Universidad de Alcalá
COMISIÓN DE ESTUDIOS OFICIALES
DE POSGRADO Y DOCTORADO

ACTA DE EVALUACIÓN DE LA TESIS DOCTORAL

Año académico 2018/19

DOCTORANDO: **RODRÍGUEZ MIGUEL, ANTONIO**
D.N.I./PASAPORTE: ****2611M**

PROGRAMA DE DOCTORADO: **D422-EPIDEMIOLOGÍA Y SALUD PÚBLICA**
DPTO. COORDINADOR DEL PROGRAMA: **CIRUGÍA, CIENCIAS MÉDICAS Y SOCIALES**
TITULACIÓN DE DOCTOR EN: **DOCTOR/A POR LA UNIVERSIDAD DE ALCALÁ**

En el día de hoy 25/07/19, reunido el tribunal de evaluación nombrado por la Comisión de Estudios Oficiales de Posgrado y Doctorado de la Universidad y constituido por los miembros que suscriben la presente Acta, el aspirante defendió su Tesis Doctoral, elaborada bajo la dirección de **FRANCISCO JOSÉ DE ABAJO IGLESIAS // MIGUEL GIL GARCÍA.**

Sobre el siguiente tema: *QUIMIOPROFILAXIS DEL CÁNCER COLORRECTAL CON ANTIAGREGANTES PLAQUETARIOS, ANALGÉSICOS Y ANTIINFLAMATORIOS NO ESTEROIDEOS YOTROS FÁRMACOSPARA EL CONTROL DEL DOLOR*

Finalizada la defensa y discusión de la tesis, el tribunal acordó otorgar la CALIFICACIÓN GLOBAL[1] de (**no apto, aprobado, notable y sobresaliente**): SOBRESALIENTE

Alcalá de Henares, 25 de Julio de 2019

EL PRESIDENTE | EL SECRETARIO | EL VOCAL

Fdo.: FRANCISCO BOLÚMAR MONTRULL | Fdo.:ELISA MARTÍN MERINO | Fdo.: LUCÍA CEA SORIANO

Con fecha 23 de septiembre de 2019 la Comisión Delegada de la Comisión de Estudios Oficiales de Posgrado, a la vista de los votos emitidos de manera anónima por el tribunal que ha juzgado la tesis, resuelve:

☒ Conceder la Mención de "Cum Laude"
☐ No conceder la Mención de "Cum Laude"

La Secretaria de la Comisión Delegada

FIRMA DEL ALUMNO,

Fdo.: RODRÍGUEZ MIGUEL, ANTONIO

[1] La calificación podrá ser "no apto" "aprobado" "notable" y "sobresaliente". El tribunal podrá otorgar la mención de "cum laude" si la calificación global es de sobresaliente y se emite en tal sentido el voto secreto positivo por unanimidad.

INCIDENCIAS / OBSERVACIONES:

Universidad de Alcalá

VICERRECTORADO DE INVESTIGACIÓN
Y TRANSFERENCIA

En aplicación del art. 14.7 del RD. 99/2011 y el art. 14 del Reglamento de Elaboración, Autorización y Defensa de la Tesis Doctoral, la Comisión Delegada de la Comisión de Estudios Oficiales de Posgrado y Doctorado, en sesión pública de fecha 23 de septiembre, procedió al escrutinio de los votos emitidos por los miembros del tribunal de la tesis defendida por ***RODRÍGUEZ MIGUEL, ANTONIO***, el día 25 de julio de 2019, titulada, *QUIMIOPROFILAXIS DEL CÁNCER COLORRECTAL CON ANTIAGREGANTES PLAQUETARIOS, ANALGÉSICOS Y ANTIINFLAMATORIOS NO ESTEROIDEOS YOTROS FÁRMACOSPARA EL CONTROL DEL DOLOR* para determinar, si a la misma, se le concede la mención "cum laude", arrojando como resultado el voto favorable de todos los miembros del tribunal.

Por lo tanto, la Comisión de Estudios Oficiales de Posgrado y Doctorado **resuelve otorgar** a dicha tesis la

MENCIÓN "CUM LAUDE"

EL VICERRECTOR DE INVESTIGACIÓN Y TRANSFERENCIA
F. Javier de la Mata de la Mata
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Doctorando: RODRÍGUEZ MIGUEL, ANTONIO
Secretario del Tribunal: ELISA MARTÍN MERINO
Directores de Tesis: FRANCISCO JOSÉ DE ABAJO IGLESIAS // MIGUEL GIL GARCÍA

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DILIGENCIA DE DEPÓSITO DE TESIS.

Comprobado que el expediente académico de D./Dª Antonio Rodríguez Miguel reúne los requisitos exigidos para la presentación de la Tesis, de acuerdo a la normativa vigente, y habiendo presentado la misma en formato: ☒ soporte electrónico ☐ impreso en papel, para el depósito de la misma, en el Servicio de Estudios Oficiales de Posgrado, con el nº de páginas: 167 se procede, con fecha de hoy a registrar el depósito de la tesis.

Alcalá de Henares a 27 de mayo de 2019

Aurora Juárez Abril

Fdo. El Funcionario

Programa de Doctorado en Epidemiología y Salud Pública

QUIMIOPROFILAXIS DEL CÁNCER COLORRECTAL CON ANTIAGREGANTES PLAQUETARIOS, ANALGÉSICOS Y ANTIINFLAMATORIOS NO ESTEROIDEOS Y OTROS FÁRMACOS PARA EL CONTROL DEL DOLOR

Tesis Doctoral presentada por

ANTONIO RODRÍGUEZ MIGUEL

Director: Dr. Francisco José de Abajo Iglesias
Co-director: Dr. Miguel Jesús Gil García

Alcalá de Henares, 2019

Francisco Bolúmar Montrull, Coordinador de la Comisión Académica del Programa de Doctorado en _Epidemiología y Salud Pública__

INFORMA que la Tesis Doctoral titulada **Quimioprofilaxis del cáncer colorrectal con antiagregantes plaquetarios, analgésicos y antiinflamatorios no esteroideos y otros fármacos para el control del dolor**, presentada por **D/_Antonio Rodríguez Miguel_,** bajo la dirección de los Drs. Francisco de Abajo y Miguel Gil, reúne los requisitos científicos de originalidad y rigor metodológicos para ser defendida ante un tribunal. Esta Comisión ha tenido también en cuenta la evaluación positiva anual del doctorando, habiendo obtenido las correspondientes competencias establecidas en el Programa, y en particular el número y calidad de las publicaciones.

Para que así conste y surta los efectos oportunos, se firma el presente informe en Alcalá de Henares a _27_ de_Mayo_ de _2019_

Fdo.:__Francisco Bolúmar Montrull__

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D. FRANCISCO JOSÉ DE ABAJO IGLESIAS, CATEDRÁTICO DE UNIVERSIDAD DEL ÁREA DE CONOCIMIENTO DE FARMACOLOGÍA, DE LA UNIVERSIDAD DE ALCALÁ,

CERTIFICA: que el trabajo: "Quimioprofilaxis del cáncer colorrectal con antiagregantes plaquetarios, analgésicos y antiinflamatorios no esteroideos y otros fármacos para el control del dolor", ha sido realizado por D. Antonio Rodríguez Miguel bajo mi dirección, y cumple todos los requisitos para su defensa pública como Tesis Doctoral.

Alcalá de Henares, a 24 de mayo de dos mil diecinueve.

UNIVERSIDAD DE ALCALÁ · DEPARTAMENTO DE CIENCIAS BIOMÉDICAS ·

Prof. Francisco J. de Abajo Iglesias

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D. MIGUEL GIL GARCÍA, EPIDEMIÓLOGO DE LA AGENCIA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS DEL MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL,

CERTIFICA: que el trabajo: "Quimioprofilaxis del cáncer colorrectal con antiagregantes plaquetarios, analgésicos y antiinflamatorios no esteroideos y otros fármacos para el control del dolor", ha sido realizado por D. Antonio Rodríguez Miguel bajo mi co-dirección, y cumple todos los requisitos para su defensa pública como Tesis Doctoral.

Madrid, a 29 de mayo de dos mil diecinueve.

Dr. Miguel Gil García

A todos los voluntarios, profesionales sanitarios e investigadores que siguen trabajando, a pesar de las dificultades, en la lucha contra el cáncer

ÍNDICE

AGRADECIMIENTOS

El autor quiere agradecer la indispensable colaboración de todos los médicos de atención primaria y pediatras que participan en BIFAP, así como a todo el equipo que forma el proyecto BIFAP por su ayuda y apoyo en el acceso a los recursos de la base de datos. Todas las opiniones expresadas, tanto en el texto de esta tesis doctoral como en los artículos incluidos, representan a las de los autores y no necesariamente a las de las instituciones implicadas. Por último, también quiero agradecer al Profesor Antonio G. García y a todo el equipo del Instituto Teófilo Hernando su apoyo durante todo el estudio.

1. GLOSARIO

AAS: ácido acetilsalicílico

AINE: análgesicos y antiinflamatorios no esteroideos

BIFAP: Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria

CCAA: comunidades autónomas

CIAP: clasificación internacional en atención primaria

CIE: clasificación internacional de enfermedades

CN: condicionante, en BIFAP

COX-1: ciclooxigenasa-1

COX-2: ciclooxigenasa-2

DI: diagnóstico, en BIFAP

IBP: inhibidores de la bomba de protones

IC 95%: intervalo de confianza al 95%

NT: antecedente personal, en BIFAP

OR: odds ratio

PGE_2: prostaglandina E2

REDECAN: Red Española de registros de Cáncer.

SYSADOA: symptomatic slow-acting drugs for osteoarthritis

TXA_2: tromboxano A_2

USPSTF: United States Preventive Services Task Force

VPN: valor predictivo negativo

VPP: valor predictivo positivo

2. RESUMEN

Título

"Quimioprofilaxis del cáncer colorrectal con antiagregantes plaquetarios, analgésicos y antiinflamatorios no esteroideos y otros fármacos para el control del dolor"

Introducción

El cáncer colorrectal es uno de los tipos de cáncer más frecuentes, contando ambos sexos, en los países desarrollados. Además de factores hereditarios, existen otros íntimamente relacionados con los hábitos de vida occidentales. En los países más desarrollados, el diagnóstico precoz y los tratamientos han mejorado en los últimos años, lo que ha hecho aumentar la supervivencia en estos pacientes. Además de una estrategia de prevención primaria basada en la modificación de ciertos hábitos de vida, existen otras intervenciones que se podrían añadir, como la quimioprofilaxis. Se han publicado numerosos estudios en los que se ha reportado una reducción de riesgo de desarrollo de cáncer colorrectal asociado al uso de diferentes fármacos como ácido acetilsalicílico (AAS) a dosis bajas, analgésicos y antiinflamatorios no esteroideos (AINE), terapia hormonal sustitutiva, bisfosfonatos y estatinas, entre otros.

Se ha descrito que en la génesis del cáncer colorrectal podrían intervenir diferentes factores, uno de ellos es la inflamación mediada por la actividad de la ciclooxigenasa-2 (COX-2). La COX-2 es una enzima, que, en general, no está presente de forma constitutiva en las células, pero es rápidamente inducible por estímulos inflamatorios. La expresión de la COX-2 conlleva a la producción de diferentes prostaglandinas,

fundamentalmente, la protaglandina E_2 (PGE_2), que es la prostaglandina principal derivada de la actividad COX-2. Concretamente, los niveles altos de PGE_2 en el tejido se han relacionado con el desarrollo tumoral debido a su actividad antiapoptótica, estimuladora del crecimiento celular y favorecedora de la migración e invasión celular. Además, se ha observado que, un porcentaje alto de adenomas y adenocarcinomas, sobre-expresan la COX-2. En el proceso inflamatorio también intervienen las plaquetas. Éstas son activadas por diferentes estímulos, como, por ejemplo, en respuesta a un daño tisular, liberando al medio el contenido de sus gránulos alfa. Estos gránulos contienen en su interior gran cantidad de sustancias como prostanoides, factores de crecimiento y factores angiogénicos, que, sobre las células adyacentes, estimulan el proceso inflamatorio en la zona, induciendo, entre otras, la expresión de la COX-2. Además, se ha observado que las plaquetas pueden formar agregados alrededor de las células tumorales, impidiendo el reconocimiento y la destrucción de estas células por el sistema inmune.

La farmacoepidemiología como ciencia que estudia los efectos del uso de los medicamentos en las poblaciones, utilizando para ello, el método y razonamiento epidemiológicos, siempre se ha servido del análisis de grandes cantidades de datos. El uso de grandes bases de datos automatizadas para investigación epidemiológica comenzó en los años 80 en EEUU y no ha parado de desarrollarse hasta nuestros días, siendo, en la actualidad, una fuente de información cada vez más empleada en estos estudios. Basándose en la evidencia publicada a partir de numerosos estudios farmacoepidemiológicos, en el año 2016, el *United States Preventive Services Task Force* recomendó, por primera vez, el uso del AAS a dosis bajas para la prevención primaria de eventos cardiovasculares y del cáncer colorrectal, en determinados grupos de población. Anteriormente, ya se había explorado el uso de otros AINE en diferentes ensayos clínicos

aleatorizados, concretamente de los AINE selectivos de la COX-2 o coxibes, para la prevención de adenomas, aunque esta indicación se descartó prematuramente debido a un balance beneficio-riesgo desfavorable, por los acontecimientos cardiovasculares asociados a su uso. Sin embargo, a pesar de que existen numerosos estudios farmacoepidemiológicos publicados sobre el uso de AAS a dosis bajas y AINE en la reducción del riesgo de cáncer colorrectal, aún quedan cuestiones no resueltas y es necesario caracterizar mejor dicho efecto. Por otra parte, en población mediterránea apenas se ha estudiado este efecto, siendo los pocos estudios publicados de pequeño tamaño.

Objetivos

El objetivo de estos tres estudios es, por un lado, validar el uso de la Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) para el estudio del cáncer colorrectal, y una vez validada, estudiar el efecto quimioprotector frente a cáncer colorrectal de: AAS a dosis bajas y de otros antiagregantes plaquetarios, como clopidogrel, de los AINE (excluyendo AAS) y de otros fármacos que comparten alguna indicación con los AINE como los *symptomatic slow-acting drugs for osteoarthritis* (SYSADOA; condroitín sulfato y glucosamina) y metamizol.

Métodos

Para el *estudio 1* se elaboró una estrategia de validación y se construyó un algoritmo de búsqueda de casos de cáncer colorrectal basado en búsquedas de códigos diagnósticos y texto libre, en las historias clínicas de los pacientes incluidos en BIFAP. Todos los

potenciales casos detectados se distribuyeron en 8 grupos homogéneos en función de la información detectada de cada sujeto. De estos 8 grupos se seleccionaron 100 historias de forma aleatoria que fueron revisadas de forma manual por dos investigadores entrenados y cegados a las prescripciones médicas. Una vez revisadas todas las historias clínicas, se calculó el porcentaje de verdaderos positivos, de falsos positivos y el valor predictivo positivo (VPP), de cada grupo y de forma global. Adicionalmente, para los estudios de casos y controles, este algoritmo se refinó incluyendo patrones de texto comunes a los falsos positivos confirmados en la validación anterior y la estrategia general de validación se completó con la revisión manual de todas las historias clínicas de los grupos en los que se obtuvo un VPP < 50%, en la validación general. Para calcular el valor predictivo negativo (VPN) se tomaron 100 historias clínicas de forma aleatoria de entre los sujetos no identificados por el algoritmo como caso potencial y posteriormente revisadas. Finalmente, se calcularon las tasas de incidencia crudas y estandarizadas por edad tomando la población europea de referencia y se compararon con las publicadas por la Red Española de registros de Cáncer (REDECAN) para los años 2012 y 2015.

Para los *estudios 2 y 3*, se realizó un estudio de casos y controles anidado en una cohorte primaria extraída de la base de datos BIFAP. En total se incluyeron 15,491 casos incidentes de cáncer colorrectal y 60.000 controles, seleccionados de forma aleatoria y apareados con los casos por frecuencia de edad, sexo y año de diagnóstico. Los fármacos estudiados fueron: AAS a dosis bajas, clopidogrel y triflusal, en el *estudio 1* y, en el *estudio 2* se estudiaron los AINE no-AAS (como grupo, en subgrupos farmacológicos en función de la selectividad COX-2 y por principio activo), los SYSADOA y metamizol. Se analizó el efecto de la exposición a los fármacos, de la duración del tratamiento, de la

persistencia del mismo (solo en AINE) y de la dosis (siempre que fue posible), además de la interacción con otros factores como la edad, el sexo o el uso concomitante con inhibidores de la bomba de protones (sólo con AINE).

La asociación entre los fármacos de interés y el cáncer colorrectal se estimó calculando los *odds ratios* (OR) y su intervalo de confianza al 95% (IC 95%) mediante un modelo de regresión logística no condicional, incluyendo las variables de apareamiento y ajustando por posibles factores de confusión.

Resultados

En el *estudio 1* se detectaron 17.008 casos potenciales de cáncer colorrectal. Se validaron de forma manual 760 historias clínicas seleccionadas de forma aleatoria de entre los 8 grupos creados. El valor predictivo positivo (VPP) global fue del 87,3% (IC 95%: 83,3% - 90,4%). El VPN fue del 100% (IC 95%: 96,3% - 100%). La información adicional que se encontró con mayor frecuencia fue la localización del cáncer (colon, recto y sigma) (94%) y el tratamiento quirúrgico (81,1%). La tasa de incidencia estandarizada según la edad de la población europea (Waterhouse, 1976) fue de 77,7 por 100.000 años-persona en hombres (IC 95%: 76,1 – 79,3) y de 38,1 por 100.000 años-persona en mujeres (IC 95%: 37,1 – 39,2), en el periodo 2001 – 2014, muy similar a las reportadas por REDECAN para los años 2012 y 2015. En la validación adicional, se revisaron manualmente 1,274 historias clínicas de los grupos con VPP < 50% y 1.097 con patrones de texto compatibles con falsos positivos. Tras esta estrategia adicional, se incluyeron 15.491 casos de cáncer colorrectal y el VPP aumentó a un 95,7%.

En el *estudio 2*, se observó una disminución del riesgo duración-dependiente de cáncer colorrectal entre los usuarios actuales de AAS a dosis bajas (OR ajustado = 0,83; IC 95%: 0,78 – 0,89), que comienza a ser estadísticamente significativa a partir de 180 días de uso. En los análisis por dosis, uso del AAS (prevención primaria o secundaria), sexo o edad, no se observaron diferencias en el estimador puntual, entre los diferentes estratos. El uso de clopidogrel en monoterapia también se asoció con una reducción del riesgo duración-dependiente de cáncer colorrectal (OR ajustado = 0,80; IC 95%: 0,69 – 0,93), comenzando a ser estadísticamente significativa a partir del año de uso. No hubo grandes diferencias en los estimadores en el análisis estratificado por edad y sexo. Con terapia dual antiagregante con AAS a dosis bajas y clopidogrel no se observaron diferencias con respecto a los fármacos por separado. Para triflusal, hubo poca prevalencia de uso, pero se observó una tendencia hacia la reducción de riesgo en duraciones mayores de un año y con dosis diarias mayores o iguales a 600 mg, aunque no estadísticamente significativa.

En el *estudio 3*, se observó una reducción de riesgo de cáncer colorrectal asociado al uso de AINE no-AAS (OR ajustado = 0,67; IC 95%: 0,63 – 0,71). Esta reducción se mantuvo presente hasta un año tras la interrupción del tratamiento. Se observó un claro efecto duración comenzando en los primeros 180 días de uso y aumentado de forma lineal hasta mas de 4 años (OR ajustado = 0,43; IC 95%: 0,27 – 0,70). La reducción de riesgo se mantuvo, aunque en menor medida, con persistencias del tratamiento del 50% o menores (OR ajustado = 0,69; IC 95%: 0,60 – 0,81). No se observaron diferencias por sexo, edad, dosis o uso concomitante con inhibidores de la bomba de protones ni en el análisis por principio activo.

El uso de SYSADOA se asoció con una reducción del riesgo de cáncer colorrectal solo durante el primer año de uso (OR ajustado = 0,69; IC 95%: 0,58 – 0,83), desapareciendo cuando se retiró del análisis a los usuarios actuales y previos de algún AINE.

El uso actual de metamizol se asoció con un aumento de riesgo de cáncer colorrectal con duraciones de uso de menos de un año y, especialmente, a dosis altas (OR ajustado = 1,62; IC 95%: 1,25 – 2,09). Con duraciones más largas, se sugiere una tendencia hacia la reducción de riesgo, pero no estadísticamente significativa.

Conclusiones

El diagnóstico de cáncer colorrectal en BIFAP se encuentra registrado adecuadamente, de forma que valida el uso de esta base de datos para el estudio farmacoepidemiológico del cáncer colorrectal. Además, la estrategia de validación y el algoritmo de búsqueda general obtuvieron un gran rendimiento al alcanzarse un VPP mayor del 80%. La validación adicional, aunque menos generalizable ya que se realizó específicamente para los estudios de casos y controles, aumentó de forma considerable el VPP hasta más del 95%. Las tasas de incidencia crudas y estandarizadas por la edad europea obtenidas en BIFAP fueron muy similares a las reportadas por REDECAN en los años 2012 y 2015.

Hemos replicado el efecto quimioprotector del AAS a dosis bajas en población de BIFAP y es similar al reportado en publicaciones anteriores en poblaciones con diferentes hábitos de vida. Además, hemos confirmado que otros antiagregantes plaquetarios, como clopidogrel, comparten este efecto, reforzando la hipótesis de que esta quimioprotección se realiza a través de sus efectos sobre la agregación plaquetaria. Para los AINE no-AAS, también hemos replicado el efecto quimioprotector en población de BIFAP y el gran tamaño muestral del estudio nos ha permitido caracterizarlo mejor. Hemos observado que

el efecto quimioprotector se observa con dosis moderadas y con dosis altas, en ambos sexos, en diferentes grupos de edad, y que permanece aún con persistencias relativamente bajas del tratamiento. La selectividad COX-2 no parece una característica determinante y todos los principios activos examinados parecen compartir el efecto protector. Hasta la fecha, este estudio es el mayor que se ha publicado. Por el contrario, no hemos confirmado el efecto quimioprotector de SYSADOA reportado en otras publicaciones, ni tampoco hemos observado un efecto relevante con metamizol.

3. ABSTRACT

Title

"Chemoprevention of colorectal cancer with antiplatelet drugs, non-aspirin nonsteroidal anti-inflammatory drugs and other drugs for pain control"

Introduction

Colorectal cancer is one of the most frequent types of cancer, counting both sexes together, in developed countries. Apart from hereditary factors, there are other factors closely related to western lifestyle habits. In developed countries, early diagnosis and treatments have improved in recent years, which has increased survival in these patients. In addition to a primary prevention strategy based on the modification of certain lifestyle habits, there are others that could be added to that strategy, such as chemoprevention. Numerous studies have been published in which a reduction of risk of colorectal cancer development was associated with the use of different drugs such as low-dose acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, bisphosphonates or statins, among many others.

It has been described that in the genesis of colorectal cancer different factors could intervene, one of them is the inflammation by means of the cyclooxygenase-2 (COX-2) activity. COX-2 is an enzyme, in general, not constitutively present in cells, but is rapidly inducible by inflammatory stimuli.

The expression of COX-2 leads to the production of different prostaglandins, mainly protaglandin E_2 (PGE2), which is the main prostaglandin derived from COX-2 activity. Specifically, high levels of PGE_2 in the adjacent tissue have been related to tumor development due to its antiapoptotic activity, cell growth and cell migration and invasion. Also, it has been observed that, a high percentage of adenomas and adenocarcinomas, overexpresses COX-2. In the inflammatory process, platelets also play a role. Platelets are activated by different inflammatory stimuli in response, such as tissue damage, then releasing the content of their alpha-granules to the environment. These alpha-granules contain a large variety of substances such as prostanoids, growth factors and angiogenic factors, which, over adjacent cells, stimulate the inflammatory process, inducing the expression of COX-2. It has also been described that platelets can form aggregates around tumor cells, preventing the recognition and destruction of these cells by the immune system.

Pharmacoepidemiology is the science that studies the effects of the use of drugs in populations, using the epidemiological method for that aim. Such study normally needs large amounts of data, and thus the use of big automated databases in pharmacoepidemiological research began early, in the 80s in the USA, and has not stopped growing to this day, being, at present, a source of information increasingly used for epidemiological studies.

Based on the evidence coming from numerous pharmacoepidemiological studies, in 2016, the United States Preventive Services Task Force recommended, for the first time, the use of low-dose ASA for the primary prevention of cardiovascular events and colorectal cancer, in a specific population group. Previously, the use of other NSAIDs

was studied in different randomized clinical trials, specifically on COX-2 selective NSAIDs or coxibes, for the prevention of adenomas, although this indication was ruled out prematurely due to an unfavorable risk-benefit balance, due to their cardiovascular harms. However, although there are numerous pharmacoepidemiological studies published on the use of low-dose ASA and NSAIDs for the reduction of the risk of colorectal cancer, there are still unsolved questions and the chemopreventive effect needs to be better characterized. On the other hand, such an effect has scarcely been studied in the Mediterranean population, being most studies of small size.

Objectives

The objective of the three studies is, at first, to validate the use of the *"Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria"* (BIFAP) for the study of colorectal cancer, and once validated, to assess the chemoprotective effect against colorectal cancer of: low-dose ASA and other non-ASA antiplatelet drugs, such as clopidogrel, NSAIDs (excluding ASA) and other drugs that share some indication with NSAIDs such as symptomatic slow-acting drugs for osteoarthritis (SYSADOA; chondroitin sulfate and glucosamine) and metamizole.

Methods

For *study 1*, a validation strategy was developed and a case-finding algorithm for colorectal cancer diagnosis based on searches of diagnostic codes and free-text, was created. All the potential colorectal cancer cases detected were distributed in 8 homogeneous groups according to the information detected for each subject. Of these 8

groups, 100 electronic health records were randomly selected and manually reviewed by two trained researchers blinded to drug prescriptions. Once all the electronic health records were reviewed, the percentage of true positives, false positives and the positive predictive value (PPV) of each group and overall was calculated. Additionally, for the case-control studies, this algorithm was refined by including text patterns found to be common in the false positives confirmed in the previous step of validation. The general validation strategy was improved with the manual review of all the electronic health records of the groups with a PPV <50%, in the general validation. To calculate the negative predictive value (NPV), 100 electronic health records from subjects not detected by the algorithm as true cases were randomly taken and reviewed. Finally, the crude and standardized (according to the European population) incidence rates were calculated and compared with those published by the Spanish Network of Cancer Registries (REDECAN) for the years 2012 and 2015.

For *studies 2 and 3*, a nested case-control study was conducted using a primary cohort extracted from BIFAP. A total of 15,491 incident cases of colorectal cancer and 60,000 randomly selected controls, matched with cases by frequency of age, sex and year of diagnosis, were included. The drugs studied were: low-dose ASA, clopidogrel and triflusal, in *study 1* and non-ASA NSAIDs (as a group, in pharmacological subgroups according COX-2 selectivity and by active principles), SYSADOAs and metamizol, in *study 2*. The effect of exposure to drugs, duration of treatment, treatment persistence (only for non-ASA NSAIDs) and daily dose (whenever possible) was analyzed, as well as the interaction with other factors such as age, sex or concomitant use with proton pump inhibitors (just for non-ASA NSAIDs).

The association between the drugs of interest and colorectal cancer was estimated by calculating the odds ratios (OR) and their 95% confidence interval (95% CI) using an unconditional logistic regression model, which included the matching variables, and adjusted for confounding factors.

Results

In *study 1*, 17,008 potential cases of colorectal cancer were detected. 760 electronic health records selected randomly from among the 8 groups created previously were reviewed. The overall PPV was 87.3% (95% CI: 83.3% - 90.4%). The NPV was 100% (95% CI: 96.3% - 100%). The additional information most frequently found was the location (colon, rectum or sigmoid) (94%) and surgical treatment (81.1%). The standardized incidence rate was 77.7 per 100,000 person-years, in men (95% CI: 76.1 - 79.3), and 38.1 per 100,000 person-years, in women (95% CI: 37.1 - 39.2), for the period 2001 - 2014, being the rates obtained very similar to those reported by REDECAN for the years 2012 and 2015.

In the additional validation strategy specifically performed for the case-control studies, we manually reviewed 1,274 electronic health records of the groups with a PPV <50% and 1,097 electronic health records with compatible false-positive text patterns. After this additional strategy, 15,491 cases of colorectal cancer were included and PPV increased to 95.7%.

In *study 2*, a duration-dependent decreased risk of colorectal cancer was observed among current users of low-dose ASA (adjusted-OR = 0.83, 95% CI: 0.78 - 0.89), which began

to be statistically significant after 180 days of use. In the analyzes by dose, indication of ASA, sex or age, no differences were observed in the point estimate. The use of clopidogrel in monotherapy was also associated with a duration-dependent risk reduction of colorectal cancer (adjusted-OR = 0.80, 95% CI: 0.69 - 0.93), starting to be statistically significant after the first year of use. There were no differences in the stratified analysis by either age or sex. For dual antiplatelet therapy with low-dose ASA and clopidogrel, no additional effect was observed over the independent effects of each drug. For triflusal, we found a low prevalence of use, but a risk reduction was suggested for durations greater than one year and with daily doses greater than or equal to 600 mg, although not statistically significant.

In *study 3*, a reduction in the risk of colorectal cancer was associated with the use of non-ASA NSAIDs (adjusted-OR = 0.67, 95% CI: 0.63 - 0.71). The risk reduction was present up to one year after the interruption of treatment. An important duration-dependent effect was observed starting in the first 180 days of use and increasing linearly to more than 4 years (adjusted-OR = 0.43, 95% CI: 0.27 - 0.70). The risk reduction, although to a lesser extent, was maintained with treatment persistence of 50% or less (adjusted-OR = 0.69, 95% CI: 0.60 - 0.81). No differences were observed by sex, age, daily dose or concomitant use with proton pump inhibitors or in the analysis by active principle.

The use of SYSADOAs was associated with a risk reduction of colorectal cancer but only in the first year of use (adjusted-OR = 0.69, 95% CI: 0.58-0.83), disappearing when current and previous users of NSAIDs were withdrawn from the analysis.

The use of metamizole was associated with an increased risk of colorectal cancer with durations of use of less than one year and, especially, at high daily doses (adjusted-OR =

1.62, 95% CI: 1.25 - 2, 09). With longer durations, a risk reduction was suggested, but not statistically significant.

Conclusions

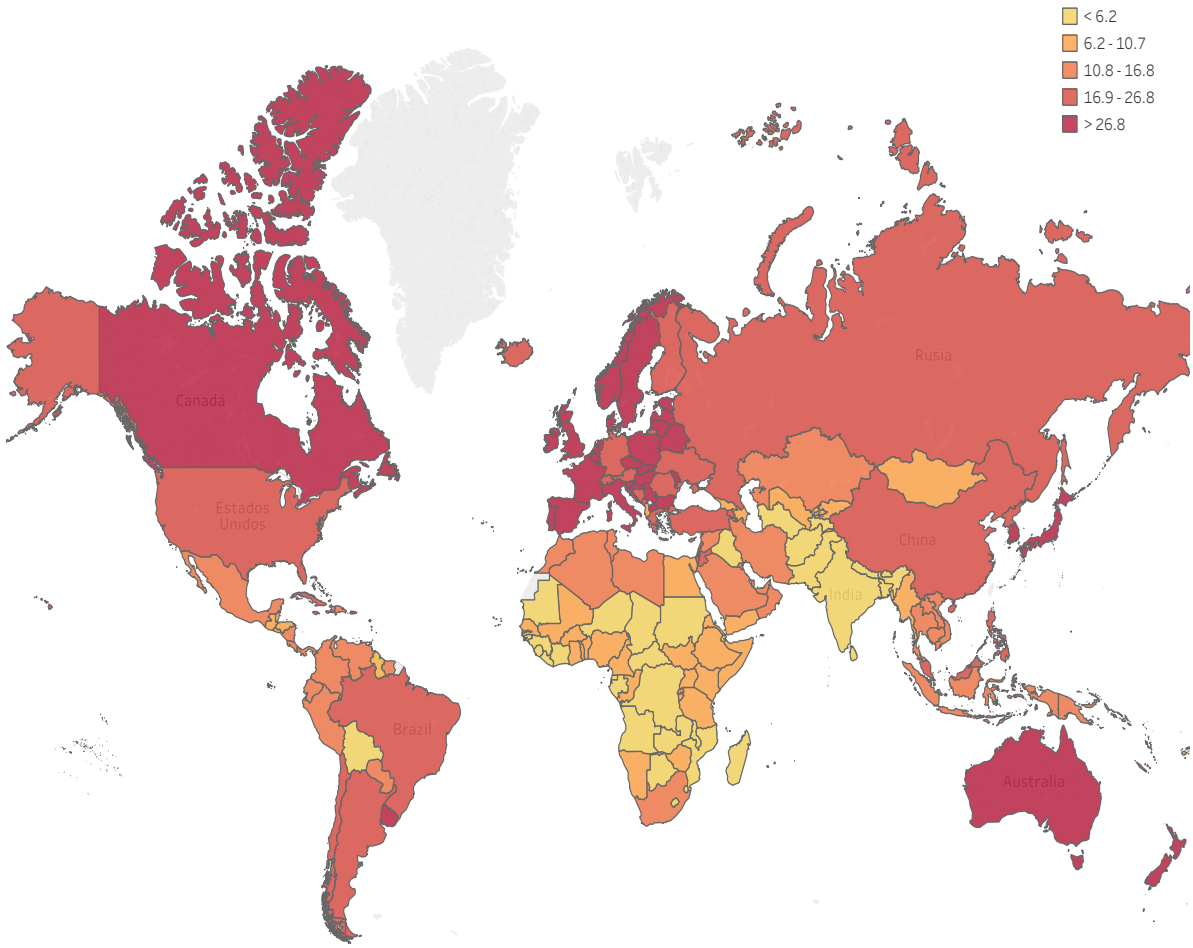
The diagnosis of colorectal cancer in BIFAP is adequately recorded, so that it validates the use of this database for the pharmacoepidemiological study of colorectal cancer. In addition, the validation strategy and the general case-finding algorithm obtained a great performance reaching a VPP greater than 80%. The additional validation exercise specifically performed for the case-control studies (which makes it less generalizable) increased the PPV considerably to more than 95%. The crude incidence and standardized incidence rates (using the European population as reference) obtained in BIFAP were very similar to those reported by REDECAN in the years 2012 and 2015. We have replicated the chemoprotective effect of low-dose ASA in BIFAP population and found to be similar to that reported in previous publications in populations with different lifestyle habits. Also, we have confirmed that clopidogrel shares this effect, giving support to the hypothesis that the chemoprotection observed with both low-dose ASA and clopidogrel is probably explained by their antiplatelet effect. For non-ASA NSAIDs, we have also replicated the chemoprotective effect, previously reported in other populations with different lifestyle habits, in the BIFAP population. We have also observed that the chemoprotective effect does not depend on daily dose, sex, age or treatment persistence, and that COX-2 selectivity is not a determinant feature, since all active principles examined showed similar effects. To date, this is the largest study ever published. On the contrary, we have not observed the chemoprotective effect of SYSADOA reported previously, nor did we find it for metamizol.

4. INTRODUCCIÓN

4.1. Epidemiología del cáncer colorrectal

El cáncer colorrectal es el tercer tipo de cáncer más frecuente en el mundo y el cuarto en mortalidad, contando ambos sexos (1). En hombres, es el tercer tipo de cáncer más incidente y el segundo en mujeres, aumentando con la edad, especialmente a partir de los 50 años (1). Según datos de la Organización Mundial de la Salud (OMS), se estima que en el año 2018 se diagnosticaron globalmente 1,8 millones de casos nuevos de cáncer colorrectal y se produjeron 861.000 defunciones por esta enfermedad (2). El mayor número de casos se diagnostican en países desarrollados, siendo las tasas de incidencia más altas en Australia, Nueva Zelanda, Europa y América del Norte, mientras que África y Asia cuentan con las tasas de incidencia más bajas (3) (Figura 1). De nuevo, según datos de la OMS, se estima que en 2030 el número de casos nuevos de cáncer colorrectal habrá aumentado en un 77% y la mortalidad en un 80%, especialmente en los países menos desarrollados, debido a la creciente occidentalización de los hábitos de vida en estas zonas del mundo (2,4). Por el contrario, las tasas de mortalidad han descendido progresivamente en los países desarrollados desde mediados de la década de los 80, especialmente en los Estados Unidos y en otros países occidentales, (5) debido, en parte, a la incorporación de programas de detección precoz de adenomas colónicos, aumentando la detección en estadios tempranos de la enfermedad, uno de los factores más importantes en el pronóstico (4), así como a las mejoras en los tratamientos, tanto quirúrgicos como quimioterapéuticos (4). Como consecuencia de ello, también la supervivencia a 5 años ha aumentado, alcanzando el 65% en los países más desarrollados como Estados Unidos, Canadá, Australia y algunos países europeos como Bélgica, Alemania o Suecia (1, 6).

Figura 1. Tasas de incidencia de cáncer colorrectal estandarizadas por la edad mundial, para ambos sexos, en el año 2018.

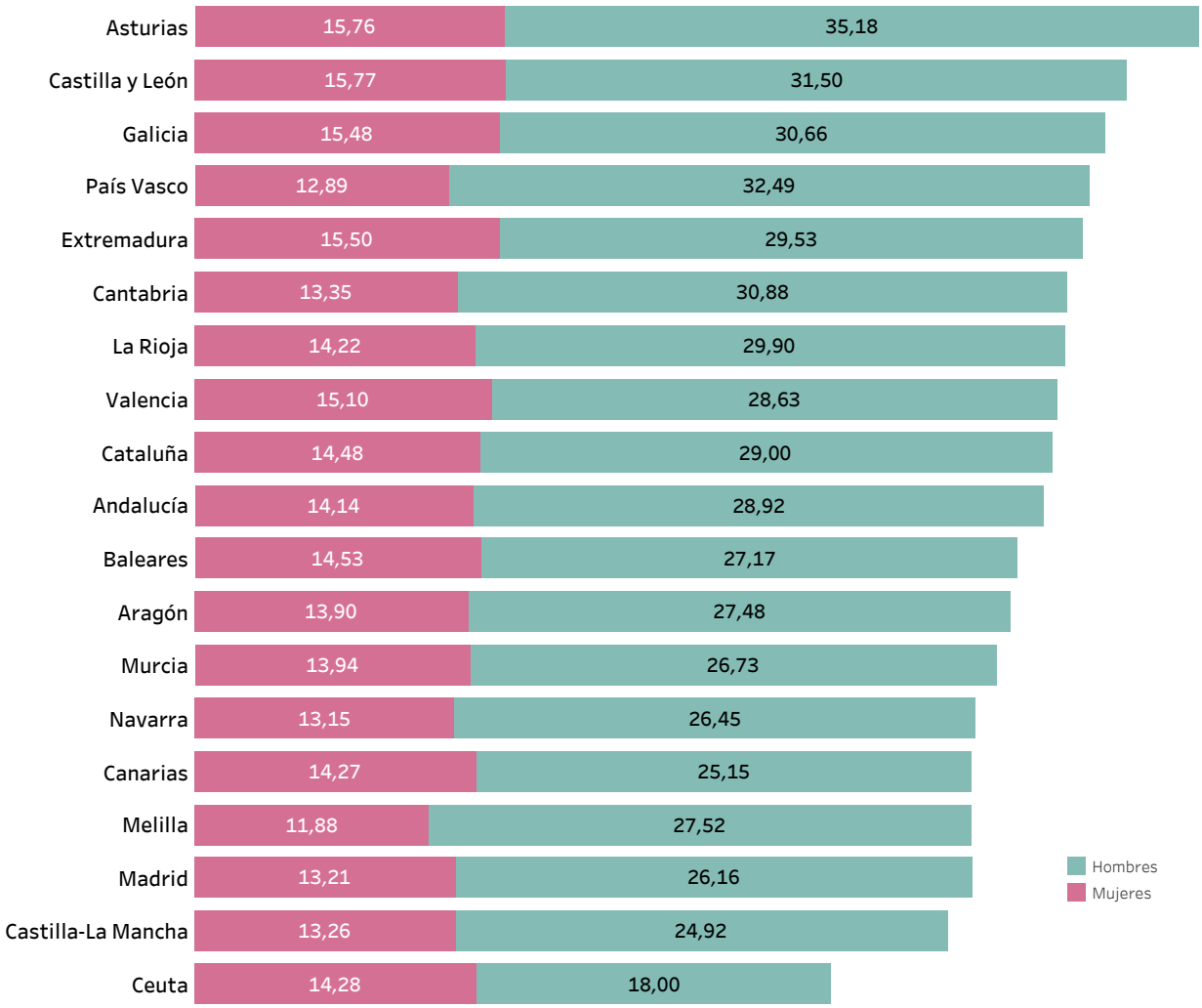


Fuente: Organización Mundial de la Salud. Observatorio global del cáncer. http://gco.iarc.fr/today/home. Accedido el 20 de mayo de 2019.

En España, la incidencia de cáncer colorrectal ha aumentado paulatinamente en las últimas décadas (6), especialmente en los hombres, situándose como el tercer tipo de cáncer más incidente en ellos, tras el cáncer de próstata y el cáncer de pulmón. En las mujeres, el cáncer colorrectal se sitúa como el segundo más incidente después del cáncer de mama (6). La tasa de incidencia estandarizada por edad, tomando como referencia la población europea, se estimó en 65,6 por 100.000 años-persona en hombres y 35,3 por

100.000 años-persona en mujeres, según datos proporcionados por la Red Española de Registros de Cáncer (REDECAN) para el año 2012 (6). La mortalidad en hombres ha aumentado en los últimos 10 años a un ritmo promedio del 0,6% anual (6), alcanzando, en el año 2012, el 14% del total de defunciones en hombres por cáncer. En cambio, la mortalidad en mujeres ha descendido en los últimos de 10 años un promedio de un 0,6% anual (6), suponiendo el 15,6% de todas las muertes por cáncer, también en 2012. Comparando estos datos con los del resto de países de Europa, la tasa de incidencia estimada y ajustada por la edad europea de cáncer colorrectal, entre los hombres, en el año 2015, se situó ligeramente por encima de la media europea, mientras que la cifra en mujeres se mantuvo en esta media (6). En cambio, la mortalidad en España (Figura 2), que tradicionalmente había registrado las tasas más bajas, ha experimentado en los últimos años un crecimiento constante, llegando a superar a la media europea, en el año 2012, especialmente en hombres, aunque esta tendencia no se observa entre las mujeres, donde la mortalidad en 2012 se sitúa en la media europea y, como se ha señalado, desciende anualmente (6). La supervivencia a 5 años en España también ha aumentado en los últimos años, situándose en el año 2012 en el 56,8%, contando ambos sexos, aunque es ligeramente superior en mujeres (6). Comparada con las del resto de Europa, se situó en la media, contando ambos sexos, aunque sigue siendo inferior a la registrada en otros países europeos como Suecia, Finlandia, Bélgica o Alemania, donde se registran las mayores tasas, en pacientes diagnosticados entre el año 2000 y el año 2007 (6).

Figura 2. Tasa de mortalidad por 100.000 habitantes, por CCAA y sexo, en el periodo 2008 – 2012, en España.



Fuente: López-Abente G, Núñez O, Pérez-Gómez B, et al. La situación del cáncer en España: Informe 2015. Instituto de Salud Carlos III. Madrid, 2015.

4.2. Factores de riesgo y prevención primaria del cáncer colorrectal

Se han descrito numerosos factores implicados en el desarrollo del cáncer colorrectal, entre ellos, factores genéticos, ambientales y otros relacionados con los hábitos de vida (1,4,6,7). Se estima que entre el 70% y el 90% de los tumores de colon y recto que se diagnostican corresponden a formas no hereditarias o esporádicas (4,6). Además del sexo y la edad como factores de riesgo importantes (4), existen otros como la historia familiar de cáncer colorrectal, la enfermedad inflamatoria intestinal, el consumo de tabaco, el consumo excesivo de alcohol, el consumo elevado de carne roja y carne procesada, el consumo de grasas saturadas, la dieta baja en fibra, el sedentarismo, la obesidad y la diabetes (1,4,6), sobre los que sería posible intervenir dentro de una estrategia de prevención primaria (4,7).

4.3. Quimioprofilaxis del cáncer colorrectal

Numerosos estudios han mostrado un efecto quimioprotector asociado al uso de ciertos grupos de fármacos frente al cáncer colorrectal, demostrando con ello que la quimioprotección primaria o secundaria del cáncer puede ser una estrategia de prevención válida a tener en cuenta (8). Los fármacos más estudiados han sido los analgésicos y antiinflamatorios no esteroídicos (AINE) (9), el ácido acetilsalicílico (AAS) a dosis bajas (8), las estatinas (10), la terapia hormonal sustitutiva (11) o los bisfosfonatos (12), entre otros (13-15).

4.3.1. AINE, actividad ciclooxigenasa-2 y cáncer colorrectal

Se han descrito diferentes mecanismos de acción por los que los AINE podrían ejercer su efecto quimioprotector frente al cáncer colorrectal (16). El principal y más estudiado se explica a través de su capacidad para inhibir la ciclooxigenasa-2 (COX-2) (7).

La ciclooxigenasa-1 (COX-1) es una enzima constitutiva en plaquetas y en la mayoría de los tejidos, mientras que la COX-2, aunque también se expresa de forma constitutiva en cerebro, corteza renal y endotelio, generalmente está ausente en la mayoría de tejidos, siendo su expresión rápidamente inducible en respuesta a estímulos inflamatorios y mitogénicos (17). La actividad COX-1 se considera que está más relacionada con el mantenimiento de la integridad fisiológica de diferentes órganos, como la protección de la mucosa gástrica, el mantenimiento del flujo renal o la agregación plaquetaria (18), mientras que la actividad COX-2 está más relacionada con la actividad inflamatoria (17, 18). Se ha descrito que los estados de inflamación sostenida mediada por la actividad COX-2 podrían estar relacionados con el desarrollo tumoral, en parte debido, a la estimulación de la proliferación celular, la angiogénesis, la inhibición de la apoptosis y la inhibición de la respuesta inmune (17,18) que ejercen ciertas prostaglandinas derivadas de su actividad, como la prostaglandina E_2 (PGE_2) (19). Además, se ha observado que la COX-2 está sobre-expresada en un porcentaje alto de adenomas y adenocarcinomas (17, 18). Debido a ello, la PGE_2 es la prostaglandina más abundantemente encontrada en tejido tumoral de colon y recto. Se han relacionado los niveles elevados de PGE_2, en este tejido, con el favorecimiento del desarrollo tumoral debido a su actividad estimuladora de la angiogénesis, la invasión celular, el crecimiento celular y la supervivencia tumoral (19). Teniendo como base esta evidencia, en la primera década del presente siglo, se diseñaron

diversos ensayos clínicos para evaluar el efecto de los AINE, especialmente de los inhibidores selectivos de la COX-2 (o coxibes), en la prevención de la recurrencia de adenomas en sujetos con antecedentes de adenomas (20-22), aunque el aumento de riesgo cardiovascular asociado al uso de estos fármacos (23-25) hizo que se descartara la búsqueda de esta nueva indicación al considerarse superiores los riesgos a los posibles beneficios. De hecho, dos coxibes, el rofecoxib y el valdecoxib, fueron retirados del mercado por un balance beneficio-riesgo desfavorable (26).

4.3.2. AAS a dosis bajas, la hipótesis de las plaquetas y cáncer colorrectal

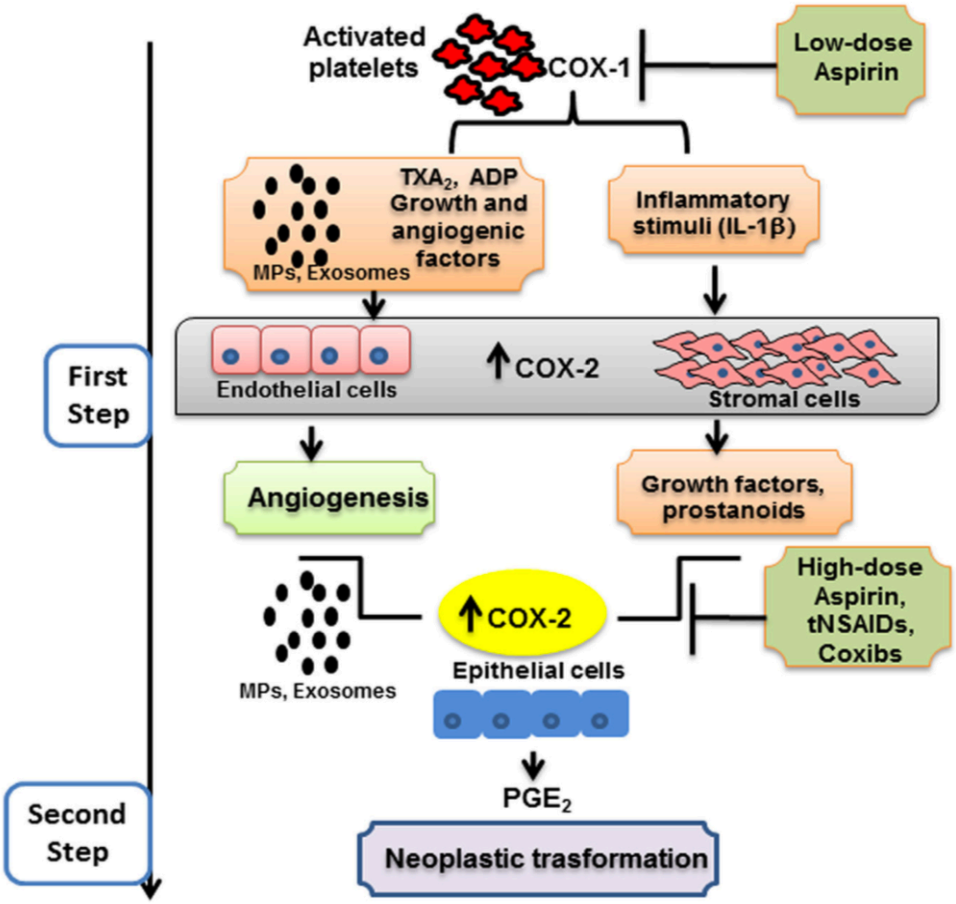
Las plaquetas, además de su actividad más conocida en la hemostasia, también intervienen en el proceso inflamatorio (27). En concreto, las plaquetas pueden activarse en respuesta a un daño tisular, liberando al medio el contenido de los gránulos alfa (28), donde está contenida una gran variedad de sustancias; prostanoides, como el tromboxano A_2 (TXA_2), factores pro-inflamatorios (IL-1β, TNF-α), factores de crecimiento (TGF-β1) y factores angiogénicos (VEGF) (27). El efecto de dichas sustancias sobre los tejidos adyacentes conduce a una sobreexpresión de la COX-2 en los mismos, favoreciendo el sostenimiento de un estado inflamatorio y creando un entorno favorable para la transformación tumoral de la mucosa intestinal (27) (Figura 3). Por otro lado, se han descrito diferentes mecanismos por los que las plaquetas podrían facilitar la metástasis tumoral, por ejemplo, las plaquetas pueden formar agregados alrededor de las células tumorales, impidiendo que éstas sean reconocidas y eliminadas por el sistema inmune (27). Estos agregados plaquetarios facilitan, además, la adhesión de las células tumorales al endotelio vascular y su extravasación hacia diferentes tejidos (27). Por último, los factores angiogénicos liberados en el tejido tumoral durante la activación plaquetaria,

intervienen en la neovascularización tumoral, favoreciendo la supervivencia, el crecimiento y la diseminación de estas células tumorales (27).

El AAS a dosis bajas tiene un efecto inhibidor irreversible de la COX-1 plaquetaria por acetilación de un residuo de serina en dicha enzima. Esta inhibición es permanente debido a la incapacidad de las plaquetas para sintetizar nuevas proteínas, al tratarse de células anucleadas (28). El bloqueo de la COX-1 plaquetar produce una reducción de la producción de prostanoides derivados del ácido araquidónico, como el tromboxano A_2 (TXA_2). El TXA_2 es liberado por las plaquetas cuando son activadas por un agonista y actúa como amplificador de la activación plaquetaria (27, 29, 30). Como el resto de los AINE, el AAS también tiene capacidad para inhibir la COX-2, pero a dosis bajas (habitualmente 75-100 mg al día) no es suficiente para alcanzar una inhibición eficaz de la misma, tanto por razones farmacodinámicas: tiene menor afinidad para inhibir la COX-2 que la COX-1, como por razones farmacocinéticas; el AAS a dosis bajas se desacetila casi completamente en el hígado perdiendo la capacidad para inhibir de forma irreversible tanto la COX-1 como la COX-2 sistémicas, de forma que, a dosis bajas, sólo inhibe de forma eficaz la COX-1 plaquetar en sangre portal (31). Por estas razones, se ha postulado que el efecto quimioprotector del AAS a dosis bajas no es debido a una actividad directa sobre la COX-2 sistémica, sino que tendría que estar mediada por su acción sobre las plaquetas. Tal como se ha comentado antes, la inhibición de la COX-1 plaquetar tendría un efecto indirecto sobre la expresión COX-2 y, por tanto, de PGE_2, en tejidos adyacentes al inhibirse la liberación de las sustancias plaquetarias que favorecen su expresión (27, 30). Este efecto es lo que se ha descrito en la literatura como un efecto COX-2 "corriente arriba" o "*upstream"* (32). Si esta hipótesis es correcta, otros antiagregantes plaquetarios, actuando por mecanismos diferentes a la ciclooxigenasa deberían tener también un efecto

quimioprotector, como, por ejemplo, clopidogrel, un antagonista del receptor $P2Y_{12}$ sobre el que actúa el ADP, uno de los mediadores más importantes de la agregación plaquetar (29).

Figura 3. Mecanismos derivados de la actividad plaquetaria en el desarrollo del cáncer.



Guillem-Llobat P, Dovizio M, Alberti S, Bruno A, Patrignani P. Platelets, cyclooxygenases, and colon cancer. Semin Oncol. 2014;41(3):385-96. Figure 2; p. 391

4.4. La Farmacoepidemiología y el uso de las bases de datos automatizadas

La farmacoepidemiología es una rama de la farmacología clínica que se define como la ciencia que tiene como objetivo estudiar el uso y los efectos del uso de los medicamentos en las poblaciones, sirviéndose, para ello, del método y razonamiento epidemiológicos (33). La farmacovigilancia es la actividad de salud pública que tiene como objetivo la identificación, la cuantificación, la evaluación y la prevención de los riesgos de los medicamentos una vez comercializados (34). La farmacovigilancia necesita, por tanto, la evidencia procedente de los estudios farmacoepidemiológicos, además de otras ciencias y fuentes de conocimiento. En este sentido, ambas disciplinas están muy relacionadas, pero la farmacoepidemiología trasciende a la farmacovigilancia, en la medida en que no solo se centra en el estudio de las reacciones adversas a los medicamentos en las poblaciones, sino que, también puede aplicarse al estudio de los efectos beneficiosos de éstos sobre las poblaciones, mediante la realización de estudios de prevención o estudios de efectividad.

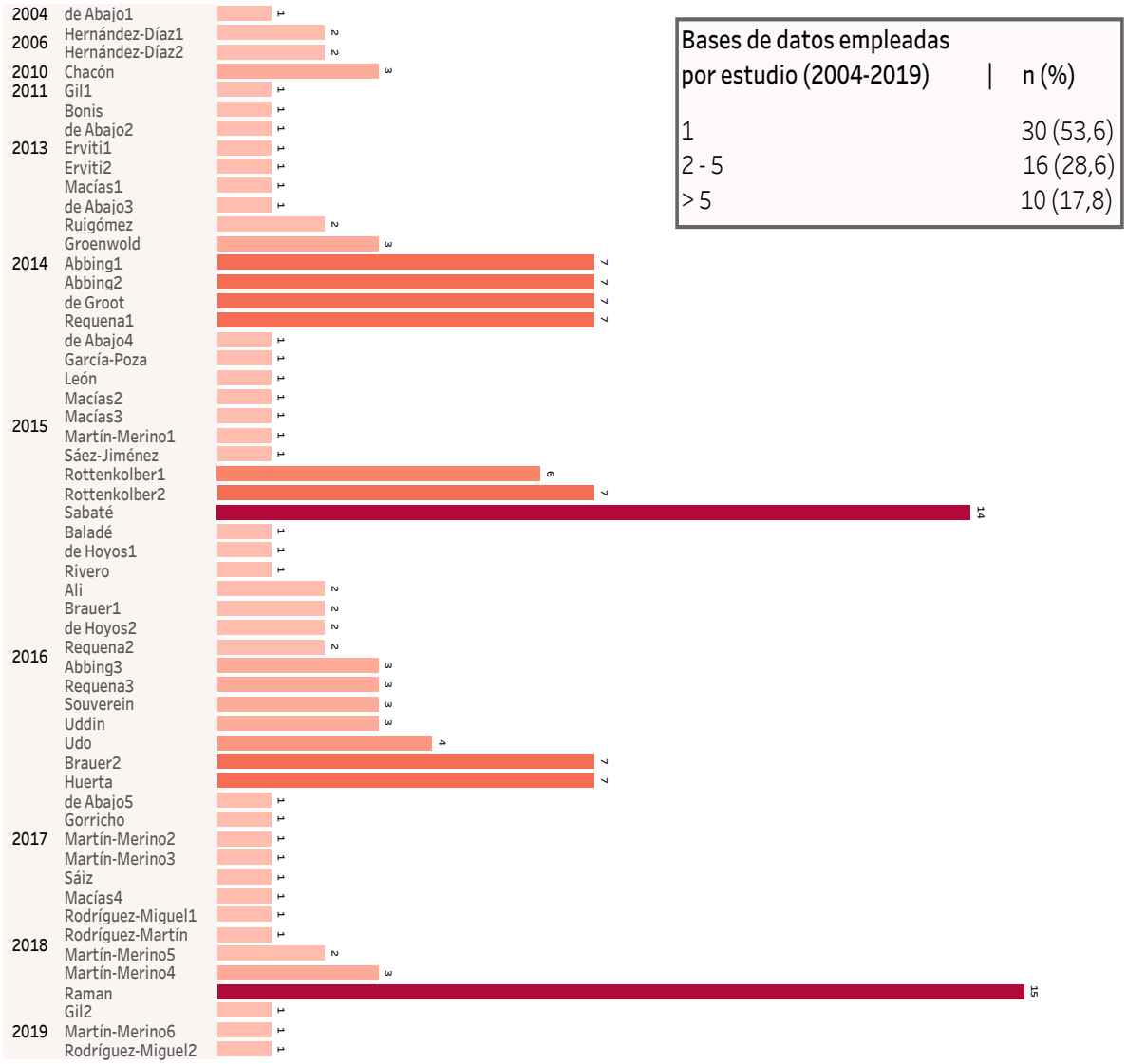
Tradicionalmente, la farmacoepidemiología se ha servido de grandes bases de datos como fuente de información para la realización de los estudios, siendo probablemente la primera disciplina biomédica que ha necesitado incorporar a su metodología el análisis de grandes cantidades de datos. Los primeros estudios farmacoepidemiológicos con grandes bases de datos automatizadas se remontan a los años ochenta. El país pionero fue, sin lugar a dudas, EEUU y uno de los personajes más destacados en este comienzo fue el Prof. Hershel Jick, fundador del *Boston Collaborative Drug Surveillance Program.* Jick comenzó a realizar los primeros estudios en bases de datos creadas para la gestión administrativa, como la *Group Health Cooperative of Puget Sound* (35). Posteriormente,

en esa misma década, se empezaron a utilizar en EEUU otras dos grandes bases de datos, *Kaiser permanente* (36), también validada por el equipo de Jick, y *Medicaid* (37). Poco tiempo después, en Canadá, se comenzaron a realizar estudios con la base de datos de Saskatchewan (38). Estas bases de datos vinculan diferentes registros médicos, farmacéuticos y demográficos a través un identificador único ("bases de datos de enlace" o "*record linkage*") y de este modo se pueden realizar diferentes tipos de estudios. En Europa, la primera base de datos se crea en 1987 en el Reino Unido, *la General Practice Research Database* (GPRD), también validada por el equipo de Jick (39). Esta base de datos, actualmente denominada *Clinical Practice Research Datalink* (CPRD), es, tal vez, la más importante del mundo si nos atenemos al número de estudios y publicaciones que se han realizado con ella. Por otra parte, es importante, porque por primera vez se crea una base de datos que tiene como finalidad la investigación, no la gestión administrativa, y, además, que incluye toda la información necesaria para realizar los estudios epidemiológicos sin necesidad de vinculación externa, conocidas como "bases de datos integrales". Esto permitía anonimizar (o pseudonimizar) la identidad del paciente y solucionar de este modo el problema de la protección de los datos de carácter personal. Este tipo de bases son las más comunes en países con sanidad pública donde el médico de atención primaria cumple un papel central en la asistencia sanitaria, como es el caso del propio Reino Unido (THIN, QRESEARCH), Holanda (IPCI, Mondriaan-AHC) o España (BIFAP, SIDIAP). A partir de los años 90 y 2000, el número de bases de datos con las que se hacen estudios ha experimentado un crecimiento exponencial, tanto en Europa (Dinamarca, Italia, España, Holanda, Alemania) como en otros continentes (Corea, Taiwan, Australia o Nueva Zelanda).

4.5. La Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP)

BIFAP es una base de datos longitudinal de base poblacional que contiene información anonimizada de las historias clínicas informatizadas de los servicios de Atención Primaria de 9 Comunidades Autónomas (CCAA) españolas. BIFAP fue creada en el año 2003 (40) y desde sus orígenes es mantenida y financiada por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), apoyada por las CCAA con las que se han suscrito convenios de colaboración, y con el apoyo de diversas sociedades científicas (41). La base de datos BIFAP se actualiza cada año. En el año 2015, BIFAP contenía información del periodo 2001 – 2014, con datos anonimizados de 7,6 millones de pacientes y un tiempo de seguimiento de 38,6 millones de años-persona (5,1 años de seguimiento medio por persona). En este mismo periodo, el número de médicos de atención primaria y pediatras colaboradores fue de 5.714 (4.871 en atención primaria y 843 pediatras). La versión de BIFAP de 2017 es aún mayor, cuenta con 9,4 millones de personas, con un tiempo de seguimiento de 67,9 millones de años-persona (un promedio de 7,2 años de seguimiento por paciente) y cuenta con la colaboración de un número mayor de médicos colaboradores (6.857 médicos de atención primaria y pediatras). La población de BIFAP es representativa de la población española en cuanto a edad y sexo, cubriendo un 17% del total nacional. Se han realizado estudios comparativos de BIFAP con otras bases de datos existentes en Europa (42) (Figura 5) y ha sido validada para la investigación farmacoepidemiológica a través de numerosos estudios (41) (Figura 6).

Figura 5. Número de bases de datos utilizadas junto con BIFAP, por estudio, autor y año de publicación.

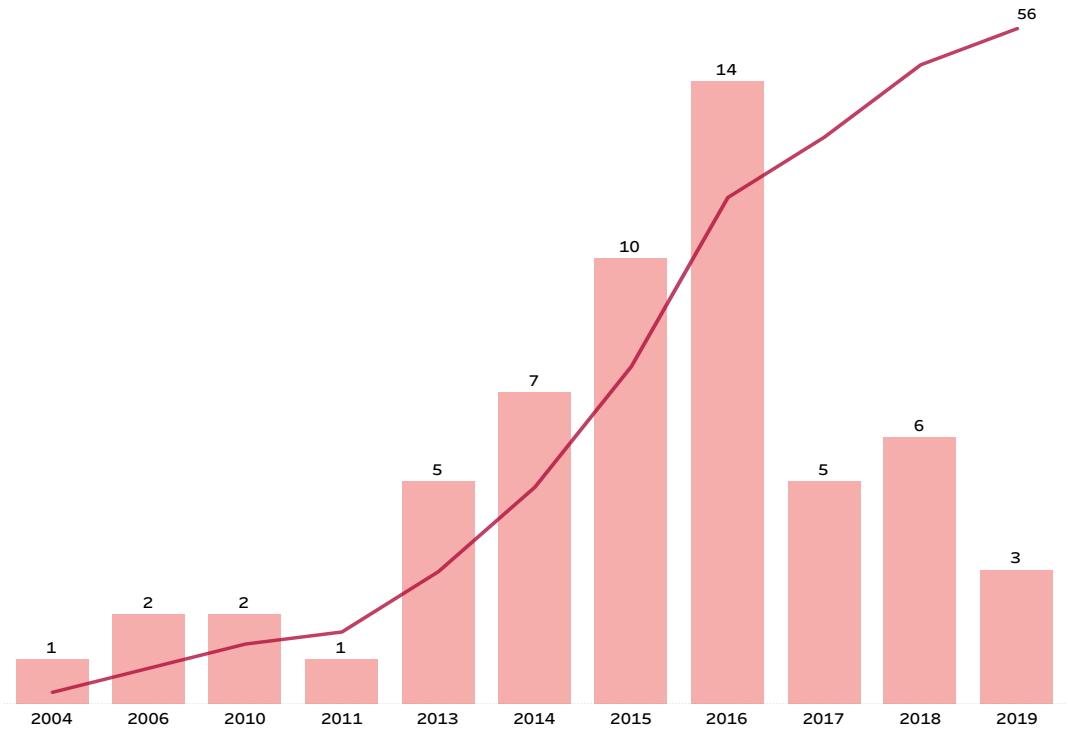


Relación de estudios publicados con BIFAP (identificados por el primer autor y año de publicación) y número de bases de datos empleadas en cada uno de ellos durante el periodo 2004-2019. Fuente: http://www.bifap.org y Pubmed.

Uno de los inconvenientes de los registros médicos que contiene BIFAP es que, a pesar de seguir un modelo armonizado común de datos, las bases de datos clínicas de donde se extrae la información no han sido creadas para la investigación epidemiológica, sino para un uso asistencial. Esto hace que BIFAP tenga una gran cantidad de información útil, pero alguna de ella no estructurada (p.ej. texto libre) y, por tanto, más difícil de analizar

por métodos estadísticos tradicionales (43). Además, BIFAP no está vinculada actualmente a fuentes de información externas como las historias clínicas de atención médica especializada, los registros de enfermedades (p. ej. cáncer) o el registro de mortalidad, aunque se están haciendo esfuerzos por lograr esto a través de las propias CC.AA. Por último, en los registros médicos, los diagnósticos se identifican mediante un código y un descriptor textual, pero en ocasiones éstos son imprecisos o no tienen la granularidad adecuada (44) En esta situación, la identificación de los casos de interés se hace más costosa.

Figura 6. Evolución del número de estudios publicado con BIFAP, por años y número acumulado.



Fuente: http://www.bifap.org y Pubmed.

5. JUSTIFICACIÓN

5.1. Estudio 1

Los registros médicos de pacientes, generalmente contenidos en una base de datos informatizada, constituyen una valiosa fuente de información por la cantidad de información útil que contienen. Es por ello que su uso en farmacoepidemiología es cada vez más frecuente (44). Sin embargo, existen ciertas limitaciones en estas bases de datos (véase epígrafe 5.5.) que hacen necesaria la realización previa de un estudio exhaustivo de validación del evento que se desea estudiar. Siendo esto más importante cuando el evento de interés se estudia por primera vez, como ocurre en el caso del cáncer colorrectal en BIFAP.

5.2. Estudio 2

El efecto quimioprotector frente al cáncer colorrectal del AAS a dosis bajas es conocido desde hace mucho tiempo (45) y confirmado en numerosos estudios posteriores (8), sin embargo, ha sido muy poco estudiado en población mediterránea (46). Se ha descrito que el efecto quimioprotector frente a cáncer colorrectal, aunque también en otros tipos de cáncer (47), podría estar mediado por su actividad antiagregante plaquetaria (27). Si esta hipótesis fuera correcta, otros antiagregantes plaquetarios deberían tener un efecto quimioprotector similar al observado con el AAS a dosis bajas. Clopidogrel, actúa como antiagregante plaquetario por un mecanismo independiente a la COX-1, bloqueando el receptor $P2Y_{12}$ (29), lo que, en caso de observarse dicho efecto quimioprotector, reforzaría notablemente la hipótesis plaquetar.

5.3. Estudio 3

Existen diferentes fármacos para los que se ha reportado un efecto quimioprotector frente a cáncer colorrectal (8-15). Entre todos ellos, destacan los AINE (9). Según los datos de una revisión sistemática y metanálisis recientemente publicado (48), muchos de los estudios publicados sobre el uso de AINE y la prevención del cáncer colorrectal se habían centrado en población específica (p. ej. enfermedad inflamatoria intestinal o poliposis adenomatosa familiar) o incluían el uso de AAS, dejando algunas cuestiones sin resolver sobre este uso de los AINE. En esta revisión sistemática y metanálisis se incluyeron 23 estudios (cohortes y caso-control) publicados hasta abril de 2018, que cumplieron los criterios de inclusión, en los que se trataba de evaluar el efecto quimioprotector de los AINE no-AAS en adultos con edad mayor de 40 años. Se estimó un efecto combinado de: OR = 0,74 (IC 95%; 0,67 – 0,81), pero la heterogeneidad era muy alta (I^2 = 75,9%) y dejaba abiertas varias incógnitas importantes. Por ejemplo, sólo se observaba un efecto protector en mujeres (de raza blanca) y a dosis altas. El metanálisis sugería, por otra parte, un importante sesgo de publicación, destacándose que la mayoría de los estudios eran muy pequeños. Parecía, por tanto, necesario realizar un estudio de mucho mayor tamaño que los llevados a cabo hasta ahora y que permitiera aclarar tales dudas y explorar el efecto protector en diferentes condiciones de uso, como dosis diaria, duración del tratamiento, regularidad del tratamiento, además del efecto del sexo, la edad y el uso concomitante con inhibidores de la bomba de protones, muy frecuentemente utilizados juntos, especialmente en nuestro país (49). Por otra parte, prácticamente ningún estudio ha proporcionado información por principio activo (9, 48) y es importante saber si se trata de un efecto compartido o no por todos ellos (efecto de clase). Finalmente, la gran mayoría de los estudios se habían realizado en EE.UU. y los países del norte de Europa

(Reino Unido y países nórdicos), sin apenas información sobre el efecto en población mediterránea (9, 48) que, como es bien sabido, tiene un estilo de vida diferente y que podría influir en el efecto quimioprotector de los distintos agentes. Hasta la fecha, solo dos estudios se han realizado en población mediterránea (48), uno de ellos realizado en España (50), en el que se incluyeron 196 casos y 228 controles, siendo, por tanto, muy necesario aportar evidencia actualizada, con mayor precisión y, si fuera posible, con mayor validez.

Por último, también parece justificado evaluar el efecto de otros fármacos con alguna actividad antiinflamatoria y que comparten alguna de las indicaciones de los AINE, como los SYSADOA, en los que también se ha reportado un efecto quimioprotector frente a cáncer colorrectal (13, 51-54), o metamizol, cuya posible actividad COX-2 (55) podría hacer suponer un posible efecto quimioprotector similar al de los AINE.

6. OBJETIVOS

6.1. Objetivo general

Validar el uso de la base de datos BIFAP como fuente de información adecuada para el estudio del cáncer colorrectal y, si se confirmara su validez, evaluar el efecto quimioprotector del AAS a dosis bajas y de otros antiagregantes plaquetarios diferentes a AAS, así como de los AINE, SYSADOA y metamizol, en población española.

6.2. Objetivos específicos

1. Construir un algoritmo general de búsqueda de casos de cáncer colorrectal en BIFAP y describir las características del registro de este diagnóstico en la base de datos.
2. Implementar una estrategia de validación general y estimar los porcentajes de casos válidos y no válidos de cáncer colorrectal, así como su valor predictivo positivo y el valor predictivo negativo.
3. Implementar una estrategia de validación adicional que permita mejorar el algoritmo de búsqueda y aumentar el valor predictivo positivo, en el contexto de los estudios de casos y controles.
4. Comparar la tasa de incidencia cruda y estandarizada (tomando la población europea como estándar) de cáncer colorrectal obtenida en BIFAP con la publicada por la Red Española de Registros de Cáncer (REDECAN) para los años 2012 y 2015.
5. Confirmar el efecto quimioprotector del AAS a dosis bajas frente a cáncer colorrectal en BIFAP y caracterizar este efecto.

6. Evaluar si clopidogrel en monoterapia comparte un efecto quimioprotector frente al cáncer colorrectal similar al reportado para el AAS a dosis bajas y caracterizar su efecto, en la población de BIFAP.
7. Confirmar el efecto quimioprotector de los AINE (excluido el AAS) en BIFAP y caracterizar este efecto en diferentes condiciones de uso (dosis diaria, duración y persistencia del tratamiento) y su posible interacción con otros factores como edad y sexo y uso concomitante con los inhibidores de la bomba de protones (IBP).
8. Evaluar el efecto quimioprotector de los AINE por principio activo y comprobar si existen diferencias entre ellos o si, por el contrario, se trata de un efecto de clase.
9. Evaluar el efecto quimioprotector frente al cáncer colorrectal de los SYSADOA y de metamizol, en BIFAP.

7. MÉTODOS

En los servicios de atención primaria de las Comunidades Autónomas (CCAA) participantes en BIFAP se utilizan dos diccionarios de términos médicos diferentes para el registro de los diagnósticos en la historia clínica del paciente: la clasificación internacional en atención primaria, versión 2 (CIAP-2), que se emplea en 8 de las 9 CCAA participantes y, en la restante, la clasificación internacional de enfermedades, en su revisión novena, modificación clínica (CIE-9-MC). En estos diccionarios el diagnóstico se identifica mediante un código numérico o alfanumérico y un descriptor de texto. CIAP-2 es mucho menos granular que CIE-9-MC (686 tipos de diagnósticos vs 23.222 en CIE-9-MC), lo que hace necesaria la inclusión de descriptores más precisos en el *software* informático. Para ello, en ocasiones, el médico puede modificar los descriptores de texto a nivel local para ajustarlo mejor al diagnóstico concreto. Esta fuente de heterogeneidad se gestiona en BIFAP con la creación de un diccionario propio basado en CIAP-2, pero mejorado, llamado CIAP-BIFAP. Este diccionario normaliza los diagnósticos recibidos mediante el mapeo de los diagnósticos similares a los códigos del diccionario CIAP-BIFAP. Además, los algoritmos de búsqueda de diagnósticos en BIFAP pueden incluir búsquedas semánticas para identificar diagnósticos que no han sido mapeados a alguno de los códigos disponibles en este diccionario. Esto aumenta considerablemente la granularidad del nuevo diccionario (5799 descriptores en CIAP-BIFAP). Los diagnósticos en el *software* de registro en atención primaria pueden introducirse fundamentalmente de tres formas diferentes; como diagnóstico (DI), como antecedente personal (NT) o como condicionante (CN). Cuando se registra un diagnóstico como DI, al mismo pueden añadirse comentarios asociados en texto libre mientras que, cuando se registra el diagnóstico como CN ó NT, no es posible asociar comentarios en texto libre. Además de los diagnósticos de enfermedades y los datos generales del

paciente, en BIFAP se registran las prescripciones médicas, las interconsultas, las vacunaciones y los resultados de analíticas y otras pruebas complementarias.

7.1. Validación general de casos (estudio 1)

Se construyó un algoritmo de búsqueda de casos potenciales de cáncer colorrectal basado en códigos diagnósticos en los diccionarios CIAP-BIFAP y CIE-9-MC, así como en búsquedas de cadenas de texto relacionadas con cáncer colorrectal en los descriptores de texto asociados a cada código de diagnóstico. Se incluyeron todos los casos potenciales de cáncer colorrectal que cumplieron los siguientes criterios de inclusión; caso de cáncer colorrectal incidente registrado entre enero de 2001 y diciembre de 2014, con edad comprendida entre 20 y 89 años, con al menos un año de registro previo con su médico de atención primaria y sin antecedentes previos de cáncer de cualquier tipo. Los potenciales casos extraídos de la base de datos fueron posteriormente segmentados en 8 grupos homogéneos en cuanto a las características de la información encontrada de cada paciente en la base de datos. De cada uno de los grupos creados se extrajo una muestra aleatoria de 100 historias clínicas, o menos si el grupo tenía un tamaño menor de 100, que fueron posteriormente validadas de forma manual por dos revisores entrenados y ciegos a las prescripciones médicas para evitar un posible sesgo de clasificación diferencial. Los casos validados manualmente se clasificaron en: casos válidos, casos no válidos y casos incidentes no confirmados. Para que se considerara un caso como válido, además de un código diagnóstico de cáncer colorrectal, debió haberse encontrado al menos uno de los siguientes elementos de información adicional que apoyara el diagnóstico principal: información de atención especializada, localización concreta del tumor, confirmación histopatológica, estadiaje, procedimientos diagnósticos (colonoscopia y/o técnicas de

imagen), tratamientos (radio y/o quimioterapia, cirugía) y/o muerte relacionada con el cáncer. Los casos no válidos fueron aquellos en los que se confirmó un diagnóstico diferente al de cáncer colorrectal. Los casos incidentes no confirmados fueron aquellos en los que se encontró únicamente un código diagnóstico de cáncer colorrectal pero sin ninguna otra información adicional que reforzara ese diagnóstico. Para cada grupo y para toda la muestra global se calculó el porcentaje de casos válidos, de casos no válidos y el valor predictivo positivo, junto con su intervalo de confianza al 95%, ponderado por el peso de cada grupo sobre la muestra total. El valor predictivo negativo y su intervalo de confianza al 95% también se calculó extrayendo una muestra aleatoria de 100 pacientes de la base de datos que no fueron detectados como potenciales casos de cáncer colorrectal por el algoritmo de búsqueda creado.

Finalmente, se calculó la tasa de incidencia cruda de cáncer colorrectal por 100.000 años-persona por sexo y edad y la tasa de incidencia de cáncer colorrectal estandarizada por edad por 100.000 años-persona utilizando la población de referencia europea (56). Ambas tasas se compararon posteriormente con las publicadas para los años 2012 y 2015 (6, 57).

7.2. Validación adicional para los estudios 2 y 3

Adicionalmente, para los dos estudios de casos y controles, se desarrollaron dos procedimientos específicos para mejorar el algoritmo de búsqueda y la estrategia de validación general y así intentar aumentar el valor predictivo positivo:

1. Se validaron de forma manual, por los mismos revisores anteriores, todos los casos potenciales de cáncer colorrectal de los grupos en los que el valor predictivo positivo obtenido en el estudio de validación general fue menor del 50%.
2. De los casos no válidos confirmados en el estudio de validación general se extrajeron los patrones comunes de palabras o cadenas de texto que los identificaban más frecuentemente como un caso como válido. Estos patrones fueron incorporados posteriormente a un nuevo algoritmo de búsqueda y los potenciales casos detectados fueron validados manualmente por los mismos revisores.

Finalmente, se calculó el porcentaje de casos válidos, no válidos y el valor predictivo positivo, con su intervalo de confianza al 95%, en las dos muestras revisadas y para todo el conjunto de grupos tras aplicar esta nueva estrategia.

7.3. Métodos para los estudios de casos y controles (estudios 2 y 3)

Se realizó un estudio de casos y controles de base poblacional empleando la base de datos BIFAP. Los sujetos que cumplieron los criterios de inclusión fueron seguidos desde la entrada en el estudio hasta que ocurriera el primero de uno de los siguientes eventos: registro de un caso incidente de cáncer colorrectal u otro tipo de cáncer, cumpliera 90 años de edad, falleciera o finalizara el periodo de estudio (31 de diciembre de 2014). Los casos de cáncer colorrectal hereditario fueron excluidos.

Los controles se seleccionaron por el método de densidad de incidencia (58) y, de la muestra total, se seleccionaron aleatoriamente 60,000 controles que fueron apareados con los casos por frecuencia de edad, sexo y año de la fecha índice.

Los fármacos estudiados en el estudio 2 fueron: AAS a dosis bajas, clopidogrel y triflusal, y en el estudio 3: los AINE (excluyendo AAS), SYSADOA (que incluye a condroitín sulfato y glucosamina) y metamizol. La exposición a los fármacos de interés se clasificó en usuarios actuales, usuarios recientes y usuarios pasados. En los usuarios actuales se evaluó el efecto de la duración del tratamiento, del sexo, de la edad, de la dosis diaria (cuando fue posible), del uso (prevención primaria o prevención secundaria cardivascular; solo para AAS a dosis bajas), de la persistencia del tratamiento (solo en AINE) y la interacción con otros fármacos como los inhibidores de la bomba de protones (junto con los AINE) o clopidogrel (en terapia dual antiagregante junto con AAS a dosis bajas).

La asociación entre los fármacos de interés y el cáncer colorrectal se estimó calculando los *odds ratios* (OR) y su intervalo de confianza al 95% mediante un modelo de regresión logística no condicional ajustado por posibles factores de confusión.

8. TRABAJOS INCLUIDOS

8.1. Estudio 1

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ORIGINAL REPORT

WILEY

Validation study of colorectal cancer diagnosis in the Spanish primary care database, BIFAP

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Abstract

Purpose: To define and validate a case-finding algorithm to identify incident colorectal cancer (CRC) in the Spanish primary care database BIFAP.

Methods: All potential incident CRC cases recorded during the study period 2001 to 2014 among patients 20 to 89 years old were identified using a defined case-finding algorithm tailored to BIFAP database characteristics and based on codes plus text mining strategies. Potential CRC cases identified by the algorithm were classified into eight homogeneous groups according to recording characteristics. Random samples of 100 cases per group were obtained, and electronic medical records were manually reviewed by two independent researchers. Positive predictive values (PPVs) were estimated per each group and for the whole sample taking into account the stratified sampling. Standardized incidence rate (SIR) of CRC was estimated and compared with that reported by the National Cancer Registry. Negative predictive value (NPV) was also estimated in a random sample of 100 non-CRC patients by the algorithm.

Results: A total of 17 008 potential CRC cases were identified. Most of them (14793; 87%) were recorded as incident diagnosis with linked clinical notes as free text, having this group a PPV of 92.1% (95%CI: 87.1%-95.3%). The overall PPV including all groups was 87.3% (95%CI: 83.3%-90.4%). SIR of CRC was 55.5 per 100.000 person-years. SIR increased with age and was higher in men as compared with women (77.7 vs 38.1 per 100.000 py, respectively) which were in line with those reported by the Network of Cancer Registries in Spain. NPV was of 100% (96.3%-100%).

Conclusions: This study shows a high validity of the CRC cases identified by the algorithm and a high level of CRC recording in BIFAP database and supports its appropriateness to validly identify incident CRC cases in BIFAP.

KEYWORDS

BIFAP, colorectal neoplasms, electronic health care records, pharmacoepidemiology, validation

List of abreviations: BIFAP, Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria; CI, Confidence interval; CPL, Clinical problem list; CRC, Colorectal cancer; DI, Incident diagnosis; PH, Personal History; EHR, Electronic health records; IR, Incidence rate; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; NHS, National Health Service; PH, Personal history; PY, Person-years; PCP, Primary care physician; PPV, Positive predictive value; SIR, Standardized incidence rate

Statement: The authors declare that this paper is original and has not been previously submitted for review to any other journal.

1 | INTRODUCTION

Information derived from databases containing electronic health records (EHR) is increasingly being used to conduct pharmacoepidemiologic research.[1] BIFAP is a primary care database increasingly being used for this purpose.[2-4] In the context of a large case-control study to assess the chemopreventive effect of certain drugs in colorectal cancer (CRC), we carried out a case-validation study of CRC outcome in BIFAP. This effort is particularly important when integral databases as BIFAP are not linked with an external source, such as a cancer registry. In this situation, the utility of the database is dependent on the validity of the recorded diagnosis and the extent to which cases are captured.[5]

To properly identify CRC, as for any other event, case-finding algorithms in EHR must take into consideration the clinical characteristics and patterns of care associated with the diagnosis and management of the disease, the potential use in the context of the study of interest, and the specific recording characteristics of the events in the EHR database.[6] Although case-finding algorithms abound in the literature, information of their accuracy is often missing, and researchers usually do not test them against a gold standard, such as manual review of the medical records.[7]

The validation process of an algorithm in a database is complex, and the resources required will vary depending on the characteristics of the EHR and the strategy implemented for validation including manual review of computerized profiles.[8] In this context, a commonly used strategy is to review all cases identified by the algorithm, in order to reduce the misclassification as much as possible. However, depending on the size of the database and the frequency of the event of interest, this might imply a large number of cases.[2-4,9-11]

To make such manual review in a more efficient way in BIFAP, a validation strategy in a limited random number of cases is proposed, based on patient segmentation into homogeneous subgroups according to recording characteristics deemed relevant for validation purposes and text mining strategies.[12] This strategy might be also helpful for decision making in order to reduce efficiently the false positive proportion.

The aims of this study were (1) to define an algorithm to identify CRC cases tailored to BIFAP characteristics and to describe the recording characteristics of the CRC in BIFAP database; (2) to implement an efficient validation strategy and estimate its positive (PPV) and negative (NPV) predictive value using as gold standard the information in the primary care physician (PCP) computerized medical records (including clinical notes as free text); and (3) to compare the standardized incidence rate (SIR) of CRC in BIFAP with that reported by the Network of Cancer Registries in Spain.

KEY POINTS

- To properly identify the event of interest, case-finding algorithms should be tailored to the specific recording characteristics of the events in the database. Although case-finding algorithms abound in the literature, researchers usually do not test them against manual review of the medical records.
- Case-finding algorithms often result in a large number of potential cases. To make manual review in a more efficient way, a validation strategy is proposed in a limited random number of cases based on patient segmentation into homogeneous subgroups according to registration characteristics deemed relevant for validation purposes. This strategy can be also helpful for decision making in order to reduce efficiently the false positive proportion.
- The algorithm implemented in BIFAP to identify colorectal cancer showed an overall positive predictive value of 87.5% (95%CI: 83.3%-90.4%) and a negative predictive value of 100% (96.3%-100%). The standardized incidence rates of colorectal cancer estimated rendered comparable figures to that reported in the National Cancer Registry. All these findings support the validity of colorectal cancer algorithm to identify CRC cases in BIFAP.

2 | PATIENTS AND METHODS

2.1 | Datasource description

In the Spanish National Health Service (NHS), primary care physicians (PCPs), both general practitioners and pediatricians, act as gatekeepers for and receivers of information from primary and secondary care. Every user of the NHS is registered with a single PCP, and most drug prescriptions are written at this level.

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria) is a longitudinal population-based, research database of EHR from nine participating Autonomous Regions (out of 17) throughout Spain (www.bifap.org). BIFAP is a non-profit program fully funded by the Spanish Agency for Medicines and Medical Devices and the Autonomous Regions take part on a voluntary basis.

In 2015, BIFAP included prospectively recorded data from 5714 PCPs (4871 general practitioners and 843 pediatricians) over the period 2001 to 2014. BIFAP is updated yearly, being the total number of patients available of 7.6 million (38.6 million person-years). BIFAP does not include personal identifiers, and its age and sex distribution is comparable to the Spanish population, covering 17.0% of the total Spanish population. This percentage increases to 55.5% if only the nine Autonomous Regions collaborating in BIFAP are considered. Information available in BIFAP is that recorded by the PCP in their daily routine activities and includes demographics, drug prescriptions, diagnoses, specialist referrals, clinical notes as free text, and other additional health data (ie, tests results, interventions, lifestyle information, etc).

Although there is some heterogeneity in how the information is provided to BIFAP, most participating Autonomous Regions share the same EHR software in primary care. The information is then harmonized into BIFAP common data model.

Currently, two coding systems, with different levels of granularity, coexist in BIFAP: the International Classification of Primary Care (ICPC) and the International Classification of Diseases (ICD-9). The ICPC is the coding system for eight out of nine participant Autonomous Regions, and its granularity is limited as compared with ICD-9 (686 vs 23222 codes, respectively).

In EHR software, the episode of interest is coded and also labeled as incident diagnosis (DI), personal history (PH), and/or clinical problem list (CPL). Any action driven by the PCP and related to that episode (referrals, prescriptions, procedures, laboratory tests, radiology, etc) and additional clinical notes as free text can only be linked to the DI but not to PH or CPL. Clinical notes as free text, once anonymized, can be used to better characterize the coded entries for validation purposes, or to identify diagnoses not properly coded.

To help PCPs to identify the episode of interest, the EHR software contains an internal thesaurus where a list of descriptors of diseases, signs, or symptoms is linked to the different dictionary codes. Often, these descriptors provide more detailed information than that in the corresponding code. Also, only for ICPC-based EHR software, new descriptors can be included at local level, and the PCPs can also modify or add information to the selected episode descriptor. This EHR software flexibility results in a huge number of different descriptors in BIFAP database (3.4 million).

To standardize this, BIFAP has developed its own research dictionary (ICPC-BIFAP) by adding, to the most frequently used descriptors, a fourth digit to the original three-digit ICPC code, increasing its granularity. In 2014, the ICPC-BIFAP dictionary included 5799 indexed terms. ICPC-BIFAP and ICD-9 codes cover about 93.2% of all diagnoses recorded in BIFAP (116.7 million).

2.2 | Definition of a case-finding algorithm for CRC in BIFAP database

An algorithm to identify potential CRC cases was built in BIFAP based on proper code selection within ICPC-BIFAP or ICD-9. To increase its sensitivity, the case-finding algorithm also included text mining strategies that identified CRC recorded as diagnosis (DI/PH/CPL) by the PCP but not indexed as code in ICPC-BIFAP (Supplementary material 1). In fact, this represented 29.2% of all potential CRC cases identified.

2.3 | Validation steps of the CRC diagnosis in BIFAP database

The validation of the CRC diagnosis in BIFAP was performed through five steps:

1. Definition of the study population and identification of potential CRC cases retrieved by the case-finding algorithm.
2. Segmentation of those into homogeneous groups according to recording characteristics deemed relevant for validation purposes.
3. Manual review of the EHR in random samples per group.
4. PPV calculation per each group and for the whole sample taking into account the design effect due to the stratified sampling method.
5. Estimation of the SIR of CRC and comparison with that reported by the Network of Spanish Cancer Registries.

Potential CRC cases fulfilled the following inclusion criteria: incident CRC diagnosis identified by the algorithm between January 2001 and December 2014; aged 20 to 89; with at least 1-year registry with their PCP and no previous record of cancer (any location). The computer detected date of the CRC was considered as index date for the study.

We identified a total of 17 008 potential incident CRC cases that were then segmented into subgroups based on the following recording criteria:

1. Firstly recorded as DI versus CPL or PH.
2. DI with or without linked clinical notes as free text.
3. More than one recorded CRC episode.
4. Availability of information supporting the validity of the CRC diagnosis like stage, diagnostic procedures, or treatments (surgery, radio/chemotherapy). Text mining search strategies were then developed to identify related semantic terms in the recorded diagnosis or in free text clinical notes linked

Given the previous criteria, eight groups were created. The detailed characteristics of the defined groups are included in Table 1.

Manual review of the PCP computerized medical records was performed in random samples of up to 100 cases per group (if a group had less then we reviewed them all) by two different researchers blinded to drug prescriptions.

This segmentation strategy was designed to gain a deep knowledge of how the information is recorded in BIFAP database, and to estimate the PPV of the different groups. This allows performing a more informed decision aiming to improve the PPV of the final cases included in the study.

In addition to the case-finding algorithm search criteria, text mining algorithms identified a total of 4828 potential cases in which CRC-related semantic terms were recorded as free text in clinical notes in the absence of a CRC diagnosis (DI/PH/CPL) captured by the CRC case-finding algorithm. However, a manual review of a random sample of 200 of them confirmed only 15 as valid cases (PPV of 8.0%), and we decided not to consider this strategy any further. However, these cases were taken into account in a sensitivity analysis for the estimation of the CRC incidence rate (see statistical methods section).

2.4 | Validation criteria used in the manual review

CRC cases reviewed were considered as valid incident cases if there was evidence supporting the CRC diagnosis, mainly as free text in clinical notes, such as follows: diagnosis based on hospital or specialist report; accurate location of the tumor; confirmation by histopathology; CRC diagnosis enriched with additional information defined as the availability of staging, diagnostic procedures (imaging techniques,

TABLE 1 Characteristics of the defined groups for validation

Group	CRC Code Label	> 1 CRC DI Registered[a]	Linked Free Text Notes[b]	Supporting Information[c]	Number of Potential Cases, %
G1	CPL or PH	NO	NA	NO	294 (1.7%)
G2	CPL or PH	NO	NA	YES	60 (0.4%)
G3	CPL or PH	YES	NA	YES	168 (1.0%)
G4	CPL or PH	YES	NA	NO	361 (2.1%)
G5	DI	NO	NO	NO	1180 (6.9%)
G6	DI	YES[d]	NO	YES[d]	152 (0.9%)
G7	DI		YES	NO	1382 (8.1%)
G8	DI		YES	YES	13 411 (78.9%)
Total					*17 008 (100%)*

Abbreviations: DI, incident diagnosis; CPL, Clinical problem list; PH, personal history; CRC, Colorectal cancer; NA, not applicable;

[a]More than one CRC DI episode in different dates registered in the EHR.

[b]Availability of free text clinical notes linked to the CRC DI. Free text clinical notes are only linked to DI, but not to CPL or PH.

[c]Availability of information supporting the validity of the CRC diagnosis like stage, diagnostic procedures, or treatments (surgery, radio/chemotherapy). Text mining search based on related semantic terms were used to identify those concepts in the registered diagnosis or in the free text clinical notes linked.

[d]Any of them.

colonoscopy), treatments (radio/chemotherapy, surgery), or cancer-related death. Valid incident cases were classified as non-hereditary CRC, hereditary CRC and in situ CRC. Non-valid cases were classified into the following categories: prevalent CRC; other primary cancer; benign tumor; screening activities; CRC of a relative or others (ie, contradictory diagnosis). For a certain number of potential cases, the reviewers only found the diagnosis without additional information allowing to classify it in any of the previous categories and were classified in an intermediate category ("not confirmed incident case").

2.5 | Statistical methods

The PPV and its corresponding 95% confidence interval (95%CI) were calculated, for each group, as the number of valid cases among the total number of potential cases. PPV and 95%CI were also calculated for the whole sample taking into account the design effect due to the stratified sampling (complex sample module, SPSS v19).

The NPV and its corresponding 95%CI were also calculated by estimating the proportion of confirmed non-CRC cases in a sample of 100 patients randomly selected among those not identified as cases by the algorithm.

CRC crude incidence rates (IR) per 100.000 person-years (py) were calculated by sex and by 10-year bands, also taking into account the stratified sampling. Age-SIR were estimated using the European population as Waterhouse et al,[13] in order to compare the rates estimated in BIFAP with those reported in a Network of Cancer Registries in Spain.[14-16]

As sensitivity analyses, SIRs were also calculated considering the previously described 8% of valid CRC cases identified as free text in clinical notes.

3 | RESULTS

The characteristics of the CRC case-finding algorithm defined are detailed in the Supplementary material 1. The number of potential CRC cases identified by the algorithm was 17 008. Most of them were firstly recorded as DI (groups G5-G8) as compared with those recorded as CPL or PH (G1-G4) (94.8% vs 5.2%, Table 1). Among the former, the majority of cases (14 793; 87.0%) had a recorded DI together with linked free text clinical notes (G7-G8), and 7.8% had a CRC recorded as DI but without linked free text clinical notes (G5-G6) (Table 1).

Among CRC cases firstly identified as CPL or PH (G1 to G4), 59.9% had later a CRC recorded as DI (G3-G4) (Table 1).

3.1 | Validation of CRC case-finding algorithm and CRC registration characteristics in BIFAP

The number of cases reviewed for validation was 760 (100 per seven groups and a group of 60 cases—actually, all patients included in such a group). In total, 525 were classified as valid and 259 as non-valid cases. The detailed information of results in the validation sample (unweighted count) and the estimations for all cases identified by the algorithm (weighted count) are included in Table 2.

The overall PPV was 87.3% (95%CI: 83.3%-90.4%). Results of the validation for each of the eight subgroups defined are displayed in Supplementary material 2.

Most CRC confirmed cases (87.0%) were recorded as DI with free text clinical notes linked (G7/G8). Among them, the PPV was 92.1% (95%CI: 87.1%-95.3%) (Table 3). When the DI did not have clinical notes linked (G5/G6), the PPV decreased to 47.0% (95%CI: 38.9%-55.3%) (Table 3).

In the small subgroup of potential CRC cases identified as CPL or PH (G1 to G4), the PPV is much higher among those with a subsequent recorded DI than those without it (91.6% vs 30.1%; Table 3).

The availability of some CRC information regarding location, stage, or treatments entered in the EHR as free text in clinical notes is included in Table 4.

The computer-detected index date was confirmed by reviewers in 64.1% of manually reviewed cases. In 28.6%, the final index date assigned by reviewers occurred within a window period of 180 days prior to the computer-detected index date, and in 7.2% of cases the re-assigned date was beyond that window.

TABLE 2 Validation categories results in the sample and all potential colorectal cancer cases

Validation Categories	Cases Reviewed (Unweighted Count)	All CRC Cases (Weighted Count (%))[a]
Confirmed incident case	*525*	*14842 (87.2%)*
Non-hereditary CRC		
In situ CRC		
Hereditary CRC		
Not confirmed incident case[b]	*51*	*560 (3.3%)*
Prevalent case	*57*	*371 (2.2%)*
Confirmed non-CRC case	*127*	1235 (7.2%)
Other primary cancer		
Benign tumor		
CRC of a relative[c]		
Screening activities		
Other reasons		
Total	**760**	**17 008 (100%)**

Abbreviation: CRC, colorectal cancer.

[a]Cases estimated and percentage by category taking into account the design effect due to the sampling method (stratified sampling).

[b]Potential cases with a CRC diagnosis but lacking additional information to classify it as a confirmed incident case, a prevalent case or a non-CRC confirmed case.

[c]The CRC episode identified by the algorithm belongs to a relative.

TABLE 3 Positive predictive value of colorectal cancer case-finding algorithm according registration characteristics

Registration Characteristics	*n* (%) of Cases	PPV (CI95%)[a]
First registered as CPL or PH (G1-G4)	883 (5.2%)	66.9% (63.7%-70.0%)
With NO further CRC DI (G1/G2)	354 (2.1%)	30.1% (24.5%-36.3%)
With further CRC DI (G3/G4)	529 (3.1%)	91.6% (87.5%-94.5%)
First registered as DI (G5-G8)	16 125 (94.8%)	88.4% (84.1%-91.6%)
With NO clinical notes linked (G5/G6)	1332 (7.8%)	47.0% (38.9%-55.3%)
With clinical notes linked (G7/G8)	14 793(87.0%)	92.1% (87.1%-95.3%)
Total (DI/PH/CPL)	**17 008**	**87.3% (83.3%-90.4%)**

Abbreviations: CPL, clinical problem list; CRC, colorectal cancer; DI, incident diagnosis; PH, personal history; PPV, positive predictive value.

[a]% estimated taking into account the design effect due to the sampling method (stratified sampling).

Among the 100 non-CRC patients randomly selected for validation, all were confirmed non-CRC cases after the manual review of the PCP computerized medical records leading to a NPV of 100% (CI95% 96.3%-100%).

3.2 | CRC incidence in BIFAP database

Crude IR and SIRs of CRC were 67.5 and 55.5 per 100.000 py, respectively. IR increased with age and was higher in men as compared with women (SIR: 77.7 vs 38.1 per 100.000 py) (Figure 1). SIR increases to 57.1 per 100.000 py when we added the 8% of confirmed cases identified as free text in clinical notes in the absence of a CRC diagnosis captured by the algorithm (sensitivity analysis. See "Validation steps of the CRC diagnosis in BIFAP database section").

Standardized incidence rates estimated in BIFAP were rather comparable to those from Network of Cancer Registries in Spain (Table 5).

4 | DISCUSSION

The present study shows that the case-finding algorithm defined to identify incident cases of CRC in BIFAP had a good performance, with a PPV and a NPV of 87.3% (95%CI:83.3%-90.4%) and 100% (CI95%:96.3%-100%), respectively, using as gold standard the manual review of the PCP computerized medical records (including clinical notes as free text). In addition, the SIR of CRC estimated in BIFAP after applying the algorithms rendered comparable figures to that reported in the Network of Cancer Registries in Spain suggesting a high level of CRC recording in BIFAP. This findings support the validity of the CRC case-finding algorithm to identify CRC cases in BIFAP database.

4.1 | Validation of the CRC case-finding algorithm and CRC recording characteristics in BIFAP

Colorectal cancer is diagnosed at specialist level. Nevertheless, CRC recording is expected to be complete in the primary care database BIFAP given: the natural history of the disease and its health care utilization resources in Spain; the PCPs acting as gatekeepers within the Spanish NHS and the characteristics of the EHR with specific ICPC and ICD-9 codes available for CRC.

To the best of our knowledge, this is the first validation study of CRC diagnosis in a Spanish computerized datasource, different from cancer registries. Results show a high validity of the BIFAP algorithm, to identify incident CRC diagnosis (PPV over 87%) using as gold standard the manual review of the PCP's computerized medical records (including clinical notes as free text). Other studies[5,17-20] have also reported high PPVs for different datasources of other European countries (UK,[5,17,20] France,[18] Denmark[19]) and using different "gold standards" (ie, cancer registries,[17-20] linkage to hospital records,[5,20] manual review of clinical records[5,20]).

In addition, no cases were identified in a sample of 100 patients of the cohort without a CRC identified by the case-finding algorithm during the follow-up, leading to a negative predictive value of 100% (CI95% 96.3%-100%).

Concerning recording characteristics, results show that, most CRC cases (94.8%, Table 1) are included in BIFAP as DI having, most of them, linked clinical notes as free text. As expected, these cases had higher PPV as compared with those without linked clinical notes (92.1% vs 47.0%, Table 2). Cases of CRC recorded with a DI but without linked clinical notes (G5-G6) represent a low percentage of all potential cases (7.8%, Table 1). Among them, confirmed cases were mostly based on additional information available as free text

TABLE 4 Characteristics of colorectal cancer registered in the primary care physicians' electronic medical records

Feature	% (95%CI)[a]	Feature	% (95%CI)[a]
Site		*Surgery*	
Colon	43.6% (35.3%-52.2%)	Yes	78.9% (71.6%-84.7%)
Rectum[b]	28.6% (21.4%-37.1%)	No	2.1% (0.6%-7.1%)
Sigma	21.9% (15.4%-30.1%)	Not specified	18.9% (13.5%-25.9%)
Not specified	6.0% (2.9%-11.9%)	*Chemotherapy*	
Stage		Yes	39.2% (30.9%-48.2%)
Dukes A	1.2% (0.3%-5.2%)	No	6.2% (3.0%-12.3%)
Dukes B1	1.0% (0.2%-5.7%)	Not specified	54.6% (45.7%-63.2%)
Dukes B2	4.1% (1.7%-9.4%)	*Radiotherapy*	
Dukes C	8.8% (4.9%-15.4%)	Yes	10.0% (5.7%-16.9%)
Dukes D	15.8% (10.4%-23.5%)	No	6.0% (2.9%-12.2%)
Not specified	69.1% (60.4%-76.6%)	Not specified	84.0% (76.2%-89.6%)

[a]% estimated taking into account the design effect due to the sampling method (stratified sampling).

[b]CRC reported to be located in rectum-sigma was included under rectum.

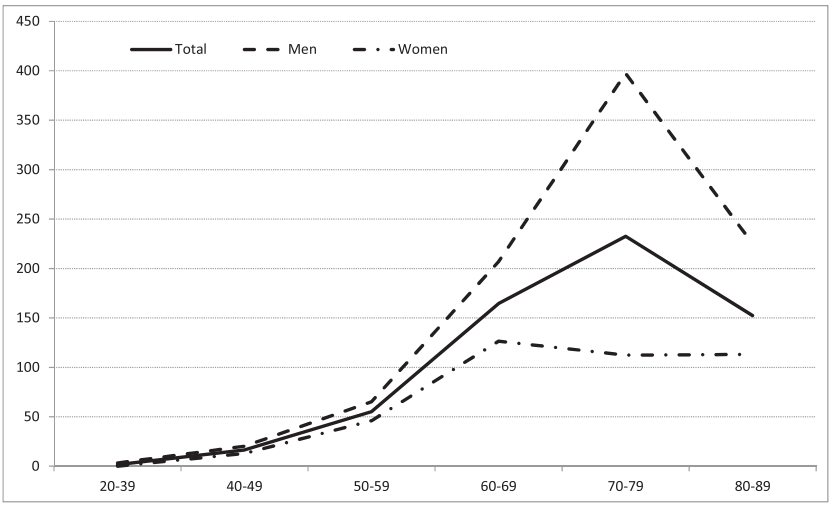

FIGURE 1 Incidence rates (per 100.000 person-years) of colorectal cancer by sex and age strata (period 2001-2014)

TABLE 5 Crude and standardized CRC incidence rates of BIFAP case-finding algorithm in different scenarios and comparison with incidence reported in the National Cancer Registry

	Crude Incidence Rates (per 100.000 py) (CI95%)			Standardized Incidence Rates (per 100.000 py) (CI95%)		
	M	F	Total	M	F	Total
IR in BIFAP case-finding algorithm (2001-2014)	84.5 (82.8-86.2)	44.1 (42.9-45.2)	63.0 (62.0-64.1)	77.7 (76.1-79.3)	38.1 (37.1-39.2)	55.5 (54.6-56.4)
Sensitivity analysis[a]	86.5	45.4	64.7	79.7 (78.1-81.3)	39.3 (38.2-40.3)	57.1 (56.1-58.0)
IR in network of Spanish cancer registries (2012)[b14]	NA	NA	NA	65.6	35.3	48.9
IR in network of Spanish cancer registries (2015)[c15]	108.7 (97.4-121-4)	70.6 (63.9-78.4)	NA	77.8 (69.8-86.8)	42.0 (38.1-46.7)	NA

Abbreviations: CI95%, 95% confidence interval; IR, incidence rate; NA, not reported in the publication.

[a]After including for calculations the 8% of confirmed cases identified as free text in clinical notes in absence of a diagnosis captured by the case-finding algorithm (see Patients and Methods).

[b]Includes information of 12 Spanish population-based cancer registries providing data for incidence calculations. CI95% not available.

[c]Information of 15 Spanish population-based cancer registries providing data for incidence calculations. Total estimations not available.

linked to episodes not captured by the algorithm or to episodes not related to a CRC diagnosis.

The percentage of cases firstly recorded as CPL or PH is very low. These entries, in the absence of a DI, usually refer to a past history of CRC. Consequently, the date of the episode might represent the date of the CRC reported to the PCP rather than the date of the CRC diagnosis. Also, clinical notes entered as free text can only be linked to DI but not to CPL or PH. This explains the higher PPV for those with an additional DI of CRC (G3/G4) as compared with those without it (G1/G2). This would support not to include CRC cases firstly identified as CPL or PH in the absence of additional DI when computer-based algorithms are used to find incident (but not prevalent) CRC cases.

Information on CRC location and surgery is usually available in the EHR. On the other hand, stage, diagnostic procedures, treatments (radio/chemotherapy), and symptoms are infrequently entered as free text in clinical notes. Similar findings have been reported for other primary care databases.[5,21] This lack of recording in BIFAP is dependent on the PCP recording habits and might be in part related to the direct access to hospital records in the office by the PCP using computer facilities in real time.

The classification of cases detected by the algorithm, according to characteristics deemed relevant for validation purposes, together with the validation of a sufficient number of CRC cases per stratum, allowed us to obtain valid PPV estimates within the various strata as well as overall. This strategy permits to inform whether additional actions are required to further reduce the proportion of false positives in the context of a particular study. As an example, the full review of groups with a PPV lower than 50% (G1/G2/G5; n = 1534, Supporting Information 2) might have increased the PPV up to 91%.

4.2 | CRC incidence in BIFAP database

The case-finding algorithm should also have a good sensitivity taking into consideration the tradeoffs between accuracy measures.[22] This would allow getting proper estimations in incidence studies and conversely would reduce the likelihood of misclassification among controls in, for example, case-control studies using incident CRC cases.

Our results show that the SIR of CRC estimated in BIFAP database using the case-finding algorithm is comparable to that reported in the Network of Cancer Registries in Spain,[1-3] suggesting a high level of CRC recording in BIFAP (external validity).

When comparing incidence rate figures obtained in BIFAP, with those from other datasources as external validation, we should take into account: the study period, the variability of figures across regions,[15] and the case definition comparability. In this regard, it is important to note that BIFAP does not include information from eight Autonomous Regions which may present some differences in the CRC incidence rates with respect to the nine regions included and that the Network of Cancer Registries in Spain does not cover the whole Spanish population and its study period (years 2012 and 2015) is different of that in BIFAP (2001-2014). Also, unlike the case definition in the Network of Cancer registries in Spain, our results include in-situ CRC, which represents 1.0% of total confirmed cases and does not include CRC cases that happens after another malignant cancer (secondary CRC cases). Nevertheless, the impact of these differences in the comparisons between both datasources is expected to be low.

Consequently, this validation study also shows a high level of CRC recording in BIFAP database and supports the appropriateness of the algorithm implemented to validly identify incident CRC cases.

5 | CHARACTERISTICS AND LIMITATIONS

BIFAP includes only information recorded by the PCP in the EHR. At present, information from other levels of care (ie, hospital records, vital statistics, cancer registries, etc) is not available by direct linkage with the corresponding datasource. Yet, patient's information at specialist level is available for the PCP given its role as gatekeeper in the Spanish NHS. Thus, main patient's diagnosis and/or procedures at specialist level are usually included in the PCP computerized medical records, either in a structured way (i.e coded) or as free text.

The strategies to properly identify cases in a database need to be tailored to the EHR characteristics. In this context, the use of list of codes, as received in BIFAP, without further processing would lead to substantial misclassification. Thus, case-finding algorithms in BIFAP include optimized dictionary codes and additional tested text mining strategies to increase their sensitivity and specificity.

In this validation study, we used the manual review of the PCP's clinical profiles as gold standard for the case-finding algorithm validation. The study was not designed to also estimate the sensitivity and specificity of the algorithm. Notwithstanding, both parameters are expected to be high given: the expected high recording of CRC given the PCP role as gatekeeper and the natural history of CRC; the similar standardized IR in BIFAP as compared with those in the Network of Cancer Registries in Spain supporting a high level of CRC recording in BIFAP database; the tested text mining strategies included in the algorithm that identified a 29.2% of total CRC recorded as diagnosis (see Supporting Information 1); the low percentage of CRC cases identified exclusively as free text in clinical notes and the high PPV and NPV figures of the CRC case-finding algorithm reported.

In spite of the good performance of the case-finding algorithm, potential misclassification of cases cannot be completely rule-out, although, if non-differential with respect to the exposure, it would bias the RR towards the null hypothesis (unless in case of perfect specificity when the RR would remain unbiased).[23]

ETHICS STATEMENT

The scientific committee of BIFAP granted a positive opinion to the study protocol (#10/2015). The investigators had access to only fully anonymized data, and under this condition, no specific ethics review was required according to Spanish law.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Coloma PM, Schuemia MJ, Trifiro G, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR project. *Pharmacoepidemiol Drug Saf*. 2011;20(1):1-11.
2. de Abajo FJ, Gil MJ, Bryant V, Timoner J, Oliva B, García-Rodríguez LA. Upper gastrointestinal bleeding associated with NSAIDs, other drugs and interactions: a nested case-control study in a new general practice database. *Eur J Clin Pharmacol*. 2013;69(3):691-701.
3. García-Poza P, de Abajo FJ, Gil MJ, Chacón A, Bryant V, García-Rodríguez LA. Risk of ischemic stroke associated with non-steroidal anti-inflammatory drugs and paracetamol: a population-based case-control study. *J Thromb Haemost*. 2015;13(5):708-718.
4. de Abajo FJ, Gil MJ, García Poza P, et al. Risk of nonfatal acute myocardial infarction associated with non-steroidal antiinflammatory drugs, non-narcotic analgesics and other drugs used in osteoarthritis: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2014;23(11):1128-1138.
5. Cea Soriano L, Soriano-Gabarró M, García Rodríguez LA. Validity and completeness of colorectal cancer diagnoses in a primary care database in the United Kingdom. *Pharmacoepidemiol Drug Saf*. 2016;25(4):385-391.
6. Lanes S, Brown JS, Haynes K, Pollack MF, Walker AM. Identifying health outcomes in healthcare databases. *Pharmacoepidemiol Drug Saf*. 2015;24(10):1009-1016.
7. Hansen RA, Gray MD, Fox BI, Hollingsworth JC, Gao J, Zeng P. How well do various health outcome definitions identify appropriate cases in observational studies? *Drug Saf*. 2013;36(Suppl 1):S27-S32.
8. García Rodriguez LA, Ruigomez A. Case validation in research using large databases. *Br J Gen Pract*. 2010;60(572):160-161.
9. Saiz LC, Garjón J, Gorricho J, Erviti J, Gil-García MJ, Martín-Merino E. Validation and incidence of community-acquired pneumonia in patients with type 2 diabetes in the BIFAP database. *Epidemiol Infect*. 2017;145(14):3056-3064.
10. Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, et al. for the EU-ADR Consortium. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. *BMJ Open*. 2013 Jun 20;3(6). pii: e002862. https://doi.org/10.1136/bmjopen-2013-002862
11. García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation*. 2004;109(24):3000-3006.
12. Lee Y, Shin SY, Ahn SM, Lee JH, Kim WS. Validation for accuracy of cancer diagnosis in electronic medical records using a text mining method. *Stud Health Technol Inform*. 2015;216:882.
13. Waterhouse, J., Muir, C.S., Correa, P., Powell, J., 1976. Cancer incidence in five continents Vol. III, IARC Scientific Publications. IARC, Lyon.
14. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.
15. Galceran J, Ameijide A, Carulla M, Mateos A, et al. Cancer incidence in Spain, 2015. *Clin Transl Oncol*. 2017;19(7):799-825.
16. López-Abente G, Núñez O, Pérez-Gómez B, Aragonés N, Pollán M. *La situación del cáncer en España: Informe 2015*. Madrid: Instituto de Salud Carlos III; 2015.
17. Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. *Cancer Epidemiol*. 2012;36(5):425-429.
18. Quantin C, Benzenine E, Hagi M, et al. Estimation of national colorectal-cancer incidence using claims databases. *J Cancer Epidemiol*. 2012;2012:298369.
19. Helqvist L, Erichsen R, Gammelager H, et al. Quality of ICD-10 colorectal cancer diagnosis codes in the Danish National Registry of Patients. *Eur J Cancer Care (Engl)*. 2012;21(6):722-727.
20. Margulis AV, Fortuny J, Kaye JA, et al. Validation of cancer cases using primary care, cancer registry, and hospitalization data in the UK. *Epidemiology*. 2017 Nov 9. https://doi.org/10.1097/EDE.0000000000000786. [Epub ahead of print];1.
21. García Rodríguez LA, Soriano-Gabarró M, Bromley S, Lanas A, Cea SL. New use of low-dose aspirin and risk of colorectal cancer by stage at diagnosis: a nested case-control study in UK general practice. *BMC Cancer*. 2017;17(1):637.
22. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. *J Clin Epidemiol*. 2012;65(3):343-349.
23. Greenland and Lash, Bias Analysis, Chapter 19, Rothman/Greenland/Lash, eds, Wolters Kluwer/Lippincott Williams & Wilkins, Third Ed, 345–38.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Material adicional no publicado. Estudio de validación

Tabla 1. Número de casos válidos y no válidos entre los sujetos con patrones de texto comunes a los no casos validados en el estudio de validación general.

	Caso válido (n=744)	**Caso no válido (n=1.016)**	**Total* (n=1.760)**
Patrón de texto (%):			
"Genético"	71 (71,7)	28 (28,3)	99
"Hereditario"	8 (38,1)	13 (61,9)	21
"Lynch"	25 (20,8)	95 (79,2)	120
"Familiar"	7 (2,2)	316 (97,8)	323
Fechas	263 (62,9)	155 (37,1)	418
Colonoscopia	191 (43,1)	252 (56,9)	443
Cribaje	179 (53,3)	157 (46,7)	336

*n=1,760 > 1097 debido a que pudo haber sujetos con varios criterios

Tabla 2. Escenarios posibles de validación

	Validación general	**Revisión completa grupos con VPP<50%**	**Mejora del algoritmo con patrones de texto**
Casos totales incluidos	17008	16136	15491
Falsos positivos (n)	2468	1456	664
Falsos positivos (%)*	14,5%	9,0%	4,3%
VPP (%)*	85,5%	91,0%	95,7%

*ponderado por el peso de cada grupo

8.2. Estudio 2

Rodríguez-Miguel A, García-Rodríguez LA, Gil M, Montoya H, Rodríguez-Martín S, de Abajo FJ. Clopidogrel and Low-Dose Aspirin, Alone or Together, Reduce Risk of Colorectal Cancer**.** ***Clin Gastroenterol Hepatol. 2018. pii: S1542-3565(18)31388-0. doi: 10.1016/j.cgh.2018.12.012. Epub ahead of print.***

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Clopidogrel and Low-Dose Aspirin, Alone or Together, Reduce Risk of Colorectal Cancer.

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Abstract

BACKGROUND & AIMS: The antiplatelet effect of low-dose aspirin, via inhibition of cyclooxygenase-1, might contribute to its ability to reduce the risk of colorectal cancer (CRC). Antiplatelet agents with a different mechanism, such as clopidogrel, might have the same effects. We aimed to quantify the effects of low-dose aspirin and clopidogrel on the risk of CRC in a Mediterranean population.

METHODS: We performed a nested case-control study using a primary care database (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria) in Spain. We collected data, from 2001 through 2014, on 15,491 incident cases of CRC and 60,000 randomly selected individuals (controls), frequency-matched to cases by age, sex, and year. To estimate the association between exposure to different antiplatelet agents and the risk of colorectal cancer, we built multiple logistic regression models and computed the adjusted-odds ratios (AORs) and their respective 95% CIs.

RESULTS: Use of low-dose aspirin was associated with a reduced risk of CRC overall (AOR, 0.83; 95% CI, 0.78-0.89) and in patients receiving treatment for more than 1 year (AOR, 0.79; 95% CI, 0.73-0.85). Use of clopidogrel was associated with a decreased risk of CRC overall (AOR, 0.8; 95% CI, 0.69-0.93) and in patients receiving treatment for more than 1 year (AOR, 0.65; 95% CI, 0.55-0.78). Dual antiplatelet therapy had the same effect as either drug taken as monotherapy. No modification by sex or age was observed.

CONCLUSIONS: In a nested case-control study of a primary care database in Spain, we found clopidogrel use, alone or in combination with low-dose aspirin, to reduce the risk of CRC by 20% to 30%, a magnitude similar to that of low-dose aspirin alone. These data support the concept that inhibiting platelets is an effective strategy for prevention of CRC.

KEYWORDS: COX-1 Inhibitor; Chemoprevention; Colon Cancer; P2Y(12) Antagonist

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CLOPIDOGREL AND LOW-DOSE ASPIRIN, ALONE OR TOGETHER, REDUCE RISK OF COLORECTAL CANCER

Short title: clopidogrel prevents colorectal cancer

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Abbreviations list:

ADP: adenosine diphosphate

AOR: adjusted odds ratio

BIFAP: base de datos para la investigación farmacoepidemiológica en atención primaria

BMI: body mass index

CI: confidence interval

COX: cyclooxygenase

CRC: colorectal cancer

DAPT: dual antiplatelet therapy

GI: gastrointestinal

ICPC: international classification in primary care

ICD: international classification of diseases

NSAID: non-steroidal anti-inflammatory drugs

OR: odds ratio

SD: standard deviation

SYSADOA: symptomatic slow action drugs for osteoarthritis

USPSTF: United States Preventive Services Task Force

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Author contributions: Francisco J. de Abajo and Luis A. García Rodríguez performed the study design and supervised the whole study, including data extraction, analysis and interpretation. Also, they made a critical revision of the manuscript for important intellectual content.

Antonio Rodríguez-Miguel performed the acquisition, analysis and interpretation of data and wrote the first draft.

Miguel Gil performed the acquisition of data and critical revision of the manuscript for important intellectual content.

Héctor Montoya and Sara Rodríguez-Martín performed the acquisition, analysis and interpretation of data.

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ABSTRACT

Background & Aims: The antiplatelet effect of low-dose aspirin, via inhibition of cyclooxygenase-1, might contribute to its ability to reduce risk of colorectal cancer (CRC). Antiplatelet agents with a different mechanism, such as clopidogrel, might have the same effects. We aimed to quantify the effects of low-dose aspirin and clopidogrel on risk of CRC in a Mediterranean population.

Methods: We performed a nested case–control study using a primary care database (BIFAP) in Spain. We collected data, from 2001 through 2014, on 15,491 incident cases of CRC and 60,000 randomly selected individuals (controls), frequency-matched to cases by age, sex, and year. To estimate the association between exposure to different antiplatelet agents and risk of colorectal cancer, we built multiple logistic regression models and computed the adjusted-odds ratios (AOR) and their respective 95% CIs.

Results: Use of low-dose aspirin was associated with a reduced risk of CRC overall (AOR, 0.83; 95% CI, 0.78–0.89) and in patients receiving treatment for more than 1 year (AOR, 0.79; 95% CI, 0.73–0.85). Use of clopidogrel was associated with a decreased risk of CRC overall (AOR, 0.8; 95% CI, 0.69–0.93) and in patients receiving treatment for more than 1 year (AOR, 0.65; 95% CI, 0.55–0.78). Dual antiplatelet therapy had the same effect as either drug taken as monotherapy. No modification by sex or age was observed.

Conclusion: In a nested case–control study of a primary care database in Spain, we found clopidogrel use, alone or in combination with low-dose aspirin, to reduce risk of

CRC by 20%–30%, a magnitude similar to that of low-dose aspirin alone. These data support the concept that inhibiting platelets is an effective strategy for prevention of CRC.

KEY WORDS: colon cancer, chemoprevention, COX-1 inhibitor, $P2Y_{12}$ antagonist

What You Need to Know

Background: The chemoprotective effect of low-dose aspirin against colorectal cancer (CRC) is likely to be mediated by its effects on platelets. We investigated whether a different antiplatelet drug, clopidogrel, which has a different anti-platelet mechanism, also affects risk of CRC.

Findings: In an analysis of a primary care database in Spain, we found that clopidogrel use reduced risk of CRC with time, similar to low-dose aspirin (20%–30% reduction in risk). The reduction in risk was observed starting at 1 year of treatment.

Implications for patient care: Patients treated with antiplatelet drugs to prevent cardiovascular disorders could receive an additional benefit of reduced risk of CRC. Such an effect could appear earlier than previously reported.

INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent types of cancer worldwide with higher incidence rates reported in western lifestyle countries in Europe, North America and Oceania[1,2]. A large number of studies have reported a protective effect of low-dose aspirin against CRC[3,4]. Based on this evidence, in 2016 the updated guidelines of the United States Preventive Services Task Force (USPSTF) endorsed the use of low-dose aspirin for prevention of cardiovascular diseases and CRC among adults aged 50-59 who have a 10% or greater 10-year cardiovascular risk and no increased risk of bleeding with a life-expectancy of at least 10 years[5]. For adults aged 60-69 with the same clinical characteristics the USPSTF recommended to individualize the decision to initiate treatment[5].

The mechanism of action of low-dose aspirin to explain its protective effect is subject to debate. Although aspirin is an NSAID and these drugs are known to prevent CRC through the inhibition of the cyclooxygenase (COX)-2 in epithelial and stromal cells in large bowel, at low-doses (75-300mg/day) aspirin has only transient effects on this isozyme, while permanently inactivating platelet-COX-1 and suppressing thromboxane A_2 production[6]. The apparent lack of dose-dependence of the chemoprotective effect of aspirin, as well as the potential role of locally activated platelets in upregulating COX-2 expression in adjacent nucleated cells of the intestinal mucosa, have led to postulate that low-dose aspirin could exert its chemoprotective effect via its antiplatelet action[6].
It is unknown whether other antiplatelet drugs with a different mechanism of action (e.g. clopidogrel), could share the chemoprotective effect of low-dose aspirin because few studies have been published so far to explore this hypothesis[7-9].

The primary aim of the present study was to test if clopidogrel shares a similar chemoprotective effect on CRC compared to low-dose aspirin. As most studies examining the association between low-dose aspirin and CRC have been carried out in non-Mediterranean populations, we tried to verify first that in a Mediterranean population low-dose aspirin shows a similar chemoprotection as in other communities.

METHODS

Data source

The present study was performed using BIFAP (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria), a longitudinal, population-based, database of electronic health records in primary care, representative of the Spanish population with respect to age and sex distribution[10]. BIFAP has been validated through multiple studies[10] and successfully compared to other well-known European databases[11]. Information in BIFAP includes: demographics, prescriptions, diagnoses, specialist referrals, laboratory results and other exploratory tests, all often enriched by free-text notes. Over the study period, BIFAP included 7.6 million patients (38.6 million person-years) and 5.1 years of mean follow-up from 9 Spanish Regions (out of 17).

Study design

We performed a case-control study nested in a primary cohort selected from BIFAP over the period January 1, 2001 to December 31, 2014. Individuals aged 20 to 89 and free of cancer entered the cohort once they were registered with their primary care physician for at least 1 year (the start date). Members of the study cohort (n=5,310,198)

were then followed-up until the earliest occurrence of an incident CRC, 90 years old, other cancer diagnosis, death or end of the study.

Case-finding algorithm and selection of cases

Extensive validation of CRC diagnosis in BIFAP was performed and published elsewhere[12]. Cases were considered valid when, additionally to a CRC record, we found supporting information as hospital or specialist referral, diagnostic procedures, accurate location, histopathology, staging, treatment or cancer-related death. Their index date was the first CRC record. Hereditary CRC were excluded. The overall positive predictive value was 95.7% (Supplementary Material, Methods 1).

Selection of controls

We randomly selected 60,000 controls frequency-matched to cases by age, sex and year of index date from the cohort using an incidence density sampling. Their index date was a random date selected from their period of observation.

Exposure definition

We categorized cases and controls as *current users* when the supply of last prescription finished within 90 days before the index date; *recent users* when the supply finished 91-365 days before the index date; *past users* when the supply finished more than one year before the index date; and as *nonusers* when there was no recorded prescription, ever.

Three antiplatelet drugs were studied: 1) low-dose aspirin (a preferential and irreversible inhibitor of platelet-COX-1); 2) clopidogrel (whose active metabolite acts

241 as an irreversible antagonist of $P2Y_{12}$-receptor) and 3) triflusal (an antiplatelet agent
242 structurally related to aspirin). The effect of clopidogrel was studied separately as
243 monotherapy (no concomitant use of low-dose aspirin), and as dual antiplatelet therapy
244 (DAPT), when used concurrently with low-dose aspirin.
245
246 Daily dose was analyzed among current users of low-dose aspirin (100mg, 125-300mg)
247 and triflusal (300mg, 600-900mg). Only one maintenance daily-dose of clopidogrel was
248 used (75 mg). We also evaluated the effect of continuous duration among current users.
249 To that end, continuous duration was defined as the sum of all consecutive periods of
250 prescription (when the interval between the end of supply of one prescription and the
251 beginning of the next one did not exceed 90 days).
252
253 ***Potential confounding variables***
254 The selection of potential confounding variables was driven by expert knowledge
255 avoiding data-driven methods as stepwise regression.
256 We ascertained the history of the following comorbidities and risk factors any time
257 before the index date: chronic gastritis, reflux, inflammatory bowel disease, irritable
258 bowel syndrome, complicated upper gastrointestinal (GI) disorders (including
259 complicated ulcer, bleeding gastritis or duodenitis and upper GI bleeding), non-
260 complicated upper GI disorders (including non-bleeding or non-complicated ulcer,
261 gastritis or duodenitis and dyspepsia), lower GI bleeding, constipation, anorectal
262 pathology (including haemorrhoids, anal fissure and anorectal abscess), alcohol abuse
263 (recorded as such by the primary care physician), smoking (current smokers, ex-
264 smokers and non-smokers), BMI (<24,99, 25-30, >30), hyperuricemia and gout.
265 Number of visits to the primary care physician was ascertained in the year before the

index date. Also, we analyzed as potential confounders the use of the following drugs: corticosteroids, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, H2-receptor antagonists, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, non-aspirin NSAIDs (non-selective and coxibs), symptomatic slow action drugs for osteoarthritis (SYSADOA), and calcium supplements with or without vitamin D.

Statistical analysis

To compute crude and adjusted odds ratios (AORs) and their 95% confidence intervals (95%CI) between the use of drugs of interest and CRC we built an unconditional logistic regression including the matching variables as covariates for the non-adjusted model and the matching variables plus the potential confounders described above for the fully adjusted model.

Covariates "smoking" (45.1% cases, 48.7% controls) and "BMI" (30.9% cases, 34.7% controls) had missing values. We applied for all analyses the missing-indicator method as the distribution of missing values is similar across the exposure[14]. As a consistency test, we also constructed a multiple imputation by chained equations model for the main analyses of low-dose aspirin and clopidogrel.

Potential effect modification by age (using the USPSTF categories[5]: <60, 60-69 or ≥70 years or ≤70 and >70, when numbers were low), sex and indication for primary or secondary prevention of cardiovascular diseases was assessed in the multiplicative scale[15] estimating the AORs and 95%CI for the drug of interest, compared with non-use, across each stratum of the potential modifier.

We also evaluated the interaction between low-dose aspirin and clopidogrel in an additive scale by creating a variable with five categories of exposure: 1) use of low-dose aspirin monotherapy; 2) use of clopidogrel monotherapy; 3) use of DAPT; 4) rest of combinations, and 5) non-use of any as reference.

Finally, two sensitivity analyses were carried out; (i) excluding users of non-aspirin NSAIDs (and also users of low-dose aspirin when clopidogrel or triflusal was studied) within 1 and 3 years before the index date; and (ii) restricting the analysis to new users. New users were defined as those with no recorded prescription before the start date.

The level of statistical significance was set at $p<0.05$. Statistical analyses were performed using STATA/SE, v.14.2 (Statacorp LLC. Texas, USA).

Ethics review

The scientific committee of BIFAP approved the study protocol (#10/2015) on September 10, 2015. The investigators only accessed to fully anonymized data and no specific Institutional Review Board evaluation was required according to the Spanish law.

RESULTS

A total of 15,491 incident CRC cases and 60,000 controls were included (Figure 1). Their main characteristics are described in Table 1. Cases and controls were perfectly matched for age (mean: 68.6, SD±11.8, years), sex (male: 59%) and year of index date. Follow-up, in days, was comparable among cases (median: 1,113; interquartile range:

518-2,185) and controls (median: 1,021; interquartile range: 478-2,041). Alcohol abuse, gout, peripheral artery disease and acute digestive diseases (anorectal pathology, complicated upper GI disorders and lower GI bleeding) were more prevalent among cases. In contrast, history of acute myocardial infarction, stroke, constipation and, chronic digestive diseases resulting in frequent consultant visits (chronic gastritis, inflammatory bowel disease and irritable bowel syndrome) were more prevalent among controls.

The number of current users of low-dose aspirin was lower among cases (1,895; 12.2%) than among controls (7,660; 12.8%) leading to an AOR of 0.83 (95%CI: 0.78-0.89) (Table 2). This effect disappeared promptly after discontinuation. No relevant differences were observed by dose (Figure 2). The reduced risk started to be statistically significant after 180 days of treatment (Table 2). AOR was 0.79 (0.73-0.85) with duration longer than one year. No effect modification was observed by sex, age, or indication for primary or secondary cardiovascular prevention (Figure 2). The exclusion of non-aspirin NSAIDs users within either 1 or 3 years before index date did not materially change the results (Table 2). Among new users of low-dose aspirin, the AOR was 0.98 (0.88-1.10) for treatments shorter than one year and, 0.85 (0.76-0.95) when longer than one year.

We found 270 current users of clopidogrel in monotherapy among cases (2.0%), and 1,047 (2.0%) among controls, yielding an AOR of 0.80 (0.69-0.93) (Table 3). This effect was more remarkable after the first year of treatment; 0.65 (0.55-0.78) (Table 3). The decreased risk remained after the exclusion of low-dose aspirin and/or non-aspirin NSAIDs users within either 1 or 3 years before index date (Table 3). No effect

modification was observed by sex or age (Figure