8 observado en el estudio realizado a nivel de todo el estado español (EuroSurvey). Si bien se debe tener en cuenta que en este último estudio también se incluyeron a los fumadores ocasionales, cuando consideramos sólo a los fumadores diarios no apreciamos una variación de la puntuación, que sólo sube a 2,90 (mientras que la puntuación de los fumadores ocasionales en el test de Fagerström fue de 0,94). A pesar de ello, la puntuación media obtenida en el estudio EuroSurvey es muy similar a la obtenida en la encuesta del Centro de Investigaciones Sociológicas de ese mismo año[95].

Contrariamente a lo que esperábamos en el estudio DCOT, la concentración de cotinina en saliva fue similar a través de los tres estadios de cambio estudiados; sin embargo, dentro de cada estadio, la concentración de cotinina aumentaba a mayor consumo diario de cigarrillos y a mayor dependencia a la nicotina, aunque sólo lo hizo de manera significativa en los grupos de fumadores precontempladores y contempladores. Parece ser que la concentración de cotinina no indica de una manera directa una progresión a través de los estadios del cambio. A pesar de ello, se pudo apreciar algunas tendencias según los estadios del cambio. Es así como los fumadores con un mayor consumo de cigarrillos tendían a estar en el estadio de precontemplación, mientras que los que tenían un menor consumo tendían a estar en la fase de preparación, de manera similar a otros estudios[96-99]. Aunque la dependencia a la nicotina fue similar en todos los estadios del cambio, la mayoría de los fumadores en el estadio de preparación tenían una dependencia baja, lo que podría apoyar la hipótesis 4 de esta tesis. Además, los fumadores en este estadio tendían a fumar cigarrillos “no

regulares" (*light*, *ultralight*,…) e inhalaban pocas veces, lo que podría reflejar una mayor preocupación por las consecuencias nocivas del consumo de tabaco, lo que parece ser consistente con las predicciones del modelo transteórico[100].

La distribución de los fumadores de Barcelona a través de los estadios del cambio fue del 68%, 22% y 11% en los precontempladores, contempladores y preparados para dejar de fumar, respectivamente. Esta distribución es similar a las descritas en algunos países europeos[75,76,99], pero diferentes de las observadas en estudios americanos[97,101]. Esto puede reflejar diferencias en el progreso de la epidemia tabáquica en diferentes poblaciones. La distribución de fumadores por sexo, muy similares en cada estadio del cambio, parece ir también en esta línea, pues reflejaría la situación actual de España en la epidemia tabáquica. Por su parte, la distribución de fumadores observada en los datos a nivel de todo el estado español fue similar a la del estudio de Barcelona e indicó que la mayoría de los fumadores se encontraban en el estadio de precontemplación y tenían una baja dependencia a la nicotina. La mayor proporción de fumadores dependientes tenían estudios primarios, tenían un mayor consumo de cigarrillos y habían iniciado el consumo a temprana edad. Al igual que en el estudio poblacional de Barcelona, no se observaron diferencias en la distribución de los fumadores según los estadios del cambio y las variables sociodemográficas estudiadas, tal como se observa en otras poblaciones[96,98,102]. Comparando estos resultados con los datos disponibles de un estudio realizado en 7 regiones de España[103], en los diez años que separan ambos estudios parece haberse producido un cambio en la distribución de los fumadores según los estadios del cambio, caracterizado por un aumento de la prevalencia de ex-fumadores, probablemente a expensas de fumadores en fase contemplativa, por lo que la proporción de precontempladores podría haber aumentado. Otros estudios realizados en diferentes poblaciones españolas en los últimos 15 años describen puntuaciones entre 2,3 y 3,8 en el test de Fagerström[104-107] y distribuciones de fumadores heterogéneas a través de los estadios del cambio[75,104,106,108]. Se observan mayores puntuaciones en el test de Fagerström en los fumadores en deshabituación tabáquica[109,110], lo que puede

explicarse porque los más dependientes a la nicotina pueden tener la percepción de menor autocontrol frente al consumo de tabaco y por ello buscan activamente la ayuda para dejar de fumar.

Los resultados expuestos demuestran la utilidad de estudiar la dependencia y los estadios del cambio en estudios poblacionales sobre consumo de tabaco. El estudio de los cambios en la prevalencia de tabaquismo en una población determinada puede interpretarse como un descenso en la cantidad de fumadores diarios, pero entre éstos la prevalencia de síntomas relacionados con la dependencia a la nicotina pueden incrementarse a través del tiempo, lo que es consistente con la hipótesis del "hardening"[111]. Sin embargo, nuestros datos indicaron un decremento a nivel nacional en la prevalencia de consumo pero no un incremento de la dependencia a la nicotina, lo que parece cuestionar la generalización de dicha hipótesis.

6.1. Ventajas y limitaciones de esta investigación

En cuanto a aspectos relativos a la validez, la utilización de cuestionarios comporta un posible sesgo de información debido a la posible infradeclaración del consumo de tabaco, especialmente si se ha utilizado una encuesta telefónica, como en el estudio EuroSurvey. Sin embargo, la información autodeclarada sobre consumo de tabaco se ha considerado precisa y suficientemente válida[112,113]. Otro posible sesgo de información que podría haber afectado el ajuste de los modelos en la estimación del aumento de la concentración de cotinina por cigarrillo fumado es la tendencia al redondeo del consumo de cigarrillos, especialmente en los grandes fumadores[114]. Por otra parte, al tratarse de dos estudios transversales de muestras representativas de la población general, es posible que exista cierto sesgo de selección, pues el rechazo a la participación podría estar asociado al consumo de tabaco. Para evaluar este posible sesgo se analizó en el caso del estudio poblacional de Barcelona la distribución por sexo,

edad, nivel de estudios y distrito de residencia de los participantes y no participantes (información derivada del padrón de habitantes) y se observó que la muestra de estudio no difería de la población de Barcelona según estas variables. La utilización de un directorio de teléfonos fijos en el caso del estudio EuroSurvey podría haber afectado la representatividad de la muestra, considerando que el uso de teléfonos móviles se ha ido extendiendo en la población en los últimos años. Finalmente, cabe señalar que el número de fumadores ha sido pequeño para poder examinar algunas asociaciones con más detalle, por la imposibilidad de estratificar por otras variables. La falta de suficiente tamaño muestral es debida a la prevalencia relativamente baja de fumadores y a que el cálculo del tamaño muestral para ambos estudios se hizo en relación al conjunto de fumadores y no fumadores.

Este trabajo ofrece ventajas sobre investigaciones precedentes: nuestro estudio de 2006 es el primero que recoge información a nivel nacional sobre consumo de tabaco, dependencia a la nicotina y preparación para dejar de fumar en una muestra representativa de la población general española. La mayoría de estudios han sido realizados en regiones geográficas concretas y en grupos seleccionados de fumadores, principalmente fumadores en programas de cesación tabáquica, pero también adolescentes, fumadores con diversas patologías asociadas o no con el tabaquismo, etc. Por otra parte, específicamente para una población concreta como es la ciudad de Barcelona, además de haber recogido información detallada sobre el consumo de tabaco por medio de un cuestionario con una validez aceptable[115], se utilizó la cotinina como biomarcador sensible y específico del consumo de tabaco, cuyos análisis se realizaron en un laboratorio con amplia experiencia en la determinación de la cotinina. Pocos estudios han relacionado la concentración de cotinina con los estadios del cambio[49,116], y no conocemos ninguno en España que haya caracterizado las concentraciones de cotinina según características claves del consumo como son el consumo de cigarrillos, la dependencia a la nicotina y los estadios del cambio.

7. CONCLUSIONES

- La concentración de cotinina en saliva está determinada principalmente por el número de cigarrillos fumados en las últimas 24 horas: las concentraciones de cotinina se elevan conforme aumenta el consumo, hasta llegar a alrededor de los 20 cigarrillos, punto en el cual la concentración de cotinina se estabiliza.

- El tiempo transcurrido desde que el fumador se despierta y se fuma el primer cigarrillo del día (ítem 1 del test de Fagerström), el número de cigarrillos que consume diariamente (ítem 4 del test) y el momento del día en que fuma más (ítem 5) estuvieron relacionados de manera independiente y significativa con la concentración de cotinina en saliva.

- Las concentraciones de cotinina en saliva son más altas en los fumadores más dependientes que en los menos dependientes.

- Si bien las concentraciones de cotinina son similares a través de los estadios del cambio, aumentan dentro de cada estadio a mayor consumo de cigarrillos y a mayor dependencia de los fumadores.

- La mayoría de los fumadores españoles se encuentran en fase de precontemplación y tienen una baja dependencia a la nicotina. La disminución de la prevalencia de fumadores observada en los últimos años no ha conllevado un aumento de fumadores dependientes.

7.1. Implicaciones en salud pública

En base a los resultados de esta tesis se pueden derivar las siguientes implicaciones en salud pública:

- El tiempo transcurrido desde que el fumador se despierta hasta que fuma el primer cigarrillo, el consumo diario de cigarrillos y el momento del día en que fuma más son indicadores que pueden ser utilizados para estudiar la dependencia en estudios poblacionales.

- Debido a que en la población general española la mayoría de fumadores se encuentra (2006) en fase de precontemplación, se debería potenciar la información a la población acerca de los efectos nocivos del tabaco, y en especial prevenir la iniciación del consumo en los jóvenes.

- Las intervenciones a nivel poblacional deberían orientar sus esfuerzos a intentar que los fumadores se muevan hacia fases más avanzadas de los estadios de cambio, motivando a los fumadores que no desean dejar de fumar y propiciando que los fumadores poco dependientes sean capaces de dejar el consumo.

- La caracterización de la distribución de las concentraciones de cotinina en saliva en fumadores ha confirmado su utilidad como biomarcador de consumo. Su medición a nivel poblacional, junto con medidas más tradicionales como la prevalencia de consumo y la valoración de la dependencia a la nicotina, permite monitorizar la epidemia tabáquica.

- La evaluación de las intervenciones en control del tabaquismo debería tener en cuenta no sólo la prevalencia de tabaquismo en la población, sino también la magnitud del consumo de tabaco, el nivel de dependencia y los estadios del cambio de manera conjunta. Todo ello permitirá describir y

caracterizar los potenciales cambios en la población de fumadores, así como la evolución de la morbilidad y mortalidad asociadas al tabaquismo.

7.2. Líneas de investigación futuras

Estudiar no sólo la prevalencia de fumadores, sino también diversas características asociadas al consumo, ha permitido conocer la situación actual del tabaquismo en la población general española, así como la de una población concreta como es población general de la ciudad de Barcelona. Es conveniente realizar este tipo de estudios de manera periódica para monitorizar los posibles cambios en la población, que permitan la revisión y evaluación continuas de las intervenciones. Esto es relevante en la situación actual española, debido a la reciente aplicación de sendas normativas sobre control del tabaquismo (leyes 28/2005 y 42/2010). Investigaciones futuras podrían aportar evidencias de la magnitud de los efectos de tales normativas en la prevalencia total de consumo, en los hábitos de consumo de la población de fumadores, en su nivel de dependencia y en su preparación para dejar de fumar (y por tanto cambios en la distribución poblacional de fumadores según los estadios del cambio). Estas investigaciones deberían incluir tanto nuevas encuestas transversales como las ya realizadas, incluyendo si es posible la recogida de saliva para la determinación de cotinina, como estudios longitudinales de los participantes en los estudios precedentes.

Por otra parte, la utilización de un biomarcador fiable y válido ha permitido una evaluación objetiva del consumo de tabaco y la dependencia a nivel poblacional, como no se había realizado antes en España. El estudio de éste y otros biomarcadores, incluyendo cancerígenos específicos del humo del tabaco, pueden aportar un mayor conocimiento de los complejos aspectos implicados en el consumo de tabaco. De especial relevancia es su posible contribución a la

comprensión de las diferencias individuales en el metabolismo de la nicotina y su influencia en el consumo de tabaco y la dependencia a la nicotina.

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ANEXOS

1. Cuestionarios de los estudios DCOT y EuroSurvey

1. Cuestionario del estudio DCOT

Se diseñó un cuestionario único para todos los participantes. Consta de un total de 101 preguntas que recogen información sobre consumo de tabaco, exposición pasiva al humo del tabaco y percepción de riesgo de esta exposición, así como información sobre el estado de salud general y morbilidad crónica, estilos de vida (consumo de alcohol y actividad física), medidas antropométricas (peso y talla) y datos sociodemográficos.

El cuestionario estaba disponible en español y en catalán. La administración del mismo se realizó cara a cara en el domicilio del participante. Cuando no fue posible que éste respondiera directamente (como los menores de 8 años o las personas con dificultades de comprensión) se pidió a un familiar que contestara las preguntas en su nombre.

Enlace al cuestionario DCOT:

http://bioinfo.iconcologia.net/es/questionaris_uct/cuest_DCOT.pdf

2. Cuestionario del estudio EuroSurvey

Este cuestionario se desarrolló en el contexto de un proyecto financiado por la Unión Europea sobre aplicación de políticas basadas en la evidencia para la

prevención de la exposición pasiva al humo de tabaco en diferentes países. Su objetivo era recoger información sobre prevalencia de consumo de tabaco y de exposición al humo del tabaco. La versión española consta de un total de 48 preguntas sobre consumo de tabaco, exposición pasiva al humo del tabaco, percepción de riesgo de esta exposición, salud general y datos sociodemográficos.

La administración del cuestionario se realizó telefónicamente, siendo asistida por ordenador (Computer Assisted Telephone Interviewing, CATI).

Enlace al cuestionario EuroSurvey:

http://bioinfo.iconcologia.net/es/questionaris_uct/cuest_EuroSurvey.pdf

2. Proceso editorial del artículo publicado en:

BMC Public Health

Carta de presentación al Editor

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L'Hospitalet de Llobregat, May 15th, 2009.

Dr. Silvano Gallus
Associate Editor, BMC Public Health
Istituto "Mario Negri"
Milan, Italy

Dear Dr. Gallus:

Please find enclosed our manuscript "Salivary cotinine concentrations in daily smokers in Barcelona, Spain" for your consideration in *BMC Public Health* as a Research Article.

We studied the relationship between salivary cotinine concentrations and tobacco consumption. This is the first assessment of tobacco exposure at the population level using a biomarker in Spain, a topic that has been seldom addressed in other populations –and mostly using non-representative samples of smokers.

The relationship between cotinine concentrations and the number of cigarettes smoked is complex. We have been able to study other factors implicated in this relationship. The results can be useful when addressing other related topics such as determinants of nicotine dependence or smoking cessation. We have studied the smokers drawn from a representative sample of the general population of Barcelona. We believed that this is one of the strengths of our study.

All the authors carefully read the manuscript and fully approve of it. In their name I also declare that the manuscript is original and it is not submitted anywhere other than your journal. The authors declare to have no conflict of interest. We would of course be ready to provide further information about our data and methods you desire.

Correspondence about the manuscript should be addressed to me as indicated in the first page of the manuscript.

Thank you very much for your kind attention.

Yours sincerely,

Esteve Fernandez, MD, PhD
Director, Tobacco Control Research Program, Institut Català d'Oncologia
Associate Professor, Universitat de Barcelona

E-mail: efernandez@ico.scs.es

Revisión realizada al manuscrito

From: BioMed Central Editorial [mailto:editorial@biomedcentral.com]
Sent: Wednesday, July 01, 2009 4:14 PM
To: Dr Esteve Fernandez
Subject: MS: 1464850188276641 - Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study

MS: 1464850188276641
Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study
Marcela Fu, Esteve Fernandez, Jose M Martínez-Sánchez, José A Pascual, Anna Schiaffino, Antoni Agudo, Carles Ariza, Josep M Borràs and Jonathan M Samet

Dear Dr Fernandez,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the links below. Do let us know if you have any problems opening the files.

Referee 2: http://www.biomedcentral.com/imedia/1788603986285650_comment.pdf

Referee 1: http://www.biomedcentral.com/imedia/6280321812849734_comment.pdf

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please could you also address the following:
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Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

The BioMed Central Editorial Team

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Informe del Revisor 1

Reviewer's report

Title: Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study

Version: 1 Date: 19 June 2009

Reviewer: Zubair Kabir

Reviewer's report:

The article by Flu and colleagues is indeed an interesting piece of tobacco and nicotine research. The findings are unique in some sense but not truly generalizable to a wider population. Statistical analyses were appropriate but could have been improved further through more robust modelling. The final model (as judged by R square value) explains only 39% of the variance and therefore a lot still remains unexplained!

Major Compulsory Revisions:

• The methods section needs further clarification, especially in terms of study subjects' recruitment, the number of eligible population estimated, the number of non-responses, and finally the method of randomization.
• The aim of this particular study (especially when the main study findings are considered post-hoc) apparently does not identify the 'determinants' of salivary cotinine concentrations-rather the relationship of number of cigarettes smoked and the cotinine concentrations was examined in this study.
• Not all the co-variates available to this study were factored into the final adjusted linear model, especially the type of tobacco and the type of cigarettes although the authors did mention that such a relation (with the type of tobacco use) was not a potential confounder and such data were not shown.
• Blond tobacco use is particularly common among the Spanish smokers and a potential overlap between the type of tobacco use and the type of cigarettes smoked might have failed to compute the exact number of cigarettes consumed per person in this study. In other words, the 'beta' estimates are to be interpreted with caution.
• Also, I notice an apparent confusion between potential effect modifiers and potential confounders for the association examined.
• Finally, it is not clear why the investigators set out to collect detailed information on all the 1,245 subjects when they were going to analyse only the current daily smokers (n=285) in this particular study-may be to compute overall smoking prevalence by gender in this study population (which was indeed quoted in the discussion section of the manuscript).

Minor Essential Revisions:

• A representative sample from 2001 Census was collected and the reason for such an approach was not explicit in the methods section.
• It is not clear how the investigators arrived at an expected sample size of 1,560 (1,245+315) between March 2004 and December 2005
• When almost half of the subjects interviewed were 'self-respondents', how were the salivary cotinine samples collected for those who were proxy-respondents
• When smoking history (that includes number of cigarettes smoked) was collected for both 24 and 48 hours prior to the interview then why 24 hrs findings alone were presented
• Information on the duration of smoking was also collected but I failed to notice any outputs related to this specific co-variate in the tables presented. Similar concern also applies to second-hand smoke exposure at home and at other workplaces, etc
• R square has to be specified (adjusted/unadjusted)

• Figures 1,2 and 3 have used only one independent variable (number of cigarettes smoked) for the quadratic model and therefore ,this particular variable is not the 'predictor' of cotinine concentrations, as stated in the results section

Discretionary Revisions:

• There is limited but controversial information on the validation of self-reported smoking history among adolescents and young adults (18-25 years of age). This study has the potential to examine such a research question among the young adults.
• The two non-filter cigarette smokers could have been excluded from the final 211 subjects

Informe del Revisor 2

Reviewer's report

Title: Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study

Version: 1 Date: 23 June 2009

Reviewer: Joaquin Barnoya

Reviewer's report:

Major compulsory revisions

In general, the paper is written in poor English and needs to be edited accordingly. Terms as "short" or "mid" (used in the first paragraph of the introduction) are ambigous and should be avoided. Authors refer to "different stages of the tobacco epidemic" yet the stages are not outlined. In the Introduction, rather than focusing on smoking prevalence, authors should focus on the determinants of cotinine concentration (e.g. depth of inhalation, cigarettes per day, genetics).

Authors emphasize the value of their data as coming from the "general population". However, it is not clear how their sample was selected. In the last paragraph of the introduction, they write "potentially useful to design suitable strategies for cessation.", please explain how this would be helpful for a cessation campaign?

The Methods section is hard to follow. It is still not clear how were subjects recruited. Were these home interviews? In addition, they write about the Spanish law banning smoking indoors, how might this affect their results? It would have been good to measures nonsmokers cotinine concentrations before and after the law. Furthermore, they note that "some changes in smoking behavior were to be expected after" the law was implemented. They need to be specific, what changes? They they happened? More detail on the law needs to be written, specially that secondhand smoke is a confounder in cotinine concentrations in smokers. If only daily smokers were included, why is the number of cigarettes smoked per day not normally distributed? How was depth and frequency of inhalation assessed other than the questionnaire? This might be a major source of bias.

The correlation, 0.33 and 0.38, are still low correlations. Authors need to explain whey they observed such low fits. The inclusion of a "quadratic component" needs to be justified and adequately described in the methods section. Specially given that their main results are based on the "quadratic component".

A GLM model would have been useful. In addition, it might be worth exploring the possibility that the relationship is not linear, as suggested in the Discussion.

In the Results section, cotinine levels were not significantly different by frequency and depth of inhalation, this is somewhat surprising. Is this biased? Table 2 needs to be controlled by number of cigarettes smoked per day.

P valued for the R square should also be presented.
What percentage of their sample smoked more than 20 cigarettes per day?

An analyisis using cut-off point of number of cigarettes per day would be useful, as opposed to using number of cigarretes per day as an continuos variable.

Minor Essential Revisions:

The BMI equation needs to be edited.

The citation of the technique to measure cotinine should be changed to the study where the technique is described as opposed to the studies where it has been used.

The word "nicotine" needs to be inserted before "gum" in the data analysis section. The excluded subjects section is hard to follow.

The variables described in the Methods section should be potential confounders. Is BMI a confounder?

The results section could be shorted by just referring to the Tables.

The first line of the Discussion refers to "smoking behavior", however, their results are mostly based on the cotinine analysis.

Last sentence of Discussion, right before Conclusion, needs to be edited.

Table 4 needs the sample size for male and female.

Discretionary Revisions

Reference 41 could be updated.

Respuesta a los comentarios de los revisores

MS: 1464850188276641
«Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study» by Marcela Fu, Esteve Fernandez, Jose M Martínez-Sánchez, José A Pascual, Anna Schiaffino, Antoni Agudo, Carles Ariza, Josep M Borràs and Jonathan M Samet

Response to the reviewers' comments

To the BioMed Central Editorial Team:

We appreciate the peer review of our manuscript "Salivary cotinine concentrations in daily smokers in Barcelona, Spain: A cross-sectional study". Here are our point-by-point responses to the reviewers' comments. They have helped to strengthen the manuscript.

First report
Reviewer: Zubair Kabir

Major Compulsory Revisions:

1. The methods section needs further clarification, especially in terms of study subjects' recruitment, the number of eligible population estimated, the number of non-responses, and finally the method of randomization.

All aspects mentioned in the comments were taken into account, and we added further description in the first paragraph of the Methods section:

> *A representative random sample by age, sex, and district was drawn from the official 2001 population census of Barcelona, a reliable source of population-based information. To detect a difference in cotinine concentration in smokers of 50 ng/ml (with a mean value of 500 ng/ml and a standard deviation of 200 ng/ml), with an alpha of 5% and a beta of 10% (statistical power of 90%), we estimated that a sample size of 337 smokers would be needed. Considering a 27% prevalence of smoking from the 2001 Health Survey of Barcelona, we estimated a needed sample size of 1560 people, taking into account smokers and non-smokers.*

As already mentioned in the Methods, the study design allowed substitution of participants to minimize non-response. Hence, with the random sample extracted from the Census, we also obtained a pool of people to be used as replacements, taking into account sex, age, and district of residence. We have clarified the selection process in the 2nd paragraph of the Methods section:

> *… The study design allowed replacement of the index person by another person of the same sex, 5-year age group, and district of residence. In 49.3% of cases the first selected index person was interviewed; 24.4% of first substitutes were interviewed; and 26.3% of second or subsequent substitutes were interviewed. The final sample interviewed included 285 daily smokers (at least 1 cigarette per day), 62 occasional (non-daily) smokers, 354 ex-smokers, 525 never-smokers, and 19 people were less than 17 years of age. The present report is based on the adults who were daily smokers.*

With regard to the "method of randomization", the participants were not randomized but selected at random. We took a random sample from the Census files (using a computer-based random seed).

2. The aim of this particular study (especially when the main study findings are considered post-hoc) apparently does not identify the 'determinants' of salivary cotinine concentrations-rather the relationship of number of cigarettes smoked and the cotinine concentrations was examined in this study.

We agree with the reviewer that all the potential determinants of cotinine concentration are not examined in the paper, and hence we have deleted this aim from the paper.

> *An understanding of cotinine concentration and smoking patterns at the population level is potentially useful to design suitable strategies for cessation. The aim of this study is to describe and characterize the distribution of salivary cotinine concentration in a representative sample of adult (>16 years old) daily smokers in Barcelona, Spain.*

3. Not all the co-variates available to this study were factored into the final adjusted linear model, especially the type of tobacco and the type of cigarettes although the authors did mention that such a relation (with the type of tobacco use) was not a potential confounder and such data were not shown.

We assessed the influence of the potential confounders in our multivariate models but none of them except the variables already mentioned (age, education, BMI) improved the model fit. We believe not necessary to include those data into the tables but only to mention it. We have now included a sentence at the end of the Results section:

> *Adjustment for other potential confounders identified in the bivariate analysis did not improve the model fit and hence these variables were not included in the final models (data not shown).*

4. Blond tobacco use is particularly common among the Spanish smokers and a potential overlap between the type of tobacco use and the type of cigarettes smoked might have failed to compute the exact number of cigarettes consumed per person in this study. In other words, the 'beta' estimates are to be interpreted with caution.

We understand the reviewer refers to the beta estimates for "use of filter tip". We agree and consequently do not mention this variable in the text. We have already mentioned that there was no consistent trend by frequency and depth of inhalation. We have now expanded this sentence by adding use of filter tip:

> *By type of tobacco, the greatest increase in cotinine concentration per one cigarette smoked was found in those smoking non-regular cigarettes (8.4 ng/ml) and in smokers of blond tobacco (6.9 ng/ml). Consistent trends were not found by use of filter tip, frequency, and depth of inhalation.*

5. Also, I notice an apparent confusion between potential effect modifiers and potential confounders for the association examined.

We assessed potential confounders in the multivariate models as mentioned in the text. The selection of confounders was based in the previous bivariate analysis, as well as their inclusion in the models to analyze the changes in the beta estimates. In Table 3 we present the stratified analyses carried out to assess potential effect-modification. Both strategies are complementary and we have not modified the text.

6. Finally, it is not clear why the investigators set out to collect detailed information on all the 1,245 subjects when they were going to analyse only the current daily smokers (n=285) in this particular study-may be to compute overall smoking prevalence by gender in this study population (which was indeed quoted in the discussion section of the manuscript).

The main objective of our study was to characterize the distribution of salivary cotinine concentrations in a representative sample of general population, and we are reporting analyses related to smokers (the

present paper) and to non-smokers in another paper (Prev Med. 2009;48:218-23).Hence the current report is focused only on daily smokers. We explained the methodology common to all participants in the Methods section, although we present the analyses based exclusively on daily smokers, the objective of this report. We think that this purpose is sufficiently clear in the manuscript.

Minor Essential Revisions:

7. A representative sample from 2001 Census was collected and the reason for such an approach was not explicit in the methods section.

If a representative sample of the general population is needed, the more direct and valid approach to obtain it is to sample from the official Census. We describe the approach in the first paragraph of Methods section:

> *A representative random sample by age, sex, and district was drawn from the official 2001 population census of Barcelona, a reliable source of population-based information.*

8. It is not clear how the investigators arrived at an expected sample size of 1,560 (1,245+315) between March 2004 and December 2005

Please see the response to comment nº 1.

9. When almost half of the subjects interviewed were 'self-respondents', how were the salivary cotinine samples collected for those who were proxy-respondents

The reviewer has concluded that only 49.3% of participants were direct interviews and the rest were proxy respondents. We have improved the description of the sampling procedure to clarify the selection and interview process, which did not involve data collection from surrogates. We have improved the paragraph, in an attempt to better describe this, in the second paragraph of the Methods section. (Also see response to comment nº 1).

10. When smoking history (that includes number of cigarettes smoked) was collected for both 24 and 48 hours prior to the interview then why 24 hrs findings alone were presented

We used the 24 hr data for several reasons: first, in daily smokers, the number of cigarettes is relatively stable from day to day; second; the prior 24 hours is most relevant to the levels in the saliva specimens, covering the last two half-lives approximately; and third, other studies have generally used the same period.

11. Information on the duration of smoking was also collected but I failed to notice any outputs related to this specific co-variate in the tables presented. Similar concern also applies to second-hand smoke exposure at home and at other workplaces, etc

Given that we are studying the correlates of a current salivary cotinine concentration, the number of years of tobacco consumption or the age at initiation are not relevant to the study goals. Similarly, in current smokers the amount of exposure to second-hand smoke is insignificant and not relevant as compared to the direct smoke inhaled. Hence, in order not to complicate the paper, we chose not to include these variables.

12. R square has to be specified (adjusted/unadjusted)

We have specified it in the text.

13. Figures 1,2 and 3 have used only one independent variable (number of cigarettes smoked) for the quadratic model and therefore ,this particular variable is not the 'predictor' of cotinine concentrations, as stated in the results section

We do not understand the reviewer's comment since we are not stating in the Results section (text) that the quadratic term is a "predictor" of cotinine. It seems clear from the text that the addition of a quadratic *term* (cig smoked^2) improved the fit, and the beta coefficients mentioned as average increases of cotinine concentration (ng/ml) per cigarette smoked correspond to those of the *simple term or variable*, as already present in Table 4. Perhaps the problem is that it could be understood (as the reviewer did in our opinion) that the beta corresponds to the quadratic term, whereas it is indicated in the row "quadratic model" (and "quadratic model adjusted for covariates"). The beta in the column is for the cigarette simple variable or term for three different models (simple, quadratic, and quadratic plus age, education and BMI). We have added a footnote to the table to highlight it.

Discretionary Revisions:

14. There is limited but controversial information on the validation of self-reported smoking history among adolescents and young adults (18-25 years of age). This study has the potential to examine such a research question among the young adults.

We agree with the reviewer and would comment that this is one of the secondary objectives of our study (this is another reason why we obtained a representative sample of the population, with both smokers and non-smokers).

15. The two non-filter cigarette smokers could have been excluded from the final 211 subjects

Yes, they could have been excluded but we decided not, since in the protocol we wanted to include all type of cigarette smokers.

Second report
Reviewer: Joaquin Barnoya

Major compulsory revisions

1. In general, the paper is written in poor English and needs to be edited accordingly. Terms as "short" or "mid" (used in the first paragraph of the introduction) are ambigous and should be avoided. Authors refer to "different stages of the tobacco epidemic" yet the stages are not outlined. In the Introduction, rather than focusing on smoking prevalence, authors should focus on the determinants of cotinine concentration (e.g. depth of inhalation, cigarettes per day, genetics).

The manuscript has been edited to improve the English. We have specified the periods of time in the Introduction:

> *Cotinine in biological materials is suitable for assessment of doses over short periods of time (from 1 to 10 days, in urine, plasma, or saliva) or longer periods (weeks or months, in hair or nails). Consequently cotinine concentration is feasibly used as a biomarker in epidemiological studies [3-5].*

We anticipate that readers will be familiar with the model of stages of the tobacco epidemic, but now include a reference for those readers who are not. We refer in one paragraph to the prevalence of smoking in Spain as background of the study to be presented. We believe more appropriate to discuss in depth the determinants of cotinine concentration in the Discussion section, not in the Introduction.

2. Authors emphasize the value of their data as coming from the "general population". However, it is not clear how their sample was selected. In the last paragraph of the introduction, they write "potentially useful to design suitable strategies for cessation.", please explain how this would be helpful for a cessation campaign?

We explain at the beginning of the Methods section that the sample was obtained from the Census, and have expanded the sentence as per request of reviewer #1 (see response to comment 1 from reviewer #1).

We believe that a comprehensive characterization, including cotinine concentrations, of the smoker population may help any cessation campaign. As we have shown, cotinine concentration is related to number of cigarettes smoked and also (not addressed in this paper) to level of addiction. Whether cotinine concentrations are related to other characteristics of smoking is also of relevance. We believe that the sentence in the Introduction does not need further clarification. We have discussed it in the Discussion section instead.

3. The Methods section is hard to follow. It is still not clear how were subjects recruited. Were these home interviews? In addition, they write about the Spanish law banning smoking indoors, how might this affect their results? It would have been good to measures nonsmokers cotinine concentrations before and after the law. Furthermore, they note that "some changes in smoking behavior were to be expected after" the law was implemented. They need to be specific, what changes? They they happened? More detail on the law needs to be written, specially that secondhand smoke is a confounder in cotinine concentrations in smokers. If only daily smokers were included, why is the number of cigarettes smoked per day not normally distributed? How was depth and frequency of inhalation assessed other than the questionnaire? This might be a major source of bias.

The interview and saliva collection were done at the participants' home. We have written that they were contacted at home and we thought it was clear from that sentence that interviews were also conducted at home. We agree with the reviewer that the sentence can be improved and have changed it:

> *Participants signed the consent form, answered a questionnaire, and provided a saliva specimen at home.*

We clearly indicate that we had to end the study because the new Spanish law may have modified the smoking behavior of the population (both in smokers and non-smokers, since the sample included both of them). The obvious hypothetical changes expected after a ban of smoking in workplaces include a decrease in smoking prevalence, a decrease in the mean number of cigarettes smoked by smokers, and a decrease in second-hand smoke (SHS) among non-smokers. It is hard to believe that SHS can be a confounder of cotinine concentrations among smokers (it is a matter of magnitude of the concentrations found in smokers and non-smokers). We added an explanation about the possible changes in smoking behavior derived from the new tobacco law:

> *(...) The study ended in December 2005 with a new Spanish law banning smoking in public places and enclosed workplaces coming into effect in January 2006 [15]. We expected changes in smoking behavior after this date (number of cigarettes smoked by smokers and passive exposure levels in nonsmokers) and hence 315 selected participants were not approached. (...)*

The reviewer also says that «It would have been good to measures nonsmokers cotinine concentrations before and after the law» and indeed it would be. However, that objective will be covered in another study, now ongoing.

Typically the distribution of number of cigarettes smoked is not normal. Because of the skew, we chose to use the median.

Data on depth and frequency of inhalation were only assessed by self-reports and, as the reviewer had mentioned, could suffer from some recall bias. However, these questions have been widely used. Additionally, there are no measurements that can be made in field settings on smoking topography.

4. The correlation, 0.33 and 0.38, are still low correlations. Authors need to explain whey they observed such low fits. The inclusion of a "quadratic component" needs to be justified and adequately described in the methods section. Specially given that their main results are based on the "quadratic component".

According to previous studies, coefficients of determination (R^2) of 0.30 to 0.40 are not particularly low for the association between number of cigarettes smoked and cotinine concentration. There are multiple determinants of cotinine concentration that contribute to variability. Additionally, the relationship is not linear across the full range of number of cigarettes smoked per day, both in this and other studies. We have improved the sentence about the quadratic term:

> *Following previous studies [9,20], we included a quadratic term for number of cigarettes to improve the models' fit.*

5. A GLM model would have been useful. In addition, it might be worth exploring the possibility that the relationship is not linear, as suggested in the Discussion.

We agree with the reviewer that a GLM is an alternative approach for data analysis. However, we chose (as previously mentioned) to fit a multiple linear regression with a quadratic term to describe the curvilinear relationship between number of cigarettes smoked and cotinine concentration.

6. In the Results section, cotinine levels were not significantly different by frequency and depth of inhalation, this is somewhat surprising. Is this biased? Table 2 needs to be controlled by number of cigarettes smoked per day.

We understand the reviewer's comment and acknowledge that recall bias could be operating. The problem is that we do not know the direction and magnitude of such a potential bias. We are more inclined to think that, given the low frequency of subjects inhaling all the time or with light inhalation, the magnitude of the random error is greater. We prefer to show the crude median cotinine concentrations in Table 2 instead of having them adjusted for number of cigarettes smoked, and explain the potential confounding effect in the text.

7. P valued for the R square should also be presented.
We have included the *p*-values in the text (all p-values <0.05)

8. What percentage of their sample smoked more than 20 cigarettes per day?

19.4% of participants smoked more than 20 cigarettes per day in the last 24 hours. We have included it in the overall description of participants in the first paragraph of Results:

> *The sample was uniformly distributed across educational levels. The majority of participants (56%) were of normal weight and 19.4% had smoked more than 20 cigarettes in the last 24 hours. The median number of cigarettes smoked according to selected sociodemographic and smoking characteristics are shown in Table 1.*

9. An analyisis using cut-off point of number of cigarettes per day would be useful, as opposed to using number of cigarretes per day as an continuos variable.

We did a categorical analysis as a first approach to the data, with a quite similar finding of the association of number of cigarettes smoked with cotinine concentrations (≤9 cig: 50 ng/ml; 10-19 cig: 146 ng/ml; 20-29 cig: 228 ng/ml; and ≥30 cig: 205 ng/ml). However, there are several reasons to maintain the number of cigarettes as a continuous variable: 1) the need to choose arbitrary cut-points; 2) any categorization of a continuous variable represents a lost of information; 3) to allow comparability with previous studies; and 4) to obtain an estimate of the increase of cotinine concentration by the increase in number of cigarettes.

Minor Essential Revisions:

10. The BMI equation needs to be edited.

We have edited the expression for BMI.

11. The citation of the technique to measure cotinine should be changed to the study where the technique is described as opposed to the studies where it has been used.
We agree with the reviewer. In fact, we referenced 4 studies: 3 of them (references 16, 18, and 19) authored by our lab colleagues where they explained the development of the technique as well as specific results, and the source reference (ref. 17). We believe that deleting "as in previous studies" and also deleting references 16 and 19 improves the text.

12. The word "nicotine" needs to be inserted before "gum" in the data analysis section. The excluded subjects section is hard to follow.

The reviewer is again right and we have inserted nicotine before gum.

13. The variables described in the Methods section should be potential confounders. Is BMI a confounder?

Yes, most of the variables described were considered potential confounders, as well as BMI. In the final model we adjusted for age, education, and BMI as confirmed confounders since the adjusted beta coefficient for number of cigarettes smoked was different from the crude coefficient.

14. The results section could be shorted by just referring to the Tables.
We partly agree with the reviewer that the Results section could be shortened. However, the "narrative" description of the main results helps the reader to surf and better understand the results, and hence we are inclined to maintain as is. We are open to shorten it if the Associate Editor finds it more appropriate.

15. The first line of the Discussion refers to "smoking behavior", however, their results are mostly based on the cotinine analysis.

We prefer to maintain the present wording as the study addresses cotinine level in relation to aspects of smoking.

16. Last sentence of Discussion, right before Conclusion, needs to be edited.

We have edited the sentence:

> *The participation rate was almost complete because the study design allowed replacement of non-respondents by subjects in the same strata of sex, age, and district of residence.*

17. Table 4 needs the sample size for male and female.
We have included the sample size for males (n=103) and females (n=104). The sum does not up 211 because there were some observations with missing values for at least one of the variables in the final model.

Discretionary Revisions

18. Reference 41 could be updated.

We have added a recent meta-analysis by Gorber et al. published in Nicotine & Tobacco Research.

Decisión del Editor

From: BioMed Central Editorial [mailto:editorial@biomedcentral.com]
Sent: Thursday, August 13, 2009 12:57 PM
To: Dr Esteve Fernandez
Subject: Your manuscript is acceptable for publication in principle.

Authors: Marcela Fu, Esteve Fernandez, Jose M Martínez-Sánchez, José A Pascual, Anna Schiaffino, Antoni Agudo, Carles Ariza, Josep M Borràs and Jonathan M Samet
Title : Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study
Journal: BMC Public Health
MS : 1464850188276641

Dear Dr Fernandez,

Peer review of your manuscript (above) is now complete, and we are delighted, in principle, to accept the manuscript for publication in BMC Public Health. The reviews are accessible in PDF format via the web links provided at the bottom of this email. Do let us know if you have any problems opening the files.

However before acceptance, our editorial production team needs to check the format of your manuscript, to ensure that it conforms to the standards of the journal. They will get in touch with you shortly to request any necessary changes or to confirm that none are needed.

If you have any problems or questions regarding your manuscript, please do get in touch.

Best wishes,

The BioMed Central Editorial Team

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Referee 1: http://www.biomedcentral.com/imedia/8547615962900130_comment.pdf

Informe del Revisor 1

Reviewer's report

Title: Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study

Version: 2 **Date:** 14 July 2009

Reviewer: Zubair Kabir

Reviewer's report:

Many thanks for the revised manuscript. I am happy that the issues that I had raised previously have been addressed adquately in this revised manuscript.

Level of interest: An article of importance in its field.

Quality of written English: Acceptable.

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declared that I have no competing interests'

3. Proceso editorial del artículo publicado en:

Nicotine & Tobacco Research

Carta de presentación al Editor

ICO
Institut Català d'Oncologia

UNIVERSITAT DE BARCELONA

L'Hospitalet de Llobregat, September 9h, 2010.

Dr. David J. K. Balfour
Editor-in-Chief
Nicotine & Tobacco Research

Dear Dr. Balfour:

Please find enclosed our manuscript **"Association between time to first cigarette after waking up and salivary cotinine concentration"** for your consideration in Nicotine & Tobacco Research as an *Original Investigation*.

We studied the time the smoker smokes his/her first cigarette after waking up as a predictor of salivary cotinine concentration. It have been suggested that the time to first cigarette is a strong predictor of nicotine intake, measured by plasma and urinary cotinine. We wanted to test whether time to first cigarette is also associated with salivary cotinine, as the collection of saliva is more feasible in population-based studies. We think our report could be of interest to the readers of your journal, as we studied the referred association with a biomarker of tobacco smoking widely used in population-based studies, and besides, our study was conducted on a random sample of smokers from the general population.

All the authors carefully read the manuscript and fully approve of it. In their name I also declare that the manuscript is original and it is not submitted anywhere other than your journal. The authors declare to have no conflict of interest. We would of course be ready to provide further information about our data and methods you desire.

Correspondence about the manuscript should be addressed to me as indicated in the first page of the manuscript.

Thank you very much for your kind attention.

Sincerely yours,

Marcela Fu, BSc.
Tobacco Control Unit, Institut Català d'Oncologia
E-mail: mfu@iconcologia.net

Revisión realizada al manuscrito

06-Oct-2010

Dear Ms Fu,

Manuscript ID NTR-2010-387 entitled "Association between time to first cigarette after waking up and salivary cotinine concentration" that you submitted to Nicotine & Tobacco Research, has been reviewed. The comments of the reviewers are included at the bottom of this letter.

The reviewers have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, we invite you to respond to the reviewers' comments and revise your manuscript.

To revise your manuscript, log into http://mc.manuscriptcentral.com/ntr and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. Please be sure that you do not submit a revision as a new manuscript.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using bold or coloured (highlighted) text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Centre.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you made to the original manuscript. To expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewers.

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

Because we are trying to facilitate timely publication of manuscripts submitted to Nicotine & Tobacco Research, your revised manuscript should be uploaded within 30 days. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Nicotine & Tobacco Research; we look forward to receiving your revision.

Yours sincerely,

Dr Karl Fagerstrom
Deputy Editor, Nicotine & Tobacco Research
Email: Karl.fagerstrom@swipnet.se

Reviewer(s)' Comments to Author:

Reviewer: 1
Comments to the Author
This is an interesting manuscript estimating the association between time to first cigarette after waking up and cigarette consumption, and cotinine levels in a sample of smokers from Barcelona, Spain. The main

limitation of the present manuscript is given by the relatively limited sample size. This notwithstanding, the study is original, the representative survey and the analysis are well-conducted, the manuscript is satisfactorily short and clear, and contributes to the scientific knowledge. Authors could consider the following minor points to improve the presentation of their findings:

1) The models used to evaluate the association between time to first cigarette and cotinine levels are correctly adjusted by number of cigarettes per day (and sex). This is of crucial importance given the relatively high correlation coefficient between time to first cigarette and smoking intensity (table 1). Thus, I suggest to put in evidence in the Conclusion sections of both the Abstract and the main text that the association between time to first cigarette and cotinine concentration is independent by the number of cigarettes per day.

2) I suggest to consider Boyle et al. (2000; Eur J Public Health 2000; 10 (Suppl 3): 5-14) and Gallus et al. (2005, Ann Oncol 16:703-6) to describe the importance of "time to first cigarette" in assessing tobacco dependence.

3) In table 2 replace <5 with ≤5

Reviewer: 2
Comments to the Author
In this paper the authors found a significant association between salivary cotinine and time to first cigarette, the number of cigarettes consumed in the last 24 hours and time to first cigarette, and salivary cotinine and cigarette consumption. As expected, they also found significant correlations between these variables.

Basically, the time to the first cigarette of the day and the number of cigarettes per day are good indicators of nicotine dependence; indeed they are the two items of the Heaviness of Smoking Index, a shorter version of the Fargestron test. For the addicted smoker the smoking pattern maintains the needed intake of nicotine, so not surprisingly this paper found associations between these two variables and salivary cotinine concentrations.

After adjustment for cigarette consumption (cigarettes smoked in the previous 24 hours), time to first cigarette (TFC) remains a significant variable and the shorter the TFC, the higher the cotinine concentrations. To this regard I ask the authors to provide some possible explanation to this finding, perhaps they could hypothesize about the role of smoking topography in this regard.

There is another finding that is barely mentioned in this paper and thus deserves some discussion from the authors which is the fact that change in salivary cotinine are similar in two groups of high and low dependent smokers.

The authors conclude that time to first cigarette is associated with salivary cotinine concentration. Considering that the amount of nicotine and its metabolites in human fluids reflects not only the amount smoked, but the balance between nicotine intake and the elimination rate, this paper could be enriched by including in the discussion some references to the pharmacokinetics of nicotine.

There are some limitations of the study that should be discussed. For example, potential for information bias due to the self-reported number of cigarettes; lack of adjustment for time of sampling during the day; lack of information on smoking topography variables such as frequency of inhalation and depth of inhalation, and lack of information on type of cigarettes (light vs. regular; filtered vs. unfiltered).

Respuesta a los comentarios de los revisores

Dear Editor:

We thank the revision process of our manuscript "Association between time to first cigarette after waking up and salivary cotinine concentration". Attached you will find the revised version according to the advices from the reviewers, that required some rewriting of the Discussion section. Here there is our point-by-point answer to their useful comments.

Reviewer: 1

Authors could consider the following minor points to improve the presentation of their findings:

1) The models used to evaluate the association between time to first cigarette and cotinine levels are correctly adjusted by number of cigarettes per day (and sex). This is of crucial importance given the relatively high correlation coefficient between time to first cigarette and smoking intensity (table 1). Thus, I suggest to put in evidence in the Conclusion sections of both the Abstract and the main text that the association between time to first cigarette and cotinine concentration is independent by the number of cigarettes per day.

We thank the observation pointed out by the reviewer. According to the advice, we added the suggestion in

- the Conclusion section of the Abstract:

> *"**Conclusion:** After adjustment for the number of cigarettes smoked in the last 24 hours, time to first cigarette is associated with salivary cotinine concentration."*

- the beginning of the Discussion section:

> *"The data show that the time to first cigarette smoked is associated with salivary cotinine concentration, regardless of the cigarettes smoked in the last 24 hours."*

- in the Conclusion text:

> *"In conclusion, this study confirms that the time to first cigarette smoked is associated with salivary cotinine concentration, regardless of the number of cigarettes smoked."*

2) I suggest to consider Boyle et al. (2000; Eur J Public Health 2000; 10 (Suppl 3): 5-14) and Gallus et al. (2005, Ann Oncol 16:703-6) to describe the importance of "time to first cigarette" in assessing tobacco dependence.

We thank the suggestion by the reviewer. We added the Boyle et al. but not Gallus et al. reference, as the latter do not study the 'time to first cigarette' item from de Fagerström Test as a unique indicator, but integrated to the test as a whole. The insertion is at the end of the first paragraph of the Introduction section:

> *"This component of the Fagerström Test for Nicotine Dependence has the strongest strength as a predictor of addiction to nicotine (Boyle et al., 2000; Heatherton, Kozlowski, Frecker, & Fagerström, 1991)."*

3) In table 2 replace <5 with ≤5

Done.

Reviewer: 2

1) After adjustment for cigarette consumption (cigarettes smoked in the previous 24 hours), time to first cigarette (TFC) remains a significant variable and the shorter the TFC, the higher the cotinine concentrations. To this regard I ask the authors to provide some possible explanation to this finding, perhaps they could hypothesize about the role of smoking topography in this regard.

We thank the author's comment. We added a brief explanation about this topic in the first paragraph of the Discussion section:

> *"Factors such as smoking topography and nicotine metabolism could explain this finding, as smokers regulate their smoking behaviour to compensate for variations of nicotine levels in the body (Benowitz, 2008). Thus, smokers from the high dependent phenotype may smoke more intensely and deeply at first minutes of the day after overnight abstinence, resulting in higher cotinine concentration compared with low dependent smokers. The effect of these factors should be investigated in future studies, focusing on interindividual differences."*

2) There is another finding that is barely mentioned in this paper and thus deserves some discussion from the authors which is the fact that change in salivary cotinine are similar in two groups of high and low dependent smokers.

We think that this result supports the relation found between salivary cotinine and the time to first cigarette, as we observed higher salivary cotinine concentration in high dependent smokers (those smoking their first cigarette ≤30 min after waking up). The figure shows that the slope is similar, indicating that this relation is independent of the number of cigarettes smoked. We added a brief comment on it, in the second paragraph:

> *"Unlike Muscat et al. (2009), our data show that changes in cotinine concentration by number of cigarettes smoked is similar in high and low dependent smokers; nevertheless, cotinine concentration was higher among the most dependent smokers. This pattern seems to support the observed relation between salivary cotinine concentration and time to first cigarette, regardless of the number of cigarettes smoked."*

3) The authors conclude that time to first cigarette is associated with salivary cotinine concentration. Considering that the amount of nicotine and its metabolites in human fluids reflects not only the amount smoked, but the balance between nicotine intake and the elimination rate, this paper could be enriched by including in the discussion some references to the pharmacokinetics of nicotine.

We thank the reviewer's advice. We inserted a brief reference on pharmacokinetics of cotinine at the end of the first paragraph of the Discussion section:

> *"Furthermore, the half-life of cotinine is about 16 hours, and its levels tend to build up throughout the day, remaining at near steady-state values, but the level of cotinine in the body in an individual is influenced by the daily exposure level and the rate of clearance (Benowitz, 1996)."*

4) There are some limitations of the study that should be discussed. For example, potential for information bias due to the self-reported number of cigarettes; lack of adjustment for time of sampling during the day; lack of information on smoking topography variables such as frequency of inhalation and depth of inhalation, and lack of information on type of cigarettes (light vs. regular; filtered vs. unfiltered).

As the reviewer advises, we expanded the limitations according to those remarks. As we had just explained that we did not include the time of the sample collection in the analyses, we did not expand in

this specific topic. Here are the modifications done in the limitations paragraph (and reference to the time of the sample collection is underlined):

> *"(...). Self-reported data from questionnaires could be a possible source of bias, although self-report on smoking are considered accurate, with an acceptable validity (Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009; Patrick et al., 1994). Although we did not take into account in the analyses the time of the day the sample was collected, the half-life of cotinine (about 16 hours) and its ability to reflect exposure after 3-4 days assure a sensitive estimate of ongoing tobacco smoke exposure, and for this reason it is considered as a biomarker for daily intake (Benowitz, Hukkanen, & Jacob III, 2009). (...) The relatively small sample size prevented us to investigate in-depth the potential interaction between time to first cigarette and other sociodemographic variables (e.g., sex, age, education or social class) or other characteristics of smoking (frequency and depth of inhalation, type of cigarettes smoked, etc.), while we were able to find out significant results for the main hypothesis of the study."*

Decisión del Editor

24-Nov-2010

Dear Ms Fu,

The editors of Nicotine & Tobacco Research are pleased to accept your manuscript entitled "Association between time to first cigarette after waking up and salivary cotinine concentration" in its current form for publication. Any comments by the reviewer(s) who reviewed the most current version of your manuscript are included at the end of this letter.

In order to publish your article, Oxford University Press requires that you complete a license agreement online. A link to the online licensing system, and instructions on how to select and complete a license, will be provided to you by the Production Editor at Oxford University Press in due course.

Thank you for your contribution. On behalf of the editors of Nicotine & Tobacco Research, we look forward to your continued contributions to the Journal.

Yours sincerely,

Dr Karl Fagerstrom
Deputy Editor, Nicotine & Tobacco Research
Email: Karl.fagerstrom@swipnet.se

Reviewer(s)' Comments to Author:

Reviewer: 1
Comments to the Author
none

Reviewer: 2
Comments to the Author
I read carefully this new version of your manuscript and I consider it is greatly improved. Thank you for taking into account my reviewing on this paper.

4. Proceso editorial del artículo aceptado en:

European Journal of Cancer Prevention

Carta de presentación al Editor

ICO
Institut Català d'Oncologia

UNIVERSITAT DE BARCELONA

L'Hospitalet de Llobregat, March 16th, 2011.

Dr. Jaak Ph Janssens
Editor
European Journal of Cancer Prevention

Dear Dr. Janssens:

Please find enclosed our manuscript "Nicotine dependence and salivary cotinine concentration in daily smokers" for consideration to peer-review process in your journal as an *Original Research Article*.

Our results show a strong relationship between salivary cotinine levels and nicotine dependence, as measured by the Fagerström Test for Nicotine Dependence, especially with the items on number of cigarettes smoked and time to first cigarette after waking up. Few papers have related the level of addiction to a specific biomarker of smoking and we believe the results may be of interest of the international audience of the European Journal of Cancer Prevention. In this sense, we have consulted Prof. Carlo La Vecchia, who encouraged us to submit our manuscript to your journal.

All the authors carefully read the manuscript and fully approved of it. In their name I also declare that the manuscript is original and it is not submitted anywhere other than your journal. The authors declare to have no conflict of interest. We would of course be ready to provide further information about our data and methods you desire.

Correspondence about the manuscript should be addressed to me as indicated in the first page of the manuscript.

Thank you very much for your kind attention.

Yours sincerely,

Esteve Fernandez, MD, PhD
Director, Tobacco Control Unit, Institut Català d'Oncologia
Associate Professor, Department of Clinical Sciences, Universitat de Barcelona
E-mail: efernandez@iconcologia.net

Revisión realizada al manuscrito

Date: Apr 06, 2011
To: "Esteve Fernandez" efernandez@iconcologia.net
From: "European Journal of Cancer Prevention" Janssens.ecp@skynet.be
Subject: EJCP Decision

Apr 06, 2011

RE: EJCP06947, entitled "Nicotine dependence and salivary cotinine concentration in daily smokers"

Dear Dr. Fernandez,

I am pleased to inform you that your paper has been found acceptable for publication pending appropriate revision. Please find the comments of the reviewers listed below.

If you are willing to revise the manuscript taking into consideration the suggestions of the reviewers, I will send the revised paper to the original reviewers for appraisal. Please include with your revised submission an itemized, point-by-point response to the comments of the reviewers. The revisions should be completed by Jun 05, 2011 to avoid being considered as a new submission.

To submit a revision, go to http://ejcp.edmgr.com/ and log in as an Author. You will see a menu item called "Submission Needing Revision." Please click on this item to obtain your submission record and begin the revision process.

Your username is: ********
Your password is: ********

With Kind Regards,

Prof. Jaak Ph. Janssens
Editor
European Journal of Cancer Prevention

Reviewer Comments:

Reviewer #1: EJCP 06947

The paper by Fu M. et al. has the objective of measuring the correlation between the score of a test (FTND) of dependence among tobacco smokers and levels of salivary cotinine. The paper may be of interest but is very difficult to read in its present form because statistical analysis and results are inadequately described and reported.
Some analyses on the relation between FTND score and cotinine concentration are presented first (a rank correlation and a subsequent p value). Then the main focus of the analysis is by single questionnaire items (i.e. in univariate and multivariable analyses the six questionnaire items are entered as independent predictors). The analysis by questionnaire's items is interpreted as if all items explain and support the relation between dependence and cotinine concentration. However there is a striking contrast between the findings and discussion since four out of six items turn out to be non significant predictors of cotinine levels in multiple linear regression. Moreover it comes as no surprise that one of the two items significant in the multivariable analysis is concerned with the number of cigarettes smoked per day.
I suggest to improve statistical analyses and reporting of results (e.g. use item response theory, IRT, techniques to explore the relation between overall test score and cotinine concentrations, transform cotinine concentration before using parametric testing, simplify the final model by excluding non significant variables) and revise discussion accordingly.
The discussion could be shortened to improve readability. For instance I found rather unclear the reasoning on the first and last cigarettes of the day and their role in determining the described relation between FTND scores and cotinine levels. Discussion of non -presented results on black tobacco could be eliminated as well.

Cases and methods
Page 4. "A representative sample (n=1,560)" Please give some more detail on sample size calculation.

Sampling strategy
If the Authors started from a general population frame to investigate the correlation between dependence test score and salivary cotinine concentrations this should be clearly stated since we start with a sample size of 1,560 to end with 196 smokers included in the analysis.

Page 4. "When a non-response occurred (refusal to participate or after seven unsuccessful attempts), it was replaced by a subject of the same sex, 5-year age group, and district, also selected at random from the population." A reference should be attached here. Replacement of persons who refuse to participate is apparently a successful strategy that allows attaining the study sample size. If, however, persons who accept to join the study are systematically different from people refusing to participate, the net result will be an increased weight of features common to people willing to participate. Thus the replacement procedure adopted has the potential to worsen bias with respect to the analysis of test respondents only. Biased results will be a concern mainly for the external validity of the study.

Page 5. "and 19 were ?16 years old". Two different classification criteria are mixed here: smoking habits and age classes.
Page 7. Statistical analyses.
Parametric tests are used in the analysis (t test ANOVA linear regression) despite variables considered being non normally distributed (e.g. cotinine concentrations) or scores (it seems that nonparametric tests were used to analyze FTND scores, see table 1, but they are not described). Transform of cotinine levels (e.g. logarithmic) may be explored to improve fit to normal distribution. Non parametric tests are reported in the results section but not in the methods section.
Results
Page 8. Ranks correlation (non parametric) is reported but it was not mentioned in the methods section. Similarly a Wilkoxon test is cited in table 1 and not in the methods section.
"The GMs of cotinine concentration were 87.45 ng/ml, 159.12 ng/ml, and 246.28 ng/ml for people with low, medium, and high dependence, respectively ($p<0.001$)."
Please explain how was obtained the attached p value and why FTND results were broken in groups; this categorization was not mentioned in the methods section.
Table 1 and table 2. Test for linearity should be specified
Table 3. Including all test items separately in a linear regression model (and other adjustment variables) requires many degrees of freedom and results in a likely overfitted model. Model fit evaluation is declared but not reported. Overall LR test for the single items could serve as a guide to simplify the model. More generally a linear regression model with a skewed dependent variable and including many test items as separate predictors is not the best choice in terms of statistical methods.
Table 3. Results in table 3 are adjusted for other variables (e.g. gender). However variables not included in table 3 are largely discussed in the text and thus these variables are not merely noise factors and their figures should be reported in the table.
Table 3. Please check response to item 3. It seems to make no sense.
Discussion
"We found consistent trends in salivary cotinine concentration by FTND: the more the single item score and the total FTND score, the more the cotinine concentration. The best predictors of cotinine concentration were items 1 and 4."
Indeed there is no consistent trend and there are only two probably significant items out of six.

"Even after controlling for tobacco consumption, we observed that differences in FTND scores by sex remain."
This finding should be reported in the results section and not simply cited in the discussion.

"Besides higher FTND scores, and subsequently higher nicotine dependence in men than in women, our results also showed that salivary cotinine concentration was higher in men, even after controlling for cigarette consumption, indicating a good relation between FTND and cotinine concentration by sex (Etter and Perneger, 2001; Huang et al., 2008)."
I find this sentence rather obscure particularly because FTND scores are not entered in the model and consequently no speculation is possible on the residual correlation between gender and cotinine levels after adjustment for the number of cigarette smoked.

"The relation mentioned above seems to indicate that smokers who are more dependent have higher tobacco consumption and have higher cotinine concentration than those who are less dependent." This is a somewhat circular argument since the number of cigarette smoked is included as an element of dependence in the FTND.

"In addition to the tobacco consumption, other factors might also have an effect on cotinine concentration and could explain the flat form of the relation in the highest strata of consumption and in the highest FTND scores."
To explore the relation between tobacco consumption and cotinine concentration, a model based on the number of cigarettes smoked per day would have been much preferable then FTND scores or the categorized items on tobacco consumption that is part of the questionnaire. As to the relation between tobacco dependency and cotinine levels a ceiling effect of the FTND and a reporting bias from heavily dependent subjects could also be considered. A few subjects report very high FTND scores and thus the present study may be inadequately powered to describe the functional form of the relation at high FTND scores.

"The participation rate was almost complete because the design allowed replacement according to strata of sex, age, and district"
Replacement is not complete participation

Reviewer #2: The authors present an interesting study on nicotine dependence and salivary cotinine. As outlined below a few interpretations of the results should be made with more caution and better discussed in view of the available literature. Otherwise, I have only very few comments on the text.

Specific comments/suggestions:

Page 5: In the description of the Questionnaire the part on second-hand exposure should be deleted.
Page 6, lines 3ff: "Cotinine was determined by gas... (GC/MS) as described by Shin et al. (2002) and quantified..." [in all papers cited, except Jacob et al., other matrices have been analysed. In Pichini et al. the analytical procedure is not described in any detail but referred to Shin H-S Kim J-G Shin Y-J Jee SH (2002) Sensitive and simple method for the determination of nicotine and cotinine in human urine, plasma and saliva by gas chromatography-mass spectrometry. J Chromatogr B 769:177-183]; another option could be to cite Fu et al., 2009 in this context.
Page 6, lines 20-21: place (1991) after the first mention of Heatherton et al. and delete "(Heatherton et al., 1991)" in the next line.
Page 6, last line: take out "with filter vs without filter" because calculations with n=2 are unsound and useless.
Page 8, lines 2ff: "...). A higher score was found in the 45-64 years age group and a lower score in the group with university education. The FTND scores differed by type of tobacco... [Differences in the BMI groups and between the groups of the two lower educational levels are small and insignificant].
Page 8, lines 16-17: Because of the bimodal distribution of FTND scores the allocation into 3 classes according to Heatherton et al. 1991 seems to be not justified [which is obvious from Figure 1.]
Page 9, discussion on sex and gender differences: here the authors should take into account results from other groups, e.g.

Dempsey D Tutka P Jacob P Allen F Schoedel K Tyndale RF Benowitz NL (2004) Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin.Pharmacol.Ther. 76:64-72
Benowitz NL Lessov-Schlaggar CN Swan GE Jacob P (2006) Female sex and oral contraceptive use accelerate nicotine metabolism. Clin.Pharmacol.Ther. 79:480-488
Malaiyandi V Lerman C Benowitz NL Jepson C Patterson F Tyndale RF (2006) Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. Mol.Psychiatr. 11:400-409
Melikian AA Djordjevic MV Hosey J Zhang J Chen S Zang E Muscat J Stellman SD (2007) Gender differences relative to smoking behavior and emissions of toxins from mainstream cigarette smoke. Nicotine Tob.Res. 9:377-387
Pauly JR (2008) Gender differences in tobacco smoking dynamics and the neuropharmacological actions of nicotine. Front.Biosci. 13:505-516
Swan GE Lessov-Schlaggar CN Bergen AW He Y Tyndale RF Benowitz NL (2009) Genetic and

environmental influences on the ratio of 3'-hydroxycotinine to cotinine in plasma and urine. Pharmacogenet.Genomics 19:388-398

In this context it should also be discussed that the ratio of 3'OH-cotinine/cotinine could be a better biomarker taking into account effects of CYP2A6 polymorphism.

Page 10, lines 3ff: There is 2 times a levelling of, first between scores 2 and 5 and then after score 7

References:
Gerstenkorn: Präventivmed
Henningfield: Book title in capitals (Tobacco and Public Health: Science and Policy).

Table 1: I suggest to take out the use of filter tip

In conclusion, the manuscript should be accepted for publication in EJCP after minor revision.

Reviewer #3: The Editor should encourage the authors to provide references to prior art from the Journal to stay in line with the educational ambitions of the Journal.

Respuesta a los comentarios de los revisores

Dear Editor:

We thank the revision process of our manuscript "Nicotine dependence and salivary cotinine concentration in daily smokers". Attached you will find the revised version according to the useful reviewers' advices. Here there is our point-by-point answer as requested.

Reviewer #1

1. I suggest to improve statistical analyses and reporting of results (e.g. use item response theory, IRT, techniques to explore the relation between overall test score and cotinine concentrations, transform cotinine concentration before using parametric testing, simplify the final model by excluding non significant variables) and revise discussion accordingly.

We really appreciate all suggestions by the reviewer. Related to the transformation of cotinine concentration before using parametric testing, we had originally followed this strategy, a log-transformation of cotinine concentrations, but only to perform parametric testing, not in descriptive analyses, where we used geometric means that allow controlling for non-normality. We recognize this was not adequately explained in Methods. We opt now for using non-transformed data to describe the data and non-parametric tests to compare groups (Wilcoxon test and Kruskal-Wallis test). The results have not substantially changed.

Related to the linear regression analyses, considering the non-normal distribution of the data, we now use log-transformed cotinine concentration. To simplify the model we include only the statistically significant variables according to the partial F-test, as explained in detail in the specific comment (please see the response to the comment #12).

2. The discussion could be shortened to improve readability. For instance I found rather unclear the reasoning on the first and last cigarettes of the day and their role in determining the described relation between FTND scores and cotinine levels.

We revised the Discussion section according to the "new" results (only few changes were obtained based on the new analyses) and tried to shorten it and improve legibility. Specifically on the case mentioned by the reviewer, the main message of the referenced comment is that very dependent smokers would smoke at very short time after waking-up comparing to less dependent smokers, resulting in more cotinine concentration. We shortened the discussion on this topic thus making it more readable:

> *"(…) While the first cigarettes of the day produce the most intense effects over physiological and behavioural responses (Henningfield and Benowitz, 2004), the last cigarettes of the day in heavy smokers would not be a meaningful contributor to cotinine concentration once smokers had reached the desired levels of nicotine in the body.(…)"*

3. Discussion of non -presented results on black tobacco could be eliminated as well.

We agree with the reviewer and consequently have deleted those results.

Cases and methods.
4. Page 4. "A representative sample (n=1,560)" Please give some more detail on sample size calculation.

More details are now provided in the first paragraph of Methods section:

> *"(…). A representative sample was drawn from the 2001 residents' register of Barcelona by simple random sampling. To detect a difference in smokers' cotinine concentration of 50 ng/ml (with a mean value of 500 ng/ml and a standard deviation of 200 ng/ml), with an alpha of 5% and a beta of 10% (statistical power of 90%), we estimated that a sample size of 337 smokers would be needed. Considering that the prevalence of smokers from the*

2001 Health Survey of Barcelona was 27%, we estimated a sample size of 1,560 people, taking into account smokers and non-smokers. (...)"

Sampling strategy.
5. If the Authors started from a general population frame to investigate the correlation between dependence test score and salivary cotinine concentrations this should be clearly stated since we start with a sample size of 1,560 to end with 196 smokers included in the analysis.

According to the reviewer remark we amended the objective, stating that the study is based in smokers from the general population (at the end of the Introduction):

"(...). The aim of this study is to analyse the relation between nicotine dependence, measured by the FTND, and salivary cotinine concentration in adult daily smokers from the general population."

And we accordingly changed the Methods description in the Abstract:

"Methods: Cross-sectional study (2004-2005) of a representative sample of the general population of Barcelona, Spain (n=1,245)."

6. Page 4. "When a non-response occurred (refusal to participate or after seven unsuccessful attempts), it was replaced by a subject of the same sex, 5-year age group, and district, also selected at random from the population." A reference should be attached here. Replacement of persons who refuse to participate is apparently a successful strategy that allows attaining the study sample size. If, however, persons who accept to join the study are systematically different from people refusing to participate, the net result will be an increased weight of features common to people willing to participate. Thus the replacement procedure adopted has the potential to worsen bias with respect to the analysis of test respondents only. Biased results will be a concern mainly for the external validity of the study.

We tried to control for the main socio-demographic variables, and we replaced individuals rejecting participation by others of the same sex, 5-year group of age, and district. We had referred to this potential bias in the Study limitations section; we compared our sample with data from Barcelona population in terms of these variables, and we did not find differences between them. In principle, as the reviewer commented on the bias introduced by substitution is similar to that provoked by non-response of eligible participants (we finally obtain responses from those wishing to participate, and if the wish of participate is related to the outcomes investigated, there is the bias). However, substitution permits to obtain the necessary sample size *a priori* calculated to perform the planned statistical analyses whereas non-substitution results in a smaller sample size, even in the case that a *a priori* non-response rate had been taken into account for sample size estimation (i.e., to consider *a priori* a refusal rate of 15% and finally have an actual refusal rate of 25%). We believe that our comments on the Discussion section do not need to be further extended.

7. Page 5. "and 19 were ?16 years old". Two different classification criteria are mixed here: smoking habits and age classes.

As our survey was conducted on the general population of Barcelona, the random sample also included individuals at young ages. Individuals under 16 years old were not surveyed on tobacco consumption or smoking behaviour, but on second-hand smoke exposure. We added this in the referenced paragraph:

"(...) From the 1,245 participants, 285 were daily smokers (at least 1 cigarette per day), 62 were occasional (non-daily) smokers, 354 ex-smokers, 525 never-smokers, and 19 were ≤16 years old, who were interviewed (either directly or using a proxy respondent) on second-hand smoke exposure only. We focused on adult people who were daily smokers."

8. Page 7. Statistical analyses. Parametric tests are used in the analysis (t test ANOVA linear regression) despite variables considered being non normally distributed (e.g. cotinine concentrations) or scores (it seems that nonparametric tests were used to analyze FTND scores, see table 1, but they are not described). Transform of cotinine levels (e.g. logarithmic) may be explored

to improve fit to normal distribution. Non parametric tests are reported in the results section but not in the methods section.

The reviewer is right; analyses were not well-described. We checked the distribution of FTND score and confirmed that it is non-normally distributed (Kolmogorov-Smirnov p= 0.003). We had decided to calculate arithmetic means in Table 1 instead of geometric means as we had done with cotinine concentration, because 18% of the smokers had a 0-score in FTND (the most frequent score obtained in the sample), that affected geometric mean. For this reason we still opt for maintaining arithmetic means of FTND. On the other hand, we also checked the distribution of cotinine concentrations and confirmed that it is also non-normally distributed (K-S test, p=0.025). In the previous version, we had used untransformed values for descriptive analysis of cotinine concentration (geometric means) and transformed values to calculate p-values derived from group comparisons in both variables. Considering the reviewer's comments, we now opt for using non-parametric tests instead. Thus, we now performed the non-parametric Wilcoxon and Kruskal-Wallis tests to assess differences in FTND scores and in salivary cotinine concentrations according to the variables of interest (table 1) and to test differences in salivary cotinine concentrations by the FTND items (table 2). We reworded the 'Statistical analyses' section according to these changes.

Results.
9. Page 8. Ranks correlation (non parametric) is reported but it was not mentioned in the methods section.
Similarly a Wilkoxon test is cited in table 1 and not in the methods section.

We added the corresponding details in the Methods section (please see response to the previous comment).

10. "The GMs of cotinine concentration were 87.45 ng/ml, 159.12 ng/ml, and 246.28 ng/ml for people with low, medium, and high dependence, respectively (p<0.001)."
Please explain how was obtained the attached p value and why FTND results were broken in groups; this categorization was not mentioned in the methods section.

According to the new analyses (using non-parametric tests; see response to the comment #8), we re-tested the differences in cotinine concentration by the levels of dependence using the Kruskal-Wallis test, and we obtained a p-value <0.001. We direct the reader to Table 2, where we added this information.

We had explained in the first version of our manuscript, in the Methods section (Strategy of analysis, Variables) that "we calculated the FTND score (0-10 points) with its constituent 6-items and used the system score and levels of nicotine dependence described by Heatherton et al.: low=0-4; medium=5; high=6-10". We reworded this explanation to make it clearer (and put a more appropriate reference):

> *"We calculated the FTND score (0-10 points) and classified the smokers according to nicotine dependence levels described by Fagerström et al. (1990)."*

We categorised the dependence variable because we wanted to explore the distribution of salivary cotinine concentration in different nicotine dependence levels in the population. Although there are different cut-points for the categorisation of nicotine dependence, we opted for using the categorisation described in Fagerstrom et al. (Ear Nose Throat J. 1990; 69:763-5) as usually used in most previous reports.

11. Table 1 and table 2. Test for linearity should be specified

We eliminated those p-values and used the p-values derived from the Kruskal-Wallis test instead (now described in Methods section; please see our response to the comment #8).

12. Table 3. Including all test items separately in a linear regression model (and other adjustment variables) requires many degrees of freedom and results in a likely overfitted model. Model fit evaluation is declared but not reported. Overall LR test for the single items could serve as a guide to simplify the model. More generally a linear regression model with a skewed dependent variable and including many test items as separate predictors is not the best choice in terms of statistical methods.

We reconsidered the strategy of analysis, following the reviewer's advices. Thus, we used log-transformed values of cotinine concentration. The first step was to consider a single model including the overall FTND score. We compared this model with a model including potential confounders: sex, age, educational level, body mass index, type of cigarettes, type of tobacco, frequency and depth of inhalation. The only significant variable was sex. The second step was to consider 6 models, one for each single FTND item plus sex. All of them were significant except the model including item 2. The next step was to consider a model including all single FTND items plus sex; in this model, the items 1, 4, and 5 were statistically significant. Finally, we considered a model including the combined score for the non-significant items in the latter model (that is, the sum of scores in items 2, 3, and 6) plus the significant single items 1, 4, and 5, plus sex. We compared all the models according to the partial F-test, and the last one was the best, including 5 variables instead of the original model with 9 variables. We evaluated the final model fit for the applicability of conditions of linear regression and all diagnostics indicated that it fulfilled the assumption. This is now indicated (in a simpler way) at the end of the Methods section:

> *"(...)We used log-transformed salivary cotinine concentration to adjust multiple linear regression models including the overall FTND score, a single FTND item, and all single FTND items, adjusting for potential confounders. We chose the model with the best fit according to the partial F-test (indicating the significant variables to maintain in every step). We tested the final model for the applicability of conditions of linear regression.(...)"*

At the end of the Results section we explained the way we performed the models and how the final model was chosen:

> *"(...) We performed multiple linear regressions to obtain the model that better explains salivary cotinine concentration. We first performed a linear regression model including the overall FTND score and then we included potential confounders (sex, age, educational level, body mass index, type of cigarettes, type of tobacco, frequency and depth of inhalation) and the only statistically significant variable was sex. Models including a single FTND item plus sex (one model per each item) were all significant except that including item 2. A model including all single items plus sex indicated that the items 1, 4, and 5 were significantly associated with cotinine concentration. Finally, a model including the sum of the scores in the items 2, 3, and 6, and the single significant items 1, 4, and 5 plus sex accounted for 41.4% of variance. We tested the final model for error specification, normality of errors, homoscedasticity, multicollinearity, outliers, and self-correlation, and all diagnostics indicated that the model fulfilled the assumptions."*

13. Table 3. Results in table 3 are adjusted for other variables (e.g. gender). However variables not included in table 3 are largely discussed in the text and thus these variables are not merely noise factors and their figures should be reported in the table.

In the first version we did not include the adjusting variables in the table in order not to lengthen it, although we had mentioned them in the footnote. According to the new analyses a new model was obtained (please see the response to the previous comment) and all variables in the model are now included in the table.

14. Table 3. Please check response to item 3. It seems to make no sense.

Thank you for noticing it. However, after reanalyses, item 3 is not included.

Discussion
15. "We found consistent trends in salivary cotinine concentration by FTND: the more the single item score and the total FTND score, the more the cotinine concentration. The best predictors of cotinine concentration were items 1 and 4."
Indeed there is no consistent trend and there are only two probably significant items out of six.

The first part of our comment was based on the results from Table 2, and the second part was based on the results from Table 3. Related to the first part, we had assessed trends in cotinine concentrations within every single FTND item using the test for linearity (with log-transformed cotinine values) and all p-values were significant. According to the new p-values derived from Wilcoxon and K-W tests now provided in Table 2 (please see response to comment #8), there are differences in all groups within all

items except in item 2 (of borderline statistical significance), thus indicating differences in cotinine concentrations in 5 out of the 6 FTND items. We slightly changed the wording in the Results section:

> *"Geometric means of salivary cotinine concentration according to the single FTND items are shown in Table 2. All items except item 2 showed differences in salivary cotinine concentrations, with higher concentrations at higher single score.(...)"*

Concerning the results about the best predictors of cotinine concentrations (information included in table 3), the new regression analyses indicated that there are 3 significant predictors of cotinine concentration: items 1, 4, and 5. The additional item #5 (if smokers smoke more in the first hours of the day) is consistent with item #1 (time to first cigarette), so we think the result is consistent with the previous one.

We rewrote the beginning of the Discussion section according to these remarks:

> *"We found that the FTND scores and the salivary cotinine concentration were related. The best predictors of cotinine concentration were items 1, 4, and 5. This is in agreement with the previous evidence (Heatherton et al., 1991); two of these items form the HSI, the FTND brief alternative to assess dependence.(...)*

16. "Even after controlling for tobacco consumption, we observed that differences in FTND scores by sex remain."
This finding should be reported in the results section and not simply cited in the discussion.

This sentence was based in an analysis not presented in Results. Moreover, our comment was based in a regression model with FTND as dependent variable and sex and tobacco consumption as predictors. However, we acknowledge multiple linear regression for FTND is not a good solution, since FTND is not normally distributed (it has two modes). Thus, we have performed non-parametric tests (Wilcoxon) to compare the distribution of FTND by sex in separate strata of tobacco consumption and we found no differences. Following the suggestion of the reviewer, we explain this result in the second paragraph of the Results section:

> *"(...)The mean FTND score for all participants was 3.27 and differed by sex (3.66 for men and 2.89 for women; $p<0.05$). No statistically significant differences in FTND scores by sex were found across different categories of tobacco consumption (data not shown).(...)"*

Accordingly, we have deleted the related sentence in the Discussion section and in its place we mention this result in the second paragraph and slightly changed the discussion about it:

> *"(...)When we compared the FTND scores by categories of tobacco consumption, the differences between men and women did not appear as significant. However, other factors related to sex (i.e., biological differences in the metabolism of men and women) or to gender (i.e., behavioural differences in the way women and men smoke) may be influencing nicotine dependence remains an open issue.(...)"*

17. "Besides higher FTND scores, and subsequently higher nicotine dependence in men than in women, our results also showed that salivary cotinine concentration was higher in men, even after controlling for cigarette consumption, indicating a good relation between FTND and cotinine concentration by sex (Etter and Perneger, 2001; Huang et al., 2008)."
I find this sentence rather obscure particularly because FTND scores are not entered in the model and consequently no speculation is possible on the residual correlation between gender and cotinine levels after adjustment for the number of cigarette smoked.

What we wanted to explain is that differences in FTND scores by sex are consistent with differences by sex observed in salivary cotinine concentration. We opted for eliminating this phrase in the way to simplify all the Discussion section.

18. "The relation mentioned above seems to indicate that smokers who are more dependent have higher tobacco consumption and have higher cotinine concentration than those who are less dependent."

This is a somewhat circular argument since the number of cigarette smoked is included as an element of dependence in the FTND.

The reviewer is right; nevertheless, dependence is not only a matter of number of cigarettes smoked: smokers of the same number of cigarettes may refer different dependence and, inversely, the same level of dependence may be referred by smokers who smoke different number of cigarettes. We rewrote this sentence to make it clearer and added a recent reference:

> *"(...)It seems that more dependent smokers have higher tobacco consumption and have higher cotinine concentration than less dependent smokers. Nevertheless, tobacco consumption is generally not closely associated with dependence, especially in groups of smokers who are quitting (West et al., 2011).(...)"*

19. "In addition to the tobacco consumption, other factors might also have an effect on cotinine concentration and could explain the flat form of the relation in the highest strata of consumption and in the highest FTND scores."
To explore the relation between tobacco consumption and cotinine concentration, a model based on the number of cigarettes smoked per day would have been much preferable then FTND scores or the categorized items on tobacco consumption that is part of the questionnaire. As to the relation between tobacco dependency and cotinine levels a ceiling effect of the FTND and a reporting bias from heavily dependent subjects could also be considered. A few subjects report very high FTND scores and thus the present study may be inadequately powered to describe the functional form of the relation at high FTND scores.

The reviewer is right; it is better to consider the number of cigarettes smoked per day to explore the relation between tobacco consumption and cotinine concentration. In the Figure, however, our intention was simply to investigate how the cotinine concentration was distributed through the FTND scores. Maybe the comparison of the shape of this distribution with that of the cotinine concentration according to the number of cigarettes smoked was not correctly presented. We wanted to say that maybe both distributions are similar because FTND scores are influenced by the number of cigarettes smoked; but we did not wanted to relate FTND to tobacco consumption; besides, as the reviewer remarks, this is only one aspect of FTND.

We reworded the reference to the distribution of cotinine concentration by FTND scores and its resemblance with the relation between cotinine concentration and number of cigarettes smoked.

> *"(...)This shape is similar to the described quadratic relation (first linear and then flat) between the cotinine concentration and the number of cigarettes smoked (Caraballo et al., 1998; Joseph et al., 2005; Blackford et al., 2006; Fu et al., 2009). This similarity could be due to the fact that the tobacco consumption is a significant contributor to the FTND scores. It seems that more dependent smokers have higher tobacco consumption and have higher cotinine concentration than less dependent smokers. Nevertheless, tobacco consumption is generally not closely associated with dependence, especially in groups of smokers who are quitting (West et al., 2011). Thus, in addition to the tobacco consumption, other factors might also have an effect on cotinine concentration and could explain the flat form of the relation in the highest strata of consumption and in the highest FTND scores.(...)"*

We also added as a limitation the remark about the potential bias in heavy smokers that could affect the form of the distribution of cotinine concentration according to FTND scores at the end of the paragraph:

> *"(...)In any case, the flat form of the distribution of salivary cotinine concentration in the highest FTND scores should be considered with caution, because the sample included few very-high-dependent smokers."*

and in the Limitations section:

> *"(...) The fit of models could be affected by the trend of the respondents to round off the tobacco consumption, specifically the heaviest smokers (Klesges et al., 1995), and hence some information bias due to digit preference cannot be disregarded. This potential bias*

could be also affecting the shape of the relation between salivary cotinine and FTND scores, because tobacco consumption is an important contributor to the FTND score.(...)"

20. "The participation rate was almost complete because the design allowed replacement according to strata of sex, age, and district"
Replacement is not complete participation
As previously mentioned (please see comment #6), we tried to avoid selection bias derived from non-response by replacement but we are aware that bias could be present if participants reasons to collaborate or not are related to the study outcomes. As suggested by the reviewer, we prefer not to say that participation was complete and have modified the sentence.

"(...)Although some loss of representativeness due to non-response might also be possible, our sample did not differ by sex, age, district of residence, and smoking behaviour from the Barcelona population because the design allowed replacement according to those variables. The prevalence of daily smokers in our sample (28.6% of men and 18.2% of women) was similar to that derived from the 2006 Health Interview Survey of Barcelona (27.3% of men and 20.6% of women) (Villalbí et al., 2009)."

Reviewer #2

1. Page 5: In the description of the Questionnaire the part on second-hand exposure should be deleted.

We are inclined to maintain this detail in the description of the questionnaire, since we had to explain what had happened with individuals less than 16 years old (please see response to comment #7 from the Reviewer 1). Nevertheless, we simplified the wording, thus paying less attention on that part of the questionnaire:

"Questionnaire. Besides sociodemographics and second-hand smoke exposure in different settings, detailed information on smoking habits was gathered from smokers: number of cigarettes smoked daily and during the previous 24 and 48 hours, age at starting smoking, brand of cigarettes usually smoked and those used in the last 24 and 48 hours, use of cigarettes with filter tips, depth and frequency of inhalation, use of other tobacco products, and use of nicotine gum or patches.(...)"

2. Page 6, lines 3ff: "Cotinine was determined by gas... (GC/MS) as described by Shin et al. (2002) and quantified..." [in all papers cited, except Jacob et al., other matrices have been analysed. In Pichini et al. the analytical procedure is not described in any detail but referred to Shin H-S Kim J-G Shin Y-J Jee SH (2002) Sensitive and simple method for the determination of nicotine and cotinine in human urine, plasma and saliva by gas chromatography-mass spectrometry. J Chromatogr B 769:177-183]; another option could be to cite Fu et al., 2009 in this context.

We thank the reviewer for the remark. We have cited the paper by Shin et al.

3. Page 6, lines 20-21: place (1991) after the first mention of Heatherton et al. and delete "(Heatherton et al., 1991)" in the next line.

We put a more specific reference regarding levels of dependence (please see comment #10, reviewer 1); nevertheless, we took into account the reviewer's recommendation for citation.

4. Page 6, last line: take out "with filter vs without filter" because calculations with n=2 are unsound and useless.

We took out the mentioned variable in the text and in Table 1.

5. Page 8, lines 2ff: "...). A higher score was found in the 45-64 years age group and a lower score in the group with university education. The FTND scores differed by type of tobacco... [Differences in

the BMI groups and between the groups of the two lower educational levels are small and insignificant].

The reviewer is right; we specified that those differences were not significant:

> *"(…) The highest scores were found in the 45-64 years age group, in the lowest educational level group, and in smokers who were obese, although these differences were non-statistically significant.(…)".*

6. Page 8, lines 16-17: Because of the bimodal distribution of FTND scores the allocation into 3 classes according to Heatherton et al. 1991 seems to be not justified [which is obvious from Figure 1.]

As we explained in the response to comment #10 from the reviewer 1, we wanted to explore if there were any differences in cotinine concentration according to different levels of dependence, commonly described in the clinical practice as does Fagerström et al., 1990 (we put now this reference, more appropriate to refer to nicotine dependence levels). We decided to use these well-known cut-points and we did not pretend to propose new cut-points based on the distribution of FTND scores in our sample.

7. Page 9, discussion on sex and gender differences: here the authors should take into account results from other groups, e.g.

Dempsey D Tutka P Jacob P Allen F Schoedel K Tyndale RF Benowitz NL (2004) Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin.Pharmacol.Ther. 76:64-72

Benowitz NL Lessov-Schlaggar CN Swan GE Jacob P (2006) Female sex and oral contraceptive use accelerate nicotine metabolism. Clin.Pharmacol.Ther. 79:480-488

Malaiyandi V Lerman C Benowitz NL Jepson C Patterson F Tyndale RF (2006) Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. Mol.Psychiatr. 11:400-409

Melikian AA Djordjevic MV Hosey J Zhang J Chen S Zang E Muscat J Stellman SD (2007) Gender differences relative to smoking behavior and emissions of toxins from mainstream cigarette smoke. Nicotine Tob.Res. 9:377-387

Pauly JR (2008) Gender differences in tobacco smoking dynamics and the neuropharmacological actions of nicotine. Front.Biosci. 13:505-516

Swan GE Lessov-Schlaggar CN Bergen AW He Y Tyndale RF Benowitz NL (2009) Genetic and environmental influences on the ratio of 3'-hydroxycotinine to cotinine in plasma and urine. Pharmacogenet.Genomics 19:388-398

In this context it should also be discussed that the ratio of 3'OH-cotinine/cotinine could be a better biomarker taking into account effects of CYP2A6 polymorphism.

We thank the reviewer contribution. We expand on this topic, albeit we did not study genetic aspects implicated in nicotine or cotinine metabolism. Although we found that FTND scores differed by sex, when we compared those scores by categories of tobacco consumption, those differences appeared not being significant. For this reason we slightly changed the discussion about this topic. The changes can be found in the second paragraph of the Discussion section:

> *"(…)When we compared the FTND scores by categories of tobacco consumption, the differences between men and women did not appear as significant. However, other factors related to sex (i.e., biological differences in the metabolism of men and women) or to gender (i.e., behavioural differences in the way women and men smoke) may be influencing nicotine dependence remains an open issue (Benowitz et al., 2006; Melikian et al., 2007; Pauly, 2008). Genetic factors may also be playing a role in dependence. While salivary or plasmatic cotinine have shown to be excellent markers of exposure, monitoring the metabolic ratio between the two nicotine metabolites, trans 3'-hydroxy-cotinine and cotinine, has been proposed as a marker of CYP2A6 activity, responsible for the metabolism of nicotine to cotinine, and therefore having a role in nicotine dependence (Dempsey et al., 2004; Malaiyandi et al., 2006). Some studies have related the ratio between these metabolites and the FTND or other questionnaires measuring dependence; but none of them have found a significant association (West et al., 2011). Other metabolic*

routes (e.g. glucuronidation) have also been proposed as genetic determinants of nicotine fate (Lessov-Schlaggar et al., 2009). However the multiple genetic factors involved produce large variations of those metabolic ratios reducing its potential use as direct markers of a specific trait (Swan et al., 2009). (...)"

8. Page 10, lines 3ff: There is 2 times a levelling of, first between scores 2 and 5 and then after score 7

The reviewer is right. The figure shows the distribution of salivary cotinine concentrations according to every FTND score, indicating the geometric mean of cotinine concentration in each scoring category. According to these geometric means, we can say that a levelling off occurred twice. This was corrected in the text:

"(...)When we described salivary cotinine concentration according to FTND scores we observed a positive relation between these variables: the more the FTND scores, the more the cotinine concentration. Geometric means showed that salivary cotinine concentration levelled off at medium and high FTND scores. This shape is similar to the described quadratic relation (first linear and then flat) between the cotinine concentration and the number of cigarettes smoked (Caraballo et al., 1998; Joseph et al., 2005; Blackford et al., 2006; Fu et al., 2009). This similarity could be due to the fact that the tobacco consumption is a significant contributor to the FTND scores. It seems that more dependent smokers have higher tobacco consumption and have higher cotinine concentration than less dependent smokers. Nevertheless, tobacco consumption is generally not closely associated with dependence, especially in groups of smokers who are quitting (West et al., 2011). Thus, in addition to the tobacco consumption, other factors might also have an effect on cotinine concentration and could explain the flat form of the relation in the highest strata of consumption and in the highest FTND scores. (...)".

References:
9. Gerstenkorn: Präventivmed

The journal's name in that year was "Sozial- und Präventivmedizin" (Soz Praventivmed. 2000;45(6):279-82), as can be checked in PubMed (PMID: 11210599) and in the journal website http://www.springerlink.com/content/j2337r6043464222/.

10. Henningfield: Book title in capitals (Tobacco and Public Health: Science and Policy).

Done.

11. Table 1: I suggest to take out the use of filter tip

We took out the mentioned variable in the text and in Table 1.

Reviewer #3

1. The Editor should encourage the authors to provide references to prior art from the Journal to stay in line with the educational ambitions of the Journal.

We added the following reference:

Strong K, Guthold R, Yang J, Lee D, Petit P, Fitzpatrick C (2008). Tobacco use in the European region. Eur J Cancer Prev 17: 162-168.

Decisión del Editor

De: "European Journal of Cancer Prevention" <janssens.ecp@skynet.be>
Data: 12 de juny de 2011 9:26:10 GMT+02:00
Per a: "Esteve Fernandez" <efernandez@iconcologia.net>
Tema: EJCP Decision

Jun 12, 2011

RE: EJCP06947R1 , entitled "Nicotine dependence and salivary cotinine concentration in daily smokers"

Dear Dr. Fernandez,

I am pleased to inform you that your paper has been found acceptable for publication pending minor revision. I anticipate that you will easily be able to answer the criticisms of the reviewers in a satisfactory manner. I will verify that this has been done upon receipt of the revised manuscript. Please find the comments of the reviewers listed below.

Please include with your revised submission an itemized, point-by-point response to the comments of the reviewers. The revisions should be completed by Aug 11, 2011 to avoid being considered as a new submission.

To submit a revision, go to http://ejcp.edmgr.com/ and log in as an Author. You will see a menu item called "Submission Needing Revision." Please click on this item to obtain your submission record and begin the revision process.

Your username is: ********
Your password is: ********

With Kind Regards,

Prof. Jaak Ph. Janssens
Editor
European Journal of Cancer Prevention

Reviewer Comments:

Reviewer #1: The Authors addressed most of my concerns and made chenges according to the recommendations. I would ask only for a statement among the study limitations acknowledging the risk of bias resulting from the adopted sampling strategy (i.e. sampling with replacement).

Respuesta al segundo informe de los revisores

Dear Editor:

We thank the revision process of our manuscript "Nicotine dependence and salivary cotinine concentration in daily smokers". Attached you will find the revised version according to the pendent reviewer's comment. Here there is our answer as requested.

Reviewer #1

The Authors addressed most of my concerns and made changes according to the recommendations. I would ask only for a statement among the study limitations acknowledging the risk of bias resulting from the adopted sampling strategy (i.e. sampling with replacement).

According to the reviewer's concern, we added a reference to the potential bias due to the adopted sampling strategy in the Limitations section:

> *"(…) This potential bias could be also affecting the shape of the relation between salivary cotinine and FTND scores, because tobacco consumption is an important contributor to the FTND score. Some loss of representativeness due to non-response might also be possible; on the other hand, the sampling strategy used (sampling with replacement) could result in a potential bias, if willingness to participate would be related to the outcomes investigated. Nevertheless, our sample did not differ by sex, age, district of residence, and smoking behaviour from the Barcelona population because the design allowed replacement according to those variables. (…)."*

Decisión final del Editor

De: em.ejcp.0.23bae3.76ef9f3a@editorialmanager.com
[mailto:em.ejcp.0.23bae3.76ef9f3a@editorialmanager.com] En nombre de European Journal of Cancer Prevention
Enviado el: miércoles, 15 de junio de 2011 18:13
Para: Esteve Fernandez
Asunto: EJCP Decision

Jun 15, 2011

RE: EJCP06947R2 , entitled "Nicotine dependence and salivary cotinine concentration in daily smokers"

Dear Dr. Fernandez,

I am pleased to inform you that your work has now been accepted for publication in European Journal of Cancer Prevention. All manuscript materials will be forwarded immediately to the production staff for placement in an upcoming issue.

Thank you for submitting your interesting and important work to the journal.

http://ejcp.edmgr.com/

Your username is: **********
Your password is: **********

With Kind Regards,

Prof. Jaak Ph. Janssens
Editor
European Journal of Cancer Prevention

5. Proceso editorial del artículo publicado en:

Preventive Medicine

Carta de presentación al Editor

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L'Hospitalet de Llobregat, March 19th, 2010.

Prof. Alfredo Morabia
Editor-in-Chief, Preventive Medicine

Dear Prof. Morabia:

Please find enclosed our manuscript **"Stages of change, smoking characteristics, and cotinine concentration in smokers – setting priorities for smoking cessation"** for your consideration in Preventive Medicine as an *Original Research Paper*. This study is based in the same population of that used in the study from Martínez-Sánchez et al. published in your journal (Prev Med 48 (2009) 218-223). In this occasion, this report is focused on smokers.

We studied the relationship between salivary cotinine concentration and motivation to quit smoking according to the theory of the stages of change by Prochaska and DiClemente. Few studies have focused on both of these aspects in representative samples of smokers from the general population, but mostly in selected samples of smokers, generally seeking help for cessation. Besides, this is the first assessment of tobacco exposure at the population level using a biomarker in a European population. For these reasons, we believe this may be of interest of the international audience of Preventive Medicine.

All the authors carefully read the manuscript and fully approve of it. In their name I also declare that the manuscript is original and it is not submitted anywhere other than your journal. The authors declare to have no conflict of interest. We would of course be ready to provide further information about our data and methods you desire.

Correspondence about the manuscript should be addressed to me as indicated in the first page of the manuscript.

Thank you very much for your kind attention.

Yours sincerely,

Esteve Fernandez, MD, PhD
Director, Tobacco Control Research Programme, Institut Català d'Oncologia
Associate Professor, Department of Clinical Sciences, Universitat de Barcelona
E-mail: efernandez@ico.scs.es

Pregunta del Editor

De: ees.pm.33d.98688.5e36c6dd@eesmail.elsevier.com
[mailto:ees.pm.33d.98688.5e36c6dd@eesmail.elsevier.com] En nombre de Alfredo Morabia
Enviado el: 7 juny 2010 02:59
Para: efernandez@iconcologia.net
CC: preventive.medicine@qc.cuny.edu; Herman.VanOyen@wiv-isp.be
Asunto: Editor query PM-10-162

Journal title: Preventive Medicine
Corresponding author: Dr. Esteve Fernandez
Article title: Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation

Manuscript number: PM-10-162

Dear Dr. Esteve Fernandez,

A reviewer of your paper made the following comments which we would like you to address before we can further consider your manuscript for publication in Preventive Medicine:

"This paper seems very similar to one previously published by this research group (Fu et al., 2009)* but with the addition of measures of stages of change and subsequent analyses based on these stages. "

*(BMC Public Health. 2009 Sep 3;9:320. Salivary cotinine concentrations in daily smokers in Barcelona, Spain: a cross-sectional study. Fu M, Fernandez E, Martínez-Sánchez JM, Pascual JA, Schiaffino A, Agudo A, Ariza C, Borràs JM, Samet JM; DCOT Study investigators.).

Sincerely,

Herman van Oyen, MD, DrPH
Associate Editor

Respuesta a la pregunta del Editor

Dear Doctors Morabia and van Oyen:

Thank you very much for your e-mail and query. The paper submitted for publication in Preventive Medicine and that already published in BMC Public Health derive from the same investigation. Thus the papers share a lot of common characteristics, including that both papers focus in the same target population (smokers from the general population). However, the papers have different objectives.

The aim of the paper published in BMC Public Health was "to describe and characterize the distribution of salivary cotinine concentration in a representative sample of adult (>16 years old) daily smokers in Barcelona, Spain.", this is, our aim was to test the association between salivary cotinine and number of cigarettes smoked, including some characteristics of the smoking behavior. That paper did not include any information on Prochaska and DiClemente stages of change, which is in turn the focus of the manuscript submitted to Preventive Medicine. The objective of this manuscript was "to describe the distribution of a sample of adult daily smokers and their salivary cotinine concentration according to their readiness to quit and selected smoking characteristics". We aimed at analyzing cotinine concentrations and other smoking characteristics according to Prochaska and DiClemente stages of change. As you may easily compare, we present in this paper a stratified analysis by the three stages of change, and all the manuscript has a different content (except the methods section, of course) than the previously published paper. We believed that the information on Stages of change (readiness to quit) was so unique to be shown in a different paper, not in a more general (and complicated) paper. Thus, we believe that both papers are different (but related) pieces of work and that both papers represent different contributions. In fact, our _a priori_ plan of analysis of the "DCOT study" included three different contributions (three papers) about smoker characteristics: 1) association between salivary cotinine and number of cigarette smoked (published BMC Public Health); 2) association between nicotine dependence and salivary cotinine (submitted); and 3) characterization of smokers (including cotinine levels) according to stages of change (submitted Prev Med).

These three papers plus two other contributions on other aspects of dependence and stages of change based in another survey conducted in Spain (a paper submitted for publication and a letter already published in Addiction in 2009) will conform the PhD dissertation of the first author (Ms. Marcela Fu, BSc Psychol).

Please do not hesitate to ask for further information about the manuscript. We are including for your help the PDF of the paper published in BMC Public Health. We look forward to hearing from you with the decision about our manuscript.

With best regards,

Esteve.-

Primera revisión realizada al manuscrito

From: **PM (ELS)** <pm@elsevier.com>
Date: 2010/6/13
Subject: PM-10-162: Decision
To: efernandez@iconcologia.net
Cc: preventive.medicine@qc.cuny.edu

Ms. No.: PM-10-162
Title: Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation
Corresponding Author: Dr. Esteve Fernandez
Authors: Marcela Fu; José A Pascual; Jose M Martínez-Sánchez; Antoni Agudo; Albert Moncada; Manel Nebot; Josep M Borràs; DCOT Study Investigators

Dear Dr. Fernandez,

Your manuscript, referenced above, has been reviewed. We invite you to revise and resubmit the manuscript along the lines suggested by the reviewers for further consideration in Preventive Medicine. The reviewer comments are below. Please keep the length of the paper below 2500 words as per PM guidelines.

Before resubmitting, please consult PM's guidelines for authors on PM's website. Make sure that you have complied with all the points in the checklist. Not doing so will result in an unwarranted loss of time because the authors have to format their paper properly before it is sent to production. Common errors include not respecting the word limit, not indicating the place and time of the study in the abstract, and in all the table and figure titles; and inadequately formatting the references.

Note that we are serious about deadlines. If you feel that you cannot make the deadline, please withdraw the paper and resubmit it when the revised version is ready, mentioning the original number of the paper, and attaching the responses to the review. The paper will not be penalized for this. We will treat it exactly in the same way as if you had not withdrawn it.

Please submit your revision online within 45 days by logging onto the Elsevier Editorial System for Preventive Medicine:
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You will find the manuscript record listed under "Submissions Needing Revisions." Click "Revise" when you are ready to submit your revision.

When submitting your revised paper, please include a separate document uploaded as "Response to Review" that carefully addresses the issues raised in the comments below, point by point, verbatim to the order of the remarks that is, please cite the full comment of the reviewer and insert your answer below. 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 should be uploaded individually as TIF or EPS files.

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

With kind regards,

Alfredo Morabia, MD, PhD

Editor-in-Chief
&
Michael C. Costanza, PhD
Editor, Statistics
Preventive Medicine

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Reviewers' comments:

Reviewer #1: The manuscript describes a large scale study of smoking characteristics, cotinine and stages of change. While the paper is generally well-written and the methods well-described I have a number of serious reservations about the paper:

This paper seems very similar to one previously published by this research group (Fu et al., 2009) but with the addition of measures of stages of change and subsequent analyses based on these stages. I am not convinced that the rationale for the focus on the stages of change is justified. The authors do not acknowledge the strong criticisms that the stages of change have received in the literature in recent years. For example, West (2005) called for the concept to be abandoned. Even if we were to accept the stages of change as valid the authors do not present a strong rationale for why we might expect cotinine to vary by stage of change. The results would appear to justify this concern i.e there were no differences by stage. The remainder of the paper focuses on other smoking characteristics in relation to cotinine. This is what the Fu et al.(2009) paper described and therefore I am not convinced that this paper adds significantly to the literature in this field.

The results presented are not clear. It is not clear what tests have been used and there appears to be no consideration of the likelihood of type 1 error: By chance we would expect tests to produce a significant result 1 in 20 times. Given these odds the reported 3/28 significant tests in Table 4 becomes questionable.

The authors report differences in cotinine concentrations in figures 1 and 2. It is not clear if these are statistically significant differences nor what tests might have been used to test for these.

The discussion seems to focus on the utility of the stages of change for describing samples and developing interventions. However neither of these concepts were tested in the manuscript and therefore are not directly relevant. This part of the manuscript also misses references to a number of studies which have shown that tailoring interventions by stage of change is unsuccessful (see Riersma et al., 2003).

Riemsma, R, P,, Pattenden, J,, Bridle, C, Sowden, A, J,, Mather,L,, Watt, I, S, & Walker, A, (2003) Systematic review of the effectiveness of stage based interventions to promote smoking cessation, BMJ, 326, 1175-1177,

West, R. (2005) Time for a change: Putting the transtheoretical (stages of change) model to rest. Addiction, 100, 1036-1039.

Reviewer #2: The purpose of the study (as described by the authors) was "to describe the distribution of daily smokers and their salivary cotinine concentration according to their readiness to quit and smoking characteristics". To do so, they conducted a cross-sectional survey study of 1245 adults in Barcelona, Spain. They found that, among daily smokers, most were in the precontemplation stage, and that while continine concentrations did not differ across stage of change, they were related to nicotine dependence, time to first cigarette, and cigarette consumption within each stage.

The strengths of this manuscript include: 1) a large, representative sample of the Barcelona population; 2)

good methodology to collect the sample; 3) selecting current daily smokers; and 4) examining differences in smokers across stages of change. However, there are also a number of weaknesses associated with this study. These are listed below:

1. In the introduction, the authors state that measuring cotinine among daily smokers could be an important predictor of cessation rates and help develop cessation programs. How so? Can you provide a reference or offer an example? How would obtaining cotinine above and beyond self-report measures of nicotine dependence and cigarette consumption aid the development of cessation programs, given their correlation and the cost associated with obtaining cotinine? While obtaining cotinine is an excellent way to verify self-reported abstinence and will add to the accuracy of self-report data, it is unclear how it would contribute to the improving treatment programs.
2. There is reference to the purpose of this study helping inform "prevention" - in the introduction and discussion sections. However, this study was conducted with daily smokers and thus any results could potentially help inform cessation intervention rather than prevention. If authors feel that these findings could indeed inform prevention efforts for individuals who haven't begun smoking or are at-risk for smoking initiation, then this needs to be made clearer in the introduction and discussion sections.
3. The introduction could be improved by the addition of hypotheses. What were the authors expecting to find?
4. Based on the description of smokers at each stage, it is unclear where smokers who were thinking of quitting in the next month but DID NOT make a quit attempt in the last year would be classified.
5. There is no rationale provided for why body mass index was included in the analyses.
6. Given the number of analyses that were conducted, there is some concern about the possibility of type I errors. What this accounted for?
7. Also, the body of the manuscript should include what statistical tests were conducted (rather than a footnote in the tables) as well as the test statistic and degrees of freedom.
8. Lastly, the discussion could be significantly improved by specifically stating how the findings from this study further the literature in this area. In other words, why are these results important, what do they add to what we already know, as well as some specific discussion of clinical implications.

Reviewer #3: The transtheoretical model (TTM) has been used by researchers to explain smoking behavior and to develop effective smoking cessation intervention programs. Coupling of the TTM's measures of intention and behavior using 5 stages of change with salivary cotinine may be informative for strategies tackling population-level smoking cessation options. In the manuscript entitled "Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation" the authors using a simple random sample of adults from the 2001 Barcelona census collect tobacco exposure information as well as salivary cotinine levels. Overall, the study authors commended for taking on a study that will certainly provide additional insight of this major public health issue. This study strengths include a population-level random sample of adults, comprehensive sample characteristics, and a combination of both self-report and biological (salivary cotinine) for select tobacco exposure and dependence measures. However, the lack of detail in the methods section of biological and survey questionnaire raises some minor concerns. In addition the authors are encouraged to consult with an English editor to enhance overall grammar flow and syntax. Below are some comments and suggestions for the study authors to consider.

MAJOR CONCERNS:
1) Data Collection / Methodology - the study design section lacks detail in the overall administration and collection of questionnaire and biological samples (Saliva). Detailed concerns are listed below.
2) Overall, the authors are encouraged to consult with an English editor to improve the overall flow, grammar and syntax of the manuscript. This reviewer largely understood what the authors were trying to convey within certain sentence structure, but other sentences had lost meaning due to word and sentence organization.

MINOR CONCERNS
ABSTRACT:
1. Methods Section - The second sentence of the methods section beginning with "We gathered information on smoking [what]. Be specific on what the author collected information on. Tobacco exposure, secondhand smoke exposure, smoking cigars, cigarettes, smokeless tobacco..

INTRODUCTION:

1. Second sentence of this first paragraph, notice the word syntax "Nicotine is the main alkaloid of tobacco, and it is the responsible.." Perhaps it should be written as "Nicotine is the main alkaloid of tobacco, and it is mainly responsible for its addictive effect." There are many of these types of syntax issues, please have an editor review the entire manuscript.
2. Page 3 - end of the last paragraph, the authors suggest the importance of using a measurement of cotinine to predict smoking cessation, yet the present study does not provide any predication analyses that could be useful to the reader and researcher. While the objective of the study was to describe "the distribution" of the sample, a more robust contribution is to actually determine predictors of smoking cessation by stage of contemplation using select smoking characteristics.
3. Page 4 last sentence of that paragraph, ".change in which smokers are." Are what? The stage they are contemplating?
4. Please provide a hypothesis for the study objective.

METHODS

1. Study Design Section - Did the interviewers collect saliva samples on the same day as the questionnaire was administered?
2. Study Design Section - Did study participants who participate in the questionnaire component, refuse to provide saliva samples, and if so, what rate.
3. Study Design Section - Could the authors briefly if the refusal rate pertains to the overall sample or to those that were classified as current smokers.
4. Was there a limit on the number of contacts the interviewer made to a particular home if the were greeted with a non-response?
5. Did the study team provide incentives for participation in the questionnaire or saliva collection process? It is noted by this reviewer that the author acknowledge "Chupa chumps spain" for smint candies.
6. Questionnaire - was the questionnaire self-administered by the participant or administered by the interviewer.
7. What the questionnaire paper-based or CASI?
8. Data Analysis - Why were the 21 adults who smoker "other types of tobacco products) included in the analysis? Did the authors check for differences with and without the addition of these 21 people? Cotinine levels have been shown to vary based on the tobacco exposure type (i.e. cigarettes versus cigars).

RESULTS

1. Page 6, first sentence: please consider presenting the full range of the age groups, just for the largest proportion.
2. Perfects describe for the reader the difference between blond and dark cigarettes, as this information may not understood by all readers.
3. The authors provide any adequate description of figure one and two in the results section, therefore the figures are not necessary for the paper.

DISCUSSION

1. The authors do not discuss any limitations with saliva sample collection, nor limitations imposed by the 24-48 hour representative of salivary cotinine and the self-report of last cigarette consumed.

TABLES

1. Table 1: footnote with an asterisk might be missing the word "add"
2. Table 3: please provide in the header section of each "stage of change" column the "range" for which the authors provide the values yet do not describe what the values mean.

Respuesta a los comentarios de los revisores

Ms. No.: PM-10-162
Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation

Corresponding Author: Dr. Esteve Fernandez
Authors: Marcela Fu; José A Pascual; Jose M Martínez-Sánchez; Antoni Agudo; Albert Moncada; Manel Nebot; Josep M Borràs; DCOT Study Investigators

Dear Prof. Morabia & Prof. Costanza:

Thank you very much for considering our manuscript *"Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation".* Here there is our point-by-point response to the helpful reviewers' comments.

Reviewer #1

The manuscript describes a large scale study of smoking characteristics, cotinine and stages of change. While the paper is generally well-written and the methods well-described I have a number of serious reservations about the paper:

This paper seems very similar to one previously published by this research group (Fu et al., 2009) but with the addition of measures of stages of change and subsequent analyses based on these stages. I am not convinced that the rationale for the focus on the stages of change is justified. The authors do not acknowledge the strong criticisms that the stages of change have received in the literature in recent years. For example, West (2005) called for the concept to be abandoned. Even if we were to accept the stages of change as valid the authors do not present a strong rationale for why we might expect cotinine to vary by stage of change. The results would appear to justify this concern i.e there were no differences by stage. The remainder of the paper focuses on other smoking characteristics in relation to cotinine. This is what the Fu et al.(2009) paper described and therefore I am not convinced that this paper adds significantly to the literature in this field.

The paper submitted for publication to Preventive Medicine and that already published in BMC Public Health derive from the same investigation. Thus, the papers share many common characteristics, including that both papers focus in the same target population (smokers from the general population). However, the papers have different objectives.
The aim of the paper published in BMC Public Health was "to describe and characterize the distribution of salivary cotinine concentration in a representative sample of adult (>16 years old) daily smokers in Barcelona, Spain"; this is, our aim was to test the association between salivary cotinine and number of cigarettes smoked, including some characteristics of the smoking behavior. That paper did not include any information on Prochaska and DiClemente stages of change, which is in turn the focus of the manuscript submitted to Preventive Medicine. The objective of this manuscript was "to describe the distribution of a sample of adult daily smokers and their salivary cotinine concentration according to their readiness to quit and selected smoking characteristics". We aimed at analyzing cotinine concentrations and other smoking characteristics according to Prochaska and DiClemente stages of change. We present in this paper a stratified analysis by the three stages of change and all the manuscript has a different content (except the methods section, of course) than the previously published paper. We believed that the information on stages of change (readiness to quit) was so unique to be shown in a different paper, not in a more general (and complicated) paper. Thus, we believe that both papers are different (but related) pieces of work and that they represent different contributions. In fact, our *a priori* plan of analysis of the "DCOT study" included three different contributions (three papers) about smoker characteristics: 1) association between salivary cotinine and number of cigarettes smoked (published BMC Public Health); 2) association between nicotine dependence and salivary cotinine (submitted); and 3) characterization of smokers (including cotinine levels) according to stages of change (submitted Prev Med).

We acknowledge that the "stages of change" model has had some criticisms (Etter & Perneger 1999; Whitelaw et al. 2000; West 2005), but it is widely used in the clinical setting and also in epidemiological assessment of readiness to quit at the population level. We agree that some reference to these criticisms is needed in the Introduction. Moreover, in the 3rd paragraph of the Introduction we summarized the reasons why we thought that the assessment of cotinine according to the stages of change could be of value. Hence, we have added a sentence in the Introduction (1st sentence, 3rd paragraph) referring to the criticisms, and are inclined to maintain the rest of the text as in the previous version, in order no to lengthen the manuscript:

> *"Some studies have criticised Prochaska and DiClemente's stages of change model (Etter and Perneger, 1999; West, 2005), and evidence of the effectiveness of stage-based interventions in smoking cessation is limited (Riemsma et al., 2003). However, the description of smokers by stage of change is widely used in the clinical setting as an approach to direct the treatment, to study different populations of smokers, or to analyse profiles of subjects by stage over time (Connors et al., 2004), (...)".*

The results presented are not clear. It is not clear what tests have been used and there appears to be no consideration of the likelihood of type 1 error: By chance we would expect tests to produce a significant result 1 in 20 times. Given these odds the reported 3/28 significant tests in Table 4 becomes questionable.

We are including in the Methods section a sentence to clarify the statistical methods. We had included the specific tests in the footnote to the tables, but it will be clearer, as suggested by the reviewer, to specify it (last sentence of the section):

> *"We used the Kruskal-Wallis test for the comparison of medians (cotinine concentration) and means (CPD and FTND score) and Pearson's $\chi 2$ test for comparison of proportions. The type I error was set at 5% ($p<0.05$). All analyses were performed with SPSS v15.0."*

As usual, we set the alpha error at 5% (now stated in the Methods section) and we believe that the reviewer's comment is not precise, and that the scope of chance should not be valued on the light of a single table. We reported 4 out of 52 significant tests (or 8 out of 58 tests, see next comment) in the manuscript whereas the expected number of significant tests by chance is 2.6 (or 2.9 considering 58 tests).

The authors report differences in cotinine concentrations in figures 1 and 2. It is not clear if these are statistically significant differences nor what tests might have been used to test for these.

Our intention was to graphically describe the differences but we did not assessed the statistically significance of the differences observed. Thus, following the reviewer comment, we have statistically tested whether the median cotinine concentrations by stage of change and dependence or CPD smoked are different, using the Kruskal-Wallis test, and have included the corresponding p-values. We have re-written this part of the Results section (at the end of the 3rd paragraph) with the corresponding p-values that are also included in Figures 1 and 2:

> *"Cotinine concentration significantly increased with increasing nicotine dependence among smokers in precontemplation ($p<0.001$) and contemplation ($p=0.002$) stages but not in smokers in preparation stage ($p=0.132$; Figure 1). Similarly, cotinine concentrations only increased according to number of CPD smoked in precontemplation ($p<0.001$) and contemplation ($p=0.004$) stages (Figure 2)."*

The discussion seems to focus on the utility of the stages of change for describing samples and developing interventions. However neither of these concepts were tested in the manuscript and therefore are not directly relevant. This part of the manuscript also misses references to a number of studies which have shown that tailoring interventions by stage of change is unsuccessful (see Riersma et al., 2003).

The conclusion of the manuscript (first sentence, Conclusion section) clearly refers to the main finding of the study. After it, we elaborated some hypothesis and suggestions for further research, but linked to the results already shown. We believe no changes are necessary.

We agree that some reference to the criticisms of the usefulness of the stages of change approach in smoking cessation treatment has to be also included (as already included in the Introduction) in the Discussion (at the end of the 1st paragraph):

> *Previous studies showed divergent results, although they are based on selected samples of smokers (Ahijevych and Parsley, 1999; Etter et al., 2000). These results could partly explain the lack of effectiveness of stage-based interventions in changing smoking behaviour (Riemsma et al. 2003; Bridle et al. 2005).*

Reviewer #2

The purpose of the study (as described by the authors) was "to describe the distribution of daily smokers and their salivary cotinine concentration according to their readiness to quit and smoking characteristics". To do so, they conducted a cross-sectional survey study of 1245 adults in Barcelona, Spain. They found that, among daily smokers, most were in the precontemplation stage, and that while continine concentrations did not differ across stage of change, they were related to nicotine dependence, time to first cigarette, and cigarette consumption within each stage.

The strengths of this manuscript include: 1) a large, representative sample of the Barcelona population; 2) good methodology to collect the sample; 3) selecting current daily smokers; and 4) examining differences in smokers across stages of change. However, there are also a number of weaknesses associated with this study. These are listed below:

1. In the introduction, the authors state that measuring cotinine among daily smokers could be an important predictor of cessation rates and help develop cessation programs. How so? Can you provide a reference or offer an example? How would obtaining cotinine above and beyond self-report measures of nicotine dependence and cigarette consumption aid the development of cessation programs, given their correlation and the cost associated with obtaining cotinine? While obtaining cotinine is an excellent way to verify self-reported abstinence and will add to the accuracy of self-report data, it is unclear how it would contribute to the improving treatment programs.

We agree the comment that makes us noticed that no references to those points were available in the text. It has been suggested that cotinine measurement may be useful to categorize smokers entering smoking cessation programmes because smokers with higher cotinine values could be considered to need higher doses of nicotine replacement as suggested by Hall et al (1984) and proposed in several clinical trials (Tønnesen et al. 1993; Paoletti et al. 1996). In fact, our sentence was not clear at all, since baseline nicotine (or cotinine) levels help to better define the dose of nicotine replacement therapy to be used. We have re-written the sentence (in the 3rd paragraph) as follows:

> *"(...) Measurement of cotinine, the major metabolite of nicotine, provides a characterization of nicotine dose received by an individual or group of individuals in a population. Therefore, baseline cotinine levels may be useful to categorize smokers entering smoking cessation programmes (Hall et al., 1984; Tønnesen et al., 1993; Paoletti et al., 1996)."*

We also agree that the implementation of routine salivary cotinine analyses in the clinical setting is difficult, mainly due not only to the associated costs but also to the need to have immediate results. In this sense, the recent developing of simple kits of semi-quantitative analysis (colorimetric assays) to be used in the cessation clinic may be of help.

2. There is reference to the purpose of this study helping inform "prevention" - in the introduction and discussion sections. However, this study was conducted with daily smokers and thus any results could potentially help inform cessation intervention rather than prevention. If authors feel that these findings could indeed inform prevention efforts for individuals who haven't begun smoking or are at-

risk for smoking initiation, then this needs to be made clearer in the introduction and discussion sections.

We believe that the misunderstanding with "prevention" applied to smokers comes from our use of the term following G. Rose concept of individual- and population-based prevention. In fact, to prevent smoking-related diseases we may adopt a high-risk strategy of prevention addressed to smokers; this is, in clinical terms, to promote cessation among smokers. As the title of the manuscript itself announces (*...**setting priorities for smoking cessation***) and note by the reviewer, our focus are smokers. We have checked the use of "prevention" across the manuscript and have changed where confusion could exist. In the Conclusion section, we maintain the terminology of "prevention" clearly indicating Rose's approach.

3. The introduction could be improved by the addition of hypotheses. What were the authors expecting to find?

Our hypothesis was that salivary cotinine concentrations would vary according to stages of change, with lower concentrations in smokers more prepared to quit. We also considered in our hypothesis that this variation could be affected by nicotine dependence and number of cigarettes smoked. The results, however, show that cotinine concentration was similar in smokers throughout the three stages of change and that within each stage there were differences in tobacco consumption, nicotine dependence, and time to first cigarette within each stage of change. Since the aim of the objective clearly reflects the hypothesis, we are inclined not to lengthen the manuscript including the hypothesis.

4. Based on the description of smokers at each stage, it is unclear where smokers who were thinking of quitting in the next month but DID NOT make a quit attempt in the last year would be classified.

According to the transtheoretical model, those individuals who were thinking of quitting in the next month but did not make a quit attempt in the last year should be classified in the precontemplation stage, as proposed by DiClemente et al. in his 1991 paper. We added this specification in the Methods sections (Data analysis subsection):

> *"Thus, smokers who were thinking in quitting smoking after six months or more and those who were not thinking in quitting smoking were classified as precontemplators; smokers who were thinking in quitting smoking during the next six months were classified as contemplators; and smokers who were thinking in quitting smoking during the next month and had had at least one attempt to quit smoking in the last 12 months were classified in the preparation stage. Those smokers who were thinking in quitting during the next month but had not had any attempt to quit in the last 12 months were classified in the contemplation stage (DiClemente et al., 1991)".*

5. There is no rationale provided for why body mass index was included in the analyses.

Body mass index (BMI) and body fat distribution may affect the metabolism and absorption of cotinine and has been used (BMI or other anthropometric indexes) for adjustment or for stratification in previous investigations (Jaakkola 2003; Blackford et al. 2006; Figueiredo 2007; Fidler 2007). We believe not necessary to expand the Methods section with this topic.

6. Given the number of analyses that were conducted, there is some concern about the possibility of type I errors. What this accounted for?

Please see our response to the second comment made by Reviewer #1.

7. Also, the body of the manuscript should include what statistical tests were conducted (rather than a footnote in the tables) as well as the test statistic and degrees of freedom.

Please see our response to the second comment made by Reviewer #1.

8. Lastly, the discussion could be significantly improved by specifically stating how the findings from this study further the literature in this area. In other words, why are these results important, what do they add to what we already know, as well as some specific discussion of clinical implications.

We have expanded the Conclusion (4th sentence):

> *"Cotinine baseline concentrations could help to better characterise smokers who want to quit and who might benefit from individual-tailored doses of nicotine replacement therapy. Before introducing this approach into the clinical practice, we need further evidence from cessation trials taking into account baseline cotinine concentrations."*

Reviewer #3

The transtheoretical model (TTM) has been used by researchers to explain smoking behavior and to develop effective smoking cessation intervention programs. Coupling of the TTM's measures of intention and behavior using 5 stages of change with salivary cotinine may be informative for strategies tackling population-level smoking cessation options. In the manuscript entitled "Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation" the authors using a simple random sample of adults from the 2001 Barcelona census collect tobacco exposure information as well as salivary cotinine levels. Overall, the study authors commended for taking on a study that will certainly provide additional insight of this major public health issue. This study strengths include a population-level random sample of adults, comprehensive sample characteristics, and a combination of both self-report and biological (salivary cotinine) for select tobacco exposure and dependence measures. However, the lack of detail in the methods section of biological and survey questionnaire raises some minor concerns. In addition the authors are encouraged to consult with an English editor to enhance overall grammar flow and syntax. Below are some comments and suggestions for the study authors to consider.

MAJOR CONCERNS:

1) Data Collection / Methodology - the study design section lacks detail in the overall administration and collection of questionnaire and biological samples (Saliva). Detailed concerns are listed below.

We believe that the Methods section contains sufficient details about the administration of questionnaire and saliva collection –we have now indicated that the questionnaire was administered face-to-face and saliva was collected at the end of the interview. Moreover, the Methods have been described in-depth in the articles already cited in the text. Interested readers in more details will be able to access those papers.

2) Overall, the authors are encouraged to consult with an English editor to improve the overall flow, grammar and syntax of the manuscript. This reviewer largely understood what the authors were trying to convey within certain sentence structure, but other sentences had lost meaning due to word and sentence organization.

We thank the comment and have had the manuscript revised by an English native speaker.

MINOR CONCERNS

ABSTRACT:

1. Methods Section - The second sentence of the methods section beginning with "We gathered information on smoking [what]. Be specific on what the author collected information on. Tobacco exposure, secondhand smoke exposure, smoking cigars, cigarettes, smokeless tobacco..
Given that the sentence is in the Abstract we are inclined to solely indicate that "We gathered information on smoking behaviour and ...". Specifying the information collected would lengthen the Abstract and the details are given in the Methods section of the manuscript.

INTRODUCTION:

1. Second sentence of this first paragraph, notice the word syntax "Nicotine is the main alkaloid of tobacco, and it is the responsible.." Perhaps it should be written as "Nicotine is the main alkaloid of tobacco, and it is mainly responsible for its addictive effect." There are many of these types of syntax issues, please have an editor review the entire manuscript.

We thank the reviewer comment. We reformulated the sentence as follows:

> *"Nicotine, the main alkaloid of tobacco, is responsible of its addictive effect".*

2. Page 3 - end of the last paragraph, the authors suggest the importance of using a measurement of cotinine to predict smoking cessation, yet the present study does not provide any predication analyses that could be useful to the reader and researcher. While the objective of the study was to describe "the distribution" of the sample, a more robust contribution is to actually determine predictors of smoking cessation by stage of contemplation using select smoking characteristics.

We agree with the reviewer that a more robust contribution would be to determine predictors of smoking cessation by stage of change but this is another study that we cannot address with the present data.

3. Page 4 last sentence of that paragraph, ".change in which smokers are." Are what? The stage they are contemplating?

We reformulated the sentence as:

> *"(...) but they have not taken into account in such description the stages of change of smokers".*

4. Please provide a hypothesis for the study objective.

Please see our response to the comment #3 from Reviewer #2.

METHODS

1. Study Design Section - Did the interviewers collect saliva samples on the same day as the questionnaire was administered?

Yes, participants were asked for a saliva sample after finishing the interview. We specified this as follows:

> *"(...) trained interviewers contacted participants at home to administer a face-to-face paper-based questionnaire and straight afterwards to collect a saliva specimen for cotinine determination".*

2. Study Design Section - Did study participants who participate in the questionnaire component, refuse to provide saliva samples, and if so, what rate.

There were 5 participants who refused to provide the saliva sample. We specified the exact number of exclusions in each case in Data analysis subsection of Methods (Data analysis subsection):

> *"From 285 adult daily smokers, we excluded 7 people with missing cotinine concentration data (5 refused to provide a saliva specimen and 2 due to technical problems during cotinine analysis)."*

3. Study Design Section - Could the authors briefly if the refusal rate pertains to the overall sample or to those that were classified as current smokers.

We understand the reviewer refers to the previous comment (he/she asked about those who refused to provide saliva sample in the questionnaire component). As we detailed in the sentence in the response to that comment, 5 out of 285 daily smokers refused to provide the saliva sample. As we are focused only on daily smokers, we did not provide the correspondent figure for the whole sample of 1245 people (smokers and non smokers). Please let us know whether we have correctly understood the reviewer suggestion.

4. Was there a limit on the number of contacts the interviewer made to a particular home if the were greeted with a non-response?

It was established by protocol a maximum of 7 contacts before substitution. We have added this detail in the Methods section:

> *"When subjects could not be contacted after 7 attempts (including also visits on weekends and during non-working hours) or they rejected to participate, a substitute of the same 5-age group, sex, and district was randomly obtained from the census."*

5. Did the study team provide incentives for participation in the questionnaire or saliva collection process? It is noted by this reviewer that the author acknowledge "Chupa chumps spain" for smint candies.

We did not use any kind of incentive for participation in this investigation. The letters of invitation to participate (in Spanish and Catalan) are available upon request. As now explained in the manuscript (see below), we used a lemon candy (Smint©) to stimulate salivation. For each participant we used a new small box of candies, and many participants (most of them) asked for the box after finishing the saliva collection.

Thanks to this comment, we noticed that the reference to the use of candies to stimulate salivation was omitted in the manuscript, and we have added it in the Measures subsection (Salivary cotinine) of Methods section (as already explained in detail in Fu et al., 2009):

> *"Participants were asked to provide a saliva specimen to determine the cotinine concentration. They were asked to rinse their mouths and suck a lemon-flavoured candy (Smint©) to stimulate salivation. They were asked to spit out a small amount of saliva, (...)".*

6. Questionnaire - was the questionnaire self-administered by the participant or administered by the interviewer.

The questionnaire was administered by the interviewer. We specified this in Methods section, Study design subsection:

> *"After sending a letter explaining the overall objective of the study, trained interviewers contacted participants at home to administer a face-to-face paper-based questionnaire (...)".*

7. What the questionnaire paper-based or CASI?

The questionnaire was paper-based. Please see the sentence referred in response to the preceding comment.

8. Data Analysis - Why were the 21 adults who smoker "other types of tobacco products) included in the analysis? Did the authors check for differences with and without the addition of these 21 people? Cotinine levels have been shown to vary based on the tobacco exposure type (i.e. cigarettes versus cigars).

We considered that these 21 smokers of other tobacco products could be also classified according to stages of change, and we included them in the analysis. They represented a 7.6% of the final sample of

278 daily smokers. These non-cigarette smokers had lower levels of salivary cotinine and a lower level of physical addiction as measured by the Fagerström Test for Nicotine Dependence. Since the study objective was to describe salivary cotinine levels in daily smokers according to stages of change we believe not necessary to restrict the sample to cigarette smokers only. However, some of the analyses are restricted to cigarette smokers, ie, cotinine concentrations by number of CPD and stages of change (this can be appreciated from the "n" available in the Tables).

RESULTS

1. Page 6, first sentence: please consider presenting the full range of the age groups, just for the largest proportion.

We believe that the brief description already given is enough to have a "picture" of the sample composition.

2. Perfects describe for the reader the difference between blond and dark cigarettes, as this information may not understood by all readers.

We added a brief explanation in brackets showing what blond and black cigarettes mean in Methods (Measures subsection, Questionnaire):

"(...), type of tobacco (blond –flue-cured– or black –air-cured–), (...)"

3. The authors provide any adequate description of figure one and two in the results section, therefore the figures are not necessary for the paper.

As we now include the p-values for all strata in both figures, we are inclined to maintain them. Nevertheless, we are opened to remove them from the manuscript if the Editors consider it more appropriate.

DISCUSSION

1. The authors do not discuss any limitations with saliva sample collection, nor limitations imposed by the 24-48 hour representative of salivary cotinine and the self-report of last cigarette consumed.

As a standardised protocol was used, we think that some kind of bias due to the method of sample collection is unlikely. On the other hand, although we collected information on tobacco consumption in the last 24 and 48 hours, we used the average daily tobacco consumption (cigarettes per day) in the present analysis, and this is the reason why we did not refer to the limitations due to use of information on tobacco consumption in the last 24-48 hours.

TABLES

1. Table 1: footnote with an asterisk might be missing the word "add"

We correct the missing word in all tables.

2. Table 3: please provide in the header section of each "stage of change" column the "range" for which the authors provide the values yet do not describe what the values mean.

The values in the Table are described in the title (medians and interquartile ranges). We believe that this indication in the title is enough.

Decisión del Editor

De: ees.pm.0.b9a95.0bdabe36@eesmail.elsevier.com
[mailto:ees.pm.0.b9a95.0bdabe36@eesmail.elsevier.com] En nombre de PM (ELS)

Enviado el: 9 setembre 2010 17:04
Para: efernandez@iconcologia.net
CC: preventive.medicine@qc.cuny.edu
Asunto: PM-10-162R1: Final Decision

Ms. No.: PM-10-162R1
Title: Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation

Corresponding Author: Dr. Esteve Fernandez
Authors: Marcela Fu; José A Pascual; Jose M Martínez-Sánchez; Antoni Agudo; Albert Moncada; Manel Nebot; Josep M Borràs; DCOT Study Investigators

Dear Dr. Fernandez,

We regret to inform you that we are unable to accept your manuscript for publication in Preventive Medicine. As you will see below, there remain too many issues with the revised paper. The reviewers don't feel that their comments were addressed appropriately. You did not follow either our request to shorten the paper.

The reviewer comments are included below so that you may better understand the basis for our decision.

Thank you for your interest in Preventive Medicine.

Most sincerely,

Alfredo Morabia, MD, PhD, FRCPE
Editor-in-Chief
&
Michael C. Costanza, PhD
Editor- Statistics
&
Herman Jozef Van Oyen, MD, DrPH, MPH, DTM&H
Associate Editor
Preventive Medicine

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Reviewers' comments:

Reviewer #2: In the authors' response to reviewer comments, there are a number of issues that remain unaddressed. These are listed below:

1. Reviewer 1 stated that "Even if we were to accept the stages of change as valid the authors do not present a strong rationale for why we might expect cotinine to vary by stage of change". The authors did not address this comment at all in their response. This is an important point and merits discussion.

2. The issue related to Type 1 error rate remains. The authors state that 4 out of 52 tests were significant and the that the error rate would be 2.6 out of 52. This would suggest that unless statistical analyses are adjusted to account for the Type I error rate, 2.6 out of 4 significant results could have been spurious - making it difficult to interpret the validity of the results.

3. In addition to the sentence added in response to Reviewer 2's first comment, more should be said about the results of this study potentially influencing decisions regarding pharmacotherapy dosing.

4. The authors response to both Reviewer 2 and 3's comments regarding hypotheses was unsatisfactory. While the objectives were presented it would be helpful to have directional hypotheses. For example, at which stage of change would you expect there to be highest levels of cotinine and/or CPD?

5. Given that the breadth of readership of Preventive Medicine may not necessarily include experts in nicotine research, it may be useful to simply state that BMI may affect absorption of cotinine and therefore needs to be included in the stratification.

Reviewer #3: This reviewer would like to thank the authors for addressing all of the listed reviewer concerns. Overall, the study design and analytic approach is more clearer than the originally submitted version.

It is evident to this reviewer that the authors however did not seek the counsel of a professional English editor rather that of a native-English speaker that has missed grammatical and syntax issues within the manuscript. The following minor issues were caught by this reviewer and should be considered by the authors:

Page 3- First sentence of first paragraph. ".is responsible FOR its addictive effect" not the word "OF".
Page 5 - First sentence of first paragraph. This reviewer believes the authors meant to say "passive some exposure at home" not passive smoking at home.

Page 5 - Salivary Cotinine paragraph "then we FROZE it at." not Frozen
Page 6 - Paragraph labeled Variables second sentence: it should be "who did not seriously consider quitting." not "considering".

Carta a los Editores relativa al rechazo del manuscrito

From: ees.pm.2ec.bbbfc.b9e2f826@eesmail.elsevier.com
[mailto:ees.pm.2ec.bbbfc.b9e2f826@eesmail.elsevier.com] On Behalf Of Esteve Fernandez
Sent: Wednesday, September 15, 2010 6:36 AM
To: PM (ELS)
Subject: Author query PM-10-162R1

Please enter your name, e-mail address and query below, then click 'Preview and Send'.

Name: Esteve Fernández
E-mail address: efernandez@iconcologia.net

Dear Editors:

We received a few days ago the rejection e-mail regarding our manuscript PM-10-162R1. First of all, we honestly want to thank you for the consideration and time invested in its review. However, as you may understand, we are a bit disappointed with the final decision after our extensive revision. We are conscious that the decision is already made but we would want to make a few considerations because we do not fully understand the basis of your decision.

We believe that the concerns made by reviewer #2 (some of them focused in comments firstly raised by another reviewer) can be addressed. First, about the rationale, we want to mention that the comment was done within a large paragraph and related to other comments, and hence we tried to answer them jointly. In fact, we extended the initial Introduction to address it. We don't agree about the interpretation of the potential spurious results and tried to justify it. We agree that adjustment for multiple testing is possible, but we found more appropriate not to complicate the paper. Following with reviewer's #2 comments, we believe that the scope of our paper was not to translate the results into "pharmacotherapy dosing". This goal is clearly beyond the study's aim. We believe that this is clearly indicated in the Conclusion section - that we believed to have improved thanks to the reviewers' comments. Regarding the inclusion of hypothesis, we believe that our response is extremely clear. In the reporting epidemiologic studies it is common (almost 100%) to omit the hypothesis since the objectives are clearly indicative of them. Moreover, the Editors recommended to shortening the manuscript, and thus we believed not necessary to extend on this. If the Editors believe that the hypothesis is necessary, it is easy to include the sentence as written for the response. Finally, although we preferred not to expand the manuscript with further details about BMI and cotinine, if this is so important for the reviewer and Editors we would easily expand the Methods as indicated in our response.

We kindly disagree with your vision that these are many issues to be addressed, since some of them seem to obey to the reviewer #3 satisfaction with our response (eg, reviewer #3 does not indicate problems with our response, except English usage, while reviewer #2 even elaborates about what the other reviewers pointed out). To conclude, we want just to remark we did our best to shortening the manuscript, with the constraint that we had to add new text to address most of the reviewers' comments --two goals difficult to conciliate.

We thank you very much for your consideration and time. We are aware that disagreement with a final decision (and ask a "re-review") is not usual, but we look forward to your understanding about our sincere and friendly reaction. We appreciate your commitment with Preventive Medicine that is a reference journal in the fields of epidemiology and public health.

With best regards from Barcelona,

Esteve.-

Respuesta del Editor

De: ees.pm.33d.bbf62.f226a7d6@eesmail.elsevier.com
[mailto:ees.pm.33d.bbf62.f226a7d6@eesmail.elsevier.com] En nombre de Alfredo Morabia
Enviado el: 16 setembre 2010 06:06
Para: efernandez@iconcologia.net
CC: preventive.medicine@qc.cuny.edu; Herman.VanOyen@wiv-isp.be
Asunto: Editor query PM-10-162R1

Journal title: Preventive Medicine
Corresponding author: Dr. Esteve Fernandez
Article title: Stages of change, smoking characteristics, and cotinine concentration in smokers - setting priorities for smoking cessation
Manuscript number: PM-10-162R1

Dear Dr Fernandez,

Thank you for your message. Our decisions are final but you always have the option to resubmit a new manuscript after having addressed the reviewer and editorial comments. We will then re-evaluate the paper and eventually send it out for a new review process.

Please understand, however, that our decision is based on what we believe is a realistic assessment that you need more space than we can give you to prepare a paper that can successfully pass the reviewer scrutiny. A revised, shorter submission may still fail to convince our reviewers. We therefore advise that you submit your work to a more specialized journal which will be interested in a long paper. At PM, we prioritize and give more space to articles about community interventions and, unfortunately, this is not what your study is.

We are sorry to disappoint you this time.

Most sincerely,

Alfredo Morabia, MD, PhD, FRCPE
Editor-in-Chief
&
Michael C. Costanza, PhD
Editor- Statistics
&
Herman Jozef Van Oyen, MD, DrPH, MPH, DTM&H
Associate Editor
Preventive Medicine

Respuesta al Editor

Dear Editors:

We thank very much your prompt answer to our message. We now understand better the decision. We also appreciate the possibility to submit a new manuscript, in the good understanding that you will re-evaluate it and eventually send it out for review.

We believe that our manuscript targets the audience of Preventive Medicine, but fully understand that some improvements are still needed, including a reduction in manuscript length. Thus, during the next weeks we will try to simplify the manuscript in order to be more concise but incorporating the suggestions already made.

Again, thanks for your consideration and valuable help with the manuscript.

Best regards,

Esteve.-

Segundo envío del manuscrito – Carta de presentación al Editor

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L'Hospitalet de Llobregat, November 5th, 2010.

Prof. Alfredo Morabia
Editor-in-Chief, Preventive Medicine

Dear Prof. Morabia:

We thank the opportunity to resend our manuscript **"Stages of change, smoking characteristics, and cotinine concentration in smokers: setting priorities for smoking cessation"** for your consideration in *Preventive Medicine* as an *Original Research Paper*. This manuscript was already reviewed and rejected under the number code PM-10-162R1. As suggested, we try a new submission. We now submit a fully revised manuscript in which we have taken into consideration all reviewers' and editor's comments. We have shortened the manuscript according to the guidelines, and it has been also revised by a professional English editor.

As we explained in such occasion, this study is based in the same population of that used in the study from Martínez-Sánchez et al. published in your journal [Prev Med. 2009; 48: 218-23]. The report now submitted is focused on smokers, and we studied the relationship between salivary cotinine concentration and readiness to quit smoking according to the stages of change model by Prochaska and DiClemente. Few studies have focused on both aspects in representative samples of smokers from the general population, but mostly in selected samples of smokers --generally seeking help for cessation. We believe our results may be of interest of the international audience of *Preventive Medicine*.

All the authors carefully read the manuscript and fully approve of it. In their name I also declare that the manuscript is original and it is not submitted anywhere other than your journal. The authors declare to have no conflict of interest. We would of course be ready to provide further information about our data and methods you desire.

Correspondence about the manuscript should be addressed to me as indicated in the first page of the manuscript.

Thank you very much for your kind attention.

Yours sincerely,

Esteve Fernandez, MD, PhD
Director, Tobacco Control Unit, Institut Català d'Oncologia
Associate Professor, Department of Clinical Sciences, Universitat de Barcelona
E-mail: efernandez@iconcologia.net

Decisión del Editor

De: "PM (ELS)" <pm@elsevier.com>
Data: 7 de desembre de 2010 21:49:31 GMT+01:00
Per a: efernandez@iconcologia.net
A/c: preventive.medicine@qc.cuny.edu
Tema: PM-10-694: Final Decision

Ms. No.: PM-10-694
Title: STAGES OF CHANGE, SMOKING CHARACTERISTICS, AND COTININE CONCENTRATIONS IN SMOKERS: SETTING PRIORITIES FOR SMOKING CESSATION
Corresponding Author: Dr. Esteve Fernandez
Authors: Marcela Fu; José A Pascual; Jose M Martínez-Sánchez; Antoni Agudo; Albert Moncada; Manel Nebot; Josep M Borràs; DCOT Study Investigators

Dear Dr. Fernandez,

We are pleased to inform you that your manuscript, referenced above, has been accepted for publication in Preventive Medicine.

PLEASE, when you receive the galleys, add to the Method section whether the whiskers of the boxplots have been set to percentiles 2.5 and 97.5 or 10 and 90.

Your manuscript has been forwarded to Elsevier's Production Department. You will be contacted by them in the near future regarding the proofs of your article.

Thank you for submitting your paper to Preventive Medicine.

Most sincerely,

Alfredo Morabia, MD, PhD, FRCPE
Editor-in-Chief
&
Michael C. Costanza, PhD
Editor- Statistics
Preventive Medicine

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6. Proceso editorial del artículo publicado en:

Adicciones

Carta de presentación al Editor

ICO
Institut Català d'Oncologia

UNIVERSITAT DE BARCELONA

L'Hospitalet de Llobregat, 22 de septiembre de 2010.

Dr. Amador Calafat
Director
Adicciones

Apreciado Dr. Calafat,

Me dirijo a usted para solicitar la revisión de nuestro manuscrito **"Dependencia a la nicotina y motivación para dejar de fumar en la población"** para su consideración en Adicciones como *Artículo Original*.

Este trabajo describe conjuntamente el grado de dependencia física y la motivación para dejar de fumar (utilizando como marco de referencia los estadios del cambio de Prochaska y DiClemente) en fumadores adultos, sobre la base de una muestra representativa de la población española. Creemos que este trabajo contribuye al estudio de las características de los fumadores en España, ya que hasta donde sabemos no existe otro estudio que describa conjuntamente ambos aspectos del tabaquismo a nivel nacional. Este trabajo ha sido parcialmente financiado por la Comisión Europea (proyecto de la European Network for Smoking Prevention), el Instituto de Salud Carlos III del Ministerio de Sanidad (Red Temática de Investigación en Cáncer), y el Department d'Universitats i Recerca de la Generalitat de Catalunya. Este estudio no tiene ningún tipo de conexión con la industria del tabaco y todos los autores declaran que no tienen conflictos de intereses. Todos ellos cumplen los criterios de autoría y han otorgado su aprobación a la versión final. En su nombre declaro que este manuscrito es original y que no ha sido enviado a ninguna otra revista más que a Adicciones. En caso de ser publicado, los autores transfieren los derechos de copyright del artículo a la revista Adicciones.

Estamos gustosos de proporcionarle cualquier información adicional relacionada con nuestro estudio que considere oportuno. La correspondencia sobre el manuscrito debería ser dirigida a mí, tal y como se indica en la primera página del mismo.

Muchas gracias por su amable atención. Le saluda cordialmente,

Marcela Fu, BSc.
Unidad de Control del Tabaquismo, Institut Català d'Oncologia
Email: mfu@iconcologia.net

Decisión del Editor

De: Adicciones [mailto:secretaria@adicciones.es]
Enviado el: jueves, 09 de diciembre de 2010 18:55
Para: Fu Balboa, Marcela
Asunto: su artículo en Adicciones
Importancia: Alta

Les notificamos que su artículo titulado 'Dependencia a la nicotina y motivación para dejar de fumar en la población" ha sido aceptado para su publicación, si bien, adjunto les remitimos los comentarios hechos por el comité de redacción que rogamos tengan en cuenta, realicen las oportunas modificaciones y nos remitan también, además del artículo modificado, un informe en que contesten argumentando a las principales objeciones que les han hecho los revisores (con los que por descontado pueden discrepar).

Solicitamos acuse de recibo y quedamos a la espera de sus noticias.
Saludos cordiales.

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Informe del Revisor 1

Comentario sobre:

'Dependencia a la nicotina y motivación para dejar de fumar en la población'

El artículo merece ser publicado por la aportación significativa que hace al conocimiento del tabaquismo en dos variables tan relevantes: la dependencia y la motivación para el abandono. En su conjunto está bien redactado y elaborado y aporta consistencia en su totalidad. Da una idea clara de lo que se pretende y lo lleva a cabo.

Las siguientes consideraciones son por tanto anotaciones para que los autores consideren la posibilidad de una mejora, un perfeccionamiento del trabajo.

En primer lugar sugiero que se incluya en el Título la palabra "…población española".

No queda claro el objetivo:
En el resumen se expone que se pretende describir la dependencia y la motivación. Sin embargo en el último párrafo de la Introducción (pag. 4) se expone que se pretende investigar una posible asociación entre ambas variables. De nuevo en el apartado Métodos: Análisis Estadístico, se menciona que se realizaron cálculos de distribución y proporción, sin embargo en el último párrafo del apartado Resultados se exponen diferencias estadísticamente significativas entre los factores de la variable motivación y dependencia alta, pero no se aportan las pruebas estadísticas ni los resultados de estas pruebas. Para que quedase todo ajustado sería necesario relacionar estos apartados.
El trabajo podría quedar más completo y aportaría una información más valiosa si se respondiese a la pregunta ¿Está relacionada la dependencia con la motivación para abandonar el tabaco?

En la introducción, párrafo 2 se dice que se ha utilizado el test de Fagerström para evaluar dependencia física a la nicotina. Es del todo correcto decirlo así, ya que el test está creado para tal fin. Sin embargo Artículos recientes dudan de que únicamente se esté midiendo dependencia física (ver Rios-Bedoya, Addictive Behaviors, 2008) y no psicológica. Sugiero que los autores usen la palabra dependencia sin aclarar si es física o psicológica. En el mismo párrafo se describe el test: "consta de seis preguntas…" se debería colocar esta descripción en el apartado método, cuando se describen los instrumentos usados, tal como efectivamente se hace (por lo que sería una repetición inadecuada colocarlo en la introducción).

En la pag. 6, apartado Resultados, Primer párrafo: no queda claro lo que se pretende exponer con este párrafo. Parece que lo que pretenden los autores es presentar los porcentajes que predominan en cada factor, pero eso, si es así, hay que deducirlo, porque no lo escriben.

A pesar de que el apartado Discusión está planteado del todo correcto, deja una reflexión en el aire sin responder: Si las puntuaciones en dependencia sitúa a los fumadores en niveles de dependencia baja, ¿Por qué se fuma? En este sentido se hace una referencia en la pag. 9 segundo párrafo, al final, cuando se menciona que las mayores puntuaciones del test de dependencia se corresponden con etapas de deshabituación (lo que concuerda con estudios realizados en dispositivos que ayudan al abandono). No considero imprescindible responder a esta difícil pregunta, aunque si los autores exponen alguna hipótesis que aporte luz al lector en este sentido completaría el trabajo tan espléndido que se ha realizado.

Informe del Revisor 2

El manuscrito presentado por Fu et alii es un buen trabajo, que aborda un tema para el que no hay datos fiables en España, y que además está correctamente escrito. Aporta información necesaria en esta fase de control de la epidemia sobre la distribución de los fumadores en los diversos estadios del cambio y el grado de dependencia a la nicotina. Como existe cierta controversia acerca de si al madurar la epidemia varia el perfil de la población fumadora, a mi juicio es oportuna su publicación en la revista.

De todas maneras se apuntan algunas cosas que podrían ser revisadas para mejorar el manuscrito. Desde el punto de vista conceptual, sería oportuno encuadrar los resultados en relación con esta hipótesis (no confirmada por los datos) de que al reducirse el tabaquismo en una población, quedan los fumadores hardcore, quizás a la luz de la discusión de Simon Chapman al respecto en su último libro. Además, los datos sobre grado de dependencia también son relevantes para plantear el papel de los tratamientos farmacológicos y especializados para dejar de fumar en este contexto, algo que también puede contrastarse con los datos empíricos de uso de fármacos en España (con el trabajo en Navarra de Azagra MJ et al).

Los datos se comparan con los del estudio IBERPOC, antecedente relevante en nuestro medio pero que no son en absoluto similares y presentan una distribución peculiar con muchos menos precontempladores, algo aún más sorprendente dado que se remontan a años atrás. Quizás sería oportuno detallar más aspectos acerca de este estudio y su representatividad en la discusión. Me consta que al menos en un Congreso se presentaron datos poblacionales de estadios del cambio derivados de la ESCA 2006, que quizás pueden también incluirse en la comparación. También se pueden contrastar estos datos poblacionales con los derivados de personas que acuden a la atención primaria, o a tratamiento especializado, de los que hay referencias en nuestro medio.

Otros aspectos. Dado el cambio en el uso de teléfonos en los últimos años, con menos teléfonos fijos ligados al territorio, se sugiere mencionar este aspecto en métodos y discusión. El bajo uso de tabaco en picadura para liar puede contextualizarse temporalmente, al haberse incrementado recientemente. En la metodología, al explicar los estadios del cambio debería detallarse como se adscriben los sujetos a una u otra fase. Tanto en el resumen como en la introducción debería explicitarse que los datos utilizados se obtuvieron en 2006.

Este revisor anima a los autores a realizar un esfuerzo para mejorar el manuscrito de cara a su publicación en la revista.

Informe del Revisor 3

Valoración del trabajo titulado:

"Dependencia a la nicotina y motivación para dejar de fumar"

Buen trabajo realizado fundamentalmente desde un punto de vista de salud pública, con una rigurosa metodología.

Sin embargo considero oportuno realizar las siguientes observaciones.

1.- En la muestra seleccionada los autores encuentran un 22,5% de fumadores diarios más ocasionales, mientras que la Encuesta Nacional de Salud de 2006 dice que el 26.4% de la población española mayor de 16 años fuma a diario y un 3.1% ocasionalmente lo que nos da un 29,5% lo que supone una diferencia muy significativa que puede cuestionar los resultados.

2.- Actualmente se tiende a diferenciar entre fumar y dependencia a la nicotina, aunque es difícil en ocasiones establecer la línea divisoria, pero existe un acuerdo en que los fumadores ocasionales no son considerados dependientes a la nicotina, por lo que es cuestionable que se incluyan en la muestra para evaluar la dependencia a la nicotina.

3.- Estando plenamente de acuerdo con las conclusiones, es importante considerar a la hora de priorizar los programas a desarrollar que como ocurre en otros procesos de salud crónicos un grupo pequeño de pacientes puede requerir por su gravedad mayor atención y más recursos, lo que puede ocurrir con los pacientes con dependencia a la nicotina grave.

RESPUESTA A LOS COMENTARIOS DE LOS REVISORES

Revisor 1

1) En primer lugar sugiero que se incluya en el Título la palabra "…población española".

Agradecemos la sugerencia. Hemos agregado el término al título.

2) No queda claro el objetivo: En el resumen se expone que se pretende describir la dependencia y la motivación. Sin embargo en el último párrafo de la Introducción (pag. 4) se expone que se pretende investigar una posible asociación entre ambas variables. De nuevo en el apartado Métodos: Análisis Estadístico, se menciona que se realizaron cálculos de distribución y proporción, sin embargo en el último párrafo del apartado Resultados se exponen diferencias estadísticamente significativas entre los factores de la variable motivación y dependencia alta, pero no se aportan las pruebas estadísticas ni los resultados de estas pruebas. Para que quedase todo ajustado sería necesario relacionar estos apartados.

Hemos modificado el objetivo del estudio en la Introducción (principio de la página 5):

> *"El objetivo del presente trabajo es describir la dependencia a la nicotina y la motivación para dejar de fumar (estadios del cambio) en la población adulta española."*

Respecto a las pruebas estadísticas, comentar que no se ha realizado ningún test formal de significación estadística, sino que se han utilizado los intervalos de confianza (IC) del 95% como se describe en Métodos. Estos IC están incluidos en todas las tablas, por lo que los lectores pueden comparar fácilmente las proporciones y saber si las diferencias entre ellas son o no estadísticamente significativas (si los IC no se solapan, la diferencia entre las proporciones es estadísticamente significativa, $p<0,05$).

3) El trabajo podría quedar más completo y aportaría una información más valiosa si se respondiese a la pregunta ¿Está relacionada la dependencia con la motivación para abandonar el tabaco?

La intención del último párrafo del manuscrito era justamente ésta, pero hemos mejorado el redactado para hacerlo más explícito:

> *"(...) Existe cierta relación entre la motivación para dejar de fumar y la dependencia a la nicotina, dado que los fumadores menos dependientes se concentran en la fase de precontemplación y los más dependientes en la fase de preparación. (...)"*

4) En la introducción, párrafo 2 se dice que se ha utilizado el test de Fagerström para evaluar dependencia física a la nicotina. Es del todo correcto decirlo así, ya que el test está creado para tal fin. Sin embargo Artículos recientes dudan de que únicamente se esté midiendo dependencia física (ver Rios-Bedoya, Addictive Behaviors, 2008) y no psicológica. Sugiero que los autores usen la palabra dependencia sin aclarar si es física o psicológica.

Agradecemos la sugerencia del revisor. Hemos quitado la palabra "física" a lo largo del manuscrito, de tal forma que sólo se lee "dependencia".

5) En el mismo párrafo se describe el test: "consta de seis preguntas…" se debería colocar esta descripción en el apartado método, cuando se describen los instrumentos usados, tal como efectivamente se hace (por lo que sería una repetición inadecuada colocarlo en la introducción).

Nuevamente estamos de acuerdo con el revisor. Hemos quitado la descripción referida de la Introducción, dejando intacta la descripción de la sección Métodos, para evitar redundancias.

6) En la pag. 6, apartado Resultados, Primer párrafo: no queda claro lo que se pretende exponer con este párrafo. Parece que lo que pretenden los autores es presentar los porcentajes que predominan en cada factor, pero eso, si es así, hay que deducirlo, porque no lo escriben.

Efectivamente; es una primera descripción que se realiza de la muestra, y para ello hemos resaltado los resultados más relevantes por cada variable. No creemos necesario especificarlo, ya que se trata simplemente de una primera aproximación a los resultados.

7) A pesar de que el apartado Discusión está planteado del todo correcto, deja una reflexión en el aire sin responder: Si las puntuaciones en dependencia sitúa a los fumadores en niveles de dependencia baja, ¿Por qué se fuma? En este sentido se hace una referencia en la pag. 9 segundo párrafo, al final, cuando se menciona que las mayores puntuaciones del test de dependencia se corresponden con etapas de deshabituación (lo que concuerda con estudios realizados en dispositivos que ayudan al abandono). No considero imprescindible responder a esta difícil pregunta, aunque si los autores exponen alguna hipótesis que aporte luz al lector en este sentido completaría el trabajo tan espléndido que se ha realizado.

Agradecemos el comentario. Efectivamente, una posible explicación podría deberse a la mayor autopercepción de "control" por parte de los fumadores con una dependencia baja, al no presentar una sintomatología "egodistónica" (que no genera malestar). Sin embargo, pensamos que no es necesario profundizar en esta interesante demanda que va algo más allá del objetivo del trabajo.

Revisor 2

1) Desde el punto de vista conceptual, sería oportuno encuadrar los resultados en relación con esta hipótesis (no confirmada por los datos) de que al reducirse el tabaquismo en una población, quedan los fumadores hardcore, quizás a la luz de la discusión de Simon Chapman al respecto en su último libro.

Aunque la hipótesis del "hardening" cuenta con numerosos seguidores, son escasas las pruebas de que este fenómeno se esté produciendo realmente. Recientemente publicamos una carta (Fu et al., Addiction 2009;104(2):326-7) con resultados empíricos que muestran cómo en España la puntuación media del FTND se mantiene al mismo nivel a pesar de haberse reducido significativamente la prevalencia de fumadores en las últimas décadas. Por ello, pensamos que no es necesario encuadrar nuestra investigación bajo esta hipótesis desde el inicio, aunque más tarde en la discusión mencionemos las estrategias poblacional y de riesgo.

2) Además, los datos sobre grado de dependencia también son relevantes para plantear el papel de los tratamientos farmacológicos y especializados para dejar de fumar en este contexto, algo que también puede contrastarse con los datos empíricos de uso de fármacos en España (con el trabajo en Navarra de Azagra MJ et al).

Estamos totalmente de acuerdo con el comentario del revisor. Pensamos que las estrategias de deshabituación a nivel poblacional deberían ir dirigidas especialmente a los fumadores en precontemplación y con baja dependencia, que son los que concentran la mayor proporción de fumadores. Desde una perspectiva de la prevención de alto riesgo [Chaiton et al., J Public Health Policy 2008; 29:307-18; Rose, Int J Epidemiol 2001; 30:427-32)], se debería prestar una especial atención a los grandes fumadores. Creemos, sin embargo, algo forzado incorporar en nuestra discusión el debate sobre el impacto real o poblacional que los tratamientos farmacológicos tienen en la deshabituación, y la controversia sobre su financiación. El artículo mencionado por el revisor externo justamente pone de manifiesto que la financiación pública del tratamiento sustitutivo no se traduce en una disminución de la prevalencia en la población.

3) Los datos se comparan con los del estudio IBERPOC, antecedente relevante en nuestro medio pero que no son en absoluto similares y presentan una distribución peculiar con muchos menos precontempladores, algo aún más sorprendente dado que se remontan a años atrás. Quizás sería oportuno detallar más aspectos acerca de este estudio y su representatividad en la discusión. Me consta que al menos en un Congreso se presentaron datos poblacionales de estadios del cambio derivados de la ESCA 2006, que quizás pueden también incluirse en la comparación. También se pueden contrastar estos datos poblacionales con los derivados de personas que acuden a la atención primaria, o a tratamiento especializado, de los que hay referencias en nuestro medio.

Hemos comparado nuestros datos principalmente con el estudio IBERPOC, porque es un estudio que recoge datos de diferentes regiones de España. Creemos que no es necesario dar más detalles de este estudio que los ya aportados y discutidos de manera extensa, ya que centraría demasiado la discusión sobre él. Pero también hacemos mención a resultados de otros estudios poblacionales, incluido el referenciado por el revisor (Valverde et al. 2007; cita 23 en nuestro trabajo), justo a continuación de la referencia al estudio IBERPOC (página 10, segundo párrafo); así como a datos provenientes de estudios desarrollados en el contexto de deshabituación tabáquica (en el mismo párrafo, a continuación).

4) Dado el cambio en el uso de teléfonos en los últimos años, con menos teléfonos fijos ligados al territorio, se sugiere mencionar este aspecto en métodos y discusión.

Hemos agregado en el párrafo de limitaciones dentro de la Discusión (segundo párrafo de la página 12) una mención a este comentario del revisor:

> *"Otra limitación se deriva del hecho de haber utilizado un directorio de teléfonos fijos para la obtención de la muestra de estudio, considerando que en los últimos años el uso del teléfono móvil se ha ido extendiendo en la población, pudiendo incluso en algunos casos llegar a sustituir el uso del teléfono fijo, lo cual podría afectar a la representatividad geográfica de la muestra."*

5) El bajo uso de tabaco en picadura para liar puede contextualizarse temporalmente, al haberse incrementado recientemente.

Efectivamente, parece ser que el uso de tabaco de liar ha aumentado en el último tiempo, siendo uno de los posibles causantes el aumento del precio del tabaco. Si embargo, este estudio fue realizado durante los primeros meses de la aplicación de la ley, y no se encontraba dentro de sus objetivos el evaluar cambios en el consumo de tabaco (ni en tipo ni en cantidad), al tratarse de un estudio transversal; y el aumento del consumo de tabaco de liar se aprecia especialmente en años posteriores a nuestro estudio. Por tanto, creemos que no es necesario hacer referencia al reciente incremento en el uso de este tipo de tabaco.

6) En la metodología, al explicar los estadios del cambio debería detallarse como se adscriben los sujetos a una u otra fase.

Agradecemos el comentario. Sin embargo, hemos optado por no detallar la manera de clasificar a los fumadores según los estadios del cambio, pues creemos que la descripción de los mismos es autoexplicativa, y mencionarlo podría ser redundante. De todas, formas, si el lector estuviera interesado específicamente en este tema, puede dirigirse a la bibliografía referenciada.

7) Tanto en el resumen como en la introducción debería explicitarse que los datos utilizados se obtuvieron en 2006.

Hemos explicitado la fecha del estudio en el Resumen. En la Introducción no es necesario citarlo, dado que es un detalle metodológico y por tanto su lugar es en la sección de Métodos, donde ya se mencionaba.

Revisor 3

1) En la muestra seleccionada los autores encuentran un 22,5% de fumadores diarios más ocasionales, mientras que la Encuesta Nacional de Salud de 2006 dice que el 26.4% de la población española mayor de 16 años fuma a diario y un 3.1% ocasionalmente lo que nos da un 29,5% lo que supone una diferencia muy significativa que puede cuestionar los resultados.

Nos gustaría remarcar que el 22,5% de fumadores de nuestro estudio corresponde a la proporción de fumadores de cigarrillos. La prevalencia de fumadores en nuestro estudio es del 23,4%, cifra que representa a todos los fumadores, diarios y ocasionales (incluyendo a los fumadores que no fuman cigarrillos). De todas formas, esta cifra sigue siendo inferior a la prevalencia de fumadores (diarios y ocasionales) del 29,5% obtenida de la ENSE. La diferencia en la proporción de fumadores de ambos estudios a nivel nacional puede ser explicada por sus principales diferencias metodológicas. Por un lado, la ENSE abarca a la población de 16 y más años, mientras que en nuestro estudio se entrevistaron a individuos de 18 y más años. Por otro lado, la ENSE es una encuesta realizada cara a cara, mientras que la encuesta del EuroSurvey es una encuesta realizada telefónicamente, lo cual puede generar un sesgo de información que no podemos obviar. Vale la pena remarcar que nuestros resultados son coincidentes con la prevalencia obtenida en una encuesta sobre consumo de tabaco realizada en noviembre de 2006 por el Centro de Investigaciones Sociológicas sobre una muestra representativa de 1.501 personas de la población española ≥ 18 años mediante entrevista telefónica.
Aunque la coincidencia con esta encuesta realizada al mismo segmento de población y con idéntico método de entrevista nos hace pensar que no existen sesgos en este sentido, hemos agregado esta posible limitación en el apartado correspondiente:

> *"(...) Además, por tratarse de una encuesta telefónica, puede existir un sesgo de información debido a la deseabilidad social, reforzada por la reciente implantación de la Ley 28/2005 en el momento del trabajo de campo. Todo lo anterior podría explicar el hecho que la prevalencia de consumo en nuestro estudio sea ligeramente menor comparada con la obtenida en la Encuesta Nacional de Salud de España del año 2006[37], aunque similar a la de la encuesta del Centro de Investigaciones Sociológicas del año 2006[38]."*

En cuanto a la prevalencia de consumo, hemos añadido en la sección de descripción de la muestra en Métodos (final de la página 5) la prevalencia total de consumo de tabaco en la muestra:

> *"(...) El 23,4% eran fumadores (22,0% fumadores diarios y 1,4% fumadores ocasionales), el 27,3% eran exfumadores y el 49,2% de los participantes no había fumado nunca."*

También hemos especificado en el Resumen que nuestro análisis se realiza sobre los fumadores de cigarrillos y que el 22,5% se refiere a fumadores de cigarrillos (tanto en el Resumen como al principio de Resultados (página 7).

2) Actualmente se tiende a diferenciar entre fumar y dependencia a la nicotina, aunque es difícil en ocasiones establecer la línea divisoria, pero existe un acuerdo en que los fumadores ocasionales no son considerados dependientes a la nicotina, por lo que es cuestionable que se incluyan en la muestra para evaluar la dependencia a la nicotina.

Estamos de acuerdo en que los fumadores ocasionales tienen unas características diferentes a los fumadores diarios. Sin embargo, creemos que es correcto incluirlos en el análisis, puesto que constituyen un grupo creciente de fumadores según diversas encuestas nacionales e internacionales, como consecuencia de la disminución del consumo diario en substitución del llamado "consumo social". Por otra parte, se ha descrito y estudiado previamente la dependencia en este grupo de fumadores, especialmente entre los adolescentes, quienes pueden presentar síntomas de dependencia incluso antes de instaurarse el consumo diario (DiFranza et al., Arch Pediatr Adolesc Med 2007;161(7):704-10; Rose & Dierker, Nicotine Tob Res 2010; 12(3):278-86; Doubeni et al, Pediatrics 2010; 125(6):1127-33). De todas formas, también hemos calculado la distribución de fumadores según nuestras variables principales excluyendo a los ocasionales (n=31), y hemos encontrado unos resultados muy similares, como se puede apreciar en la tabla más abajo. Por estas razones, hemos optado por no excluirlos.

		Dependencia a la nicotina*					
		baja		Media		alta	
Estadios del cambio	**n**	**%**	**IC 95%**	**%**	**IC 95%**	**%**	**IC 95%**
precontemplación	343	73,5	68,8 - 78,1	11,1	7,8 - 14,4	15,5	11,6 - 19,3
contemplación	139	73,4	66,0 - 80,7	10,8	5,6 - 15,9	15,8	9,8 - 21,9
preparación	55	67,3	54,9 - 79,7	10,9	2,7 - 19,1	21,8	10,9 - 32,7

3) Estando plenamente de acuerdo con las conclusiones, es importante considerar a la hora de priorizar los programas a desarrollar que como ocurre en otros procesos de salud crónicos un grupo pequeño de pacientes puede requerir por su gravedad mayor atención y más recursos, lo que puede ocurrir con los pacientes con dependencia a la nicotina grave.

Sí, estamos totalmente de acuerdo con el comentario del revisor. Pensamos que las estrategias de deshabituación a nivel poblacional deberían ir dirigidas especialmente a los fumadores en precontemplación y con baja dependencia, que son los que concentran la mayor proporción de fumadores. Sin embargo, desde una perspectiva de la prevención de alto riesgo [Chaiton et al., J Public Health Policy 2008;29:307-18; Rose, Int J Epidemiol 2001;30:427-32)], se debería prestar una especial atención a los grandes fumadores.

Finalmente queremos mencionar que el término “preparación para dejar de fumar” (del inglés *readiness to quit*) es más correcto que el de “motivación para dejar de fumar” que habíamos utilizado. Por tanto, lo hemos corregido a lo largo del manuscrito. Este cambio requiere cambiar el título del manuscrito, que esperamos sea aceptado por el comité de redacción.

Comunicación de galeradas

De: Adicciones [mailto:secretaria@adicciones.es]
Enviado el: lunes, 14 de febrero de 2011 16:43
Para: Fu Balboa, Marcela
Asunto: revisión PDF de su artículo

Buenas tardes.

Por favor, lea atentamente y siga las instrucciones.

Adjunto le remitimos, en formato PDF, su artículo tal y como saldrá publicado en nuestra revista. Le rogamos que se sirva revisarlo **con urgencia** y, en caso de que haya alguna corrección a hacer, nos lo indique. En caso contrario indíquelo también, por favor.

Debe entenderse que nos referimos a posibles erratas de imprenta en el texto o en las tablas o gráficos, **no a modificaciones o ampliaciones del texto.**

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Agradecidos, quedamos a la espera de sus noticias.
Reciban un cordial saludo.

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7. Proceso editorial de la carta al Editor

publicada en: Addiction

Carta de presentación al Editor

ICO
Institut Català d'Oncologia

UNIVERSITAT POMPEU FABRA

Barcelona, July 21st, 2008

Dear Editor-in-Chief:

Please find enclosed our manuscript "A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence across countries: updated data from Spain." for your consideration in *Addiction* as an Letter to the Editor. After reading the interesting paper by Fagerström and Furberg in the May issue, we thought that the data on the prevalence of smoking and nicotine dependence in Spain were too old (from 1997) and based on a regional survey (not representative for the whole Spain). Since we conducted a cross-sectional survey in a representative sample of the general population of Spain in 2006, we believe that the updated data and a further elaboration on the "hardening hypothesis" would be of you interest.

All the authors carefully read the manuscript and fully approve of it. In their name I also declare that the manuscript is original and it is not submitted anywhere other than *Addiction*. We would of course be ready to provide further information about our data and methods you so desire.

All the persons included in the survey gave oral informed consent to participate (telephone interview) and the study was revised and approved by the Ethics and Research Committee of the Bellvitge University Hospital.

Correspondence about the manuscript should be addressed to myself as indicated in the first page of the manuscript.

Thank you very much for your kind attention. With best regards,

Esteve Fernandez, MD, PhD
Head, Tobacco Control Research Unit, Institut Català d'Oncologia
Assistant Professor, Master of Public Health, Universitat Pompeu Fabra
E-mail: efernandez@ico.scs.es

Decisión del Editor

From: Louisa Strain [mailto:louisa@addictionjournal.org]
Sent: Thursday, July 31, 2008 5:33 PM
To: efernandez@ico.scs.es
Subject: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Dr. Fernandez,

RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence across countries: updated data from Spain. [Letter to Editor]

Thank you very much for submitting the above letter to Addiction. We take letters very seriously as they are quite likely to get cited. I have sought the advice from a referee and although we think the data are potentially interesting from a national perspective it does not add substantially to the debate around hardening. Unfortunately we cannot accept your letter for publication this time.

Please accept my apologies and feel free to contact me should you have further questions.

Best wishes,

Robert West

Editor-in-Chief

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Carta al Editor relativa al rechazo de la carta

From: Fernandez Munoz, Esteve
Sent: Friday, August 01, 2008 11:48 AM
To: 'louisa@addictionjournal.org'
Subject: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Dr West:

Thank you very much for your e-mail and prompt response to our submission. However, let me cordially disagree with the points mentioned in your e-mail to reject the letter.

The letter provides updated information from one country that the authors of the Research Report should consider and incorporate in the analysis. We were surprised by the use of data of more than 10 years (not only for Spain) and from a small region within Spain, assuming that it will be representative of the whole country. We did not want in any case to flame the authors because of this or because they almost ignore it in the discussion.

We also believe that there is a contribution to a clearer understanding of the hardening hypothesis when trying to interpret inter-countries differences at the light of the stages of the development of the tobacco epidemic from the particular case of Spain (and Italy). Hence, we believe that the data presented from Spain (and the comment about Italy) are of interest to an international audience. However, it is clear now to me that the 7th paragraph explaining the recent progress in tobacco control in Spain does not fit with the aim of the letter.

Finally, we also provide clear indications of a different approach (not published to our knowledge) to further investigate the hardening hypothesis, such as the analysis over time for several years within countries of the joint evolution of smoking prevalence and nicotine dependence.

I would ask, if at all possible, you reconsider your initial decision following this clarification. I understand and know how difficult is to manage and handle with submissions, and of course, will accept your final decision.

Again, thank you very much for your kind attention and valuable time. Looking forward to hearing from you,

Sincerely

Esteve Fernandez.-

Esteve Fernández, MD, PhD
Head, Tobacco Control & Research Unit, Cancer Prevention & Control Dept, Institut Català d'Oncologia
Assistant Professor of Epidemiology & Biostatistics, Dept. of Clinical Sciences, Universitat de Barcelona
www.xtpt.net/efm.htm
www.researcherid.com/rid/A-9750-2008

Pregunta del *Commissioning Editor*

From: Louisa Strain [mailto:louisa@addictionjournal.org]
Sent: Thursday, August 28, 2008 5:41 PM
To: 'Fernandez Munoz, Esteve'
Subject: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Dr Fernandez,

RE: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence...

It has fallen to me as Commissioning Editor to handle your appeal regarding your letter to the editor. I was wondering if I might ask you for a bit further detail. Your letter appears to me to be based on the premise that your survey is more generalisable than the data presented by Fagerström. However, I find I have no way of determining this from the method you describe in the letter - no doubt because of tight word limits - and I am afraid my Spanish language skills are not up to reading the methodology of the paper you reference. So could I ask you to detail your methodology for me in greater detail. Specifically, CATI surveys generally fail to adequately reach groups of lowers socio-economic status, who also happen to be those who are most resistant to changing their substance use (and smoking) patterns. Could you outline for me the measure you undertook to address this common flaw and any other possible biases of the CATI method.

Many thanks

Peter Miller - Commissioning Editor

Respuesta al *Commissioning Editor*

De: Fernandez Munoz, Esteve
Enviado el: miércoles, 03 de septiembre de 2008 14:55
Para: louisa@addictionjournal.org
Asunto: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Dr. Miller,

Thank you very much for your e-mail and consideration. I'm sorry for the delay in my response, but I was out of the office still on holidays at the end of August.

Our letter is based on two premises:

1) the data from Spain in the paper, although of value, derive from Galicia, a region with a slight higher prevalence of smoking (38%) than the overall nation (33%, derived form the Spanish National Health Interview Survey for the same year 1997);

2) but of more concern was the fact that the data were 10 years old (and hence we thought that updated data would be of interest).

Unfortunately, at the time Fagerstrom and Furberg wrote the paper, no other population data on smoking including the FTND was available, including our 2006 survey. In this cross-sectional survey on smoking, we included the FTND for current smokers. This was the reason we wrote the letter to update the prevalence rate of smoking and the mean FTND score for Spain. We also elaborated on the meaning of the inter-countries differences considering the stages of progression of the tobacco epidemic (Lopez model), a point not addressed by Fagerstrom and Furberg beside the differences in the data presented (surveys from different countries in different calendar years).

Regarding our survey, a version in English of our paper has been just published: the journal "Revista Española de Cardiología" is published in print in Spanish but there is an English version on the web (that appears with some weeks of delay to the Spanish version, not available at the time we wrote the letter). I'm attaching a PDF file with it.

As you may read in our paper, we prepared a theoretical sample adjusted for region (Autonomous communities), size of the municipality, sex, and age, and allowed substitutions of non-respondents by persons in the same strata. CATI surveys may lead to selection biases and we tried to avoid them using a two phase strategy for participants' selection: in the first phase we chose homes (not persons) from a directory of fixed telephones and thereafter, in the second phase, we selected a person from the home corresponding to the strata previously defined. It is important to note that the real problem in our country with CATI surveys is not the lack of telephone in less-favoured or deprived social groups (as seen in the U.S., for example), since telephone services were considered a "public service" and spread over all the population without almost social differences. The problem we tried to solve with the two phase strategy was the new phenomenon of mobile (cellular) telephones: we were afraid by the "feeling" that young people have opted to use only cell phones, which are not listed in the traditional phone directories. With our strategy, we selected homes and persons within homes, not sampling directly the persons, and hence being able to fit the theoretical sample.

The final sample interviewed was representative of the Spanish general population in terms of the stratification variables and also educational level.

Also discussed in the paper attached, we are confident with our data since a survey on smoking conducted some months later (in 2006) by the National Center for Sociological Research (CIS) provided similar figures on smoking prevalence. Both surveys were conducted independently --we knew about the CIS survey during the peer review process of our manuscript thanks to a reviewer's comment.

We believe that our survey is almost free (impossible to say completely free, of course) of selection bias due to the CATI method used.

Again, thanks for your consideration and valuable time. I hope that the answer provided together with the attached paper may help you in the evaluation of our appeal. Please, do not hesitate to contact me if further clarifications are needed.

Best regards,

Esteve.-

Esteve Fernández, MD, PhD
Head, Tobacco Control Research Unit, Cancer Prevention & Control Dept, Institut Català d'Oncologia
Assistant Professor, Dept . of Experimental & Health Sciences, Master of Public Health, Universitat Pompeu Fabra www.xtpt.net/efm.htm
www.researcherid.com/rid/A-9750-2008

Respuesta del *Commissioning Editor*

From: Louisa Strain [mailto:louisa@addictionjournal.org]
Sent: Tuesday, September 23, 2008 1:14 PM
To: 'Fernandez Munoz, Esteve'
Subject: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Esteve,

RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence

Thank you for your e mail and apologies for the delay in responding to you. I have read your letter carefully and have sought the advice of an editorial colleague who has made some suggested changes to your letter (see attached document). If you are happy with these amendments we can go to publication.

I will look forward to hearing from you shortly,

Kind regards,

Peter

Peter Miller, Commissioning Editor

Respuesta al *Commissioning Editor*

From: Fernandez Munoz, Esteve
Sent: Monday, September 29, 2008 12:54 PM
To: 'louisa@addictionjournal.org'
Subject: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Peter,
Thank you very much for your kind e-mail I received past week, whilst out of the office (and with poor internet connection).

I will share with my co-authors your suggestion and reply you as soon as possible. As a first reaction, I feel that the original sense of our letter is not in the revised version you sent, and would try to shorten it but maintaining the original meaning. I'll send you a detailed response within the next days.

With best regards,
Esteve,-

Esteve Fernández, MD, PhD
Head, Tobacco Control Research Unit, Cancer Prevention & Control Dept, Institut Català d'Oncologia
Assistant Professor, Dept. of Clinical Sciences, Campus of Bellvitge, Universitat de Barcelona
Editor-in-Chief, Gaceta Sanitaria (Journal of the Spanish Society of Public Health)
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Respuesta a los cambios sugeridos por los editores

De: Fernandez Munoz, Esteve
Enviado el: miércoles, 01 de octubre de 2008 18:02
Para: louisa@addictionjournal.org
Asunto: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision
Importancia: Alta

Dear Peter,
First of all, let me express again my gratitude for your kind attention.
We have revised the edited version you sent, and agree with almost all the changes introduced. We understand that some of the paragraphs are not necessary and we are ready to delete them. However, we don't agree with the new paragraph introduced because of two reasons:

1) As the editorial colleague did, our first reaction was to compute the "corrected" correlation coefficient using our new figures for Spain and that already provided by Fagerström and Furberg in the paper. We also try to replicate the correlation coefficient shown by them (-0.73) with the available data, and obtained an r=-0.67. Why? Simply because the prevalence rates in Table 2 of the original paper are rounded without decimal figures. Then, we opted not to compute the new "r" and even thought that this could be part of the reply of the authors to our letter (using the actual prevalence rates and not the rounded values). We cannot compare the newly estimated r=-0.56 with that published (r=-0.73) and believe that, if computed with the actual values, the difference between them would reduce to less than one decimal point;
2) We don't think nor have suggested in our letter that the updated Spanish data go against the hardening hypothesis. In fact, a change in the correlation coefficient of less than 1 decimal point does not provide support for such a strong statement –hope you will agree with me. And "why" does this occur should be then addressed. On the contrary, the intention of our letter is, from the basis that the hardening hypothesis is appealing, to highlight the need to put into the context of the different development of the tobacco epidemic across countries. This was the aim of one of the paragraphs deleted (6th paragraph, that in the new version has been shortened to 2 brief sentences), and also of the last paragraph, mentioning a possible way for future research –this is, trend analysis across time of the association between dependence and prevalence within countries (we have not identified such studies in the literature).

Thus, we have revised the letter taking into account your revision and the comments above. We would greatly appreciate, if at all possible, your considering the attached new version for publication. Again, thank you very much for your valuable time and patience.

Kind regards,

Esteve.-

Esteve Fernández, MD, PhD
Head, Tobacco Control Research Unit, Cancer Prevention & Control Dept, Institut Català d'Oncologia
Assistant Professor, Dept. of Clinical Sciences, Campus of Bellvitge, Universitat de Barcelona
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www.researcherid.com/rid/A-9750-2008

Respuesta del *Commissioning Editor*

From: Louisa Strain [mailto:louisa@addictionjournal.org]
Sent: Monday, October 13, 2008 5:08 PM
To: 'Fernandez Munoz, Esteve'
Subject: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Esteve,

RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence

Apologies for the delay in responding to you, I have now had a chance to look over your comments and consider your proposed changes. I am happy with your first point, but am afraid I am not willing for a letter to go into a discussion of 'why'. It is simply too brief to provide a meaningful analysis and think this should be left for a research report or review article - I hope you understand. With that in mind, I suggest deleting the following sentence: "*The different pattern observed could be likely attributed to differences in the development of the tobacco epidemic in Spain where, as compared to the USA and Northern European countries, smoking spread among the population with some decades of delay and did not achieve similar high prevalence rates –and not similar dependence levels [10]*". I would also prefer that you find a peer-reviewed article to reference in place of number 7 - which appears to a conference presentation, or delete the reference entirely and name the study.

If you can accept these two changes, we can move to publication.

Kind regards

Peter Miller

Respuesta a los cambios sugeridos por el *Commissioning Editor*

De: Fernandez Munoz, Esteve
Enviado el: martes, 14 de octubre de 2008 9:33
Para: louisa@addictionjournal.org
Asunto: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Peter,
Thank you very much for your e-mail and consideration of our letter.
We understand your reasons to avoid the "why" in such a short piece of work as letters are. Hence, we are ready to accept this change and also the change about the reference of the European study (you are right, it refers to unpublished results presented a congress).
Please find enclosed the letter with the requested changes already done.
Again, thank you very much for your kind attention.
Best regards from Barcelona,
Esteve.-

Esteve Fernández, MD, PhD
Head, Tobacco Control Research Unit, Cancer Prevention & Control Dept, Institut Català d'Oncologia
Assistant Professor, Dept. of Clinical Sciences, Campus of Bellvitge, Universitat de Barcelona
Editor-in-Chief, Gaceta Sanitaria (Journal of the Spanish Society of Public Health)
www.xtpt.net/efm.htm
www.researcherid.com/rid/A-9750-2008

Decisión final del Editor

From: Louisa Strain [mailto:louisa@addictionjournal.org]
Sent: Monday, October 27, 2008 12:40 PM
To: 'Fernandez Munoz, Esteve'
Subject: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Esteve,

RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence...

Peter is now happy with your letter, if you could very kindly accept all the changes and update the reference list (I have attached the latest version) we can go to publication. Please be sure to include any conflicts of interest you may have.

Kind regards, Louisa

Respuesta al Editor

Dear Louisa,
Thank you very much for your e-mail and acceptance of the letter for publication in Addiction. We are now very happy, too.
Please find enclosed the latest version with the list of references updated. We have added the conflict of interests (none) and acknowledgements (to funding sources) previously missed statements.
We thank very much again your kind attention and help.
With best regards,
Esteve

Esteve Fernández, MD, PhD
Head, Tobacco Control Research Unit, Institut Català d'Oncologia
Assistant Professor, Dept. of Clinical Sciences, Campus of Bellvitge, Universitat de Barcelona
Editor-in-Chief, Gaceta Sanitaria (Journal of the Spanish Society of Public Health)

Respuesta del Editor

De: Louisa [mailto:louisa@addictionjournal.org]
Enviado el: lunes, 03 de noviembre de 2008 16:27
Para: Fernandez Munoz, Esteve
CC: Fu Balboa, Marcela; 'Maria José López'; Martinez Sanchez, Jose Maria; monica.perez.rios@usc.es
Asunto: RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence... Decision

Dear Esteve,

RE: 08-0564 A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence...

Peter is now happy with your letter and we will send to the publishers.

Kind regards, Louisa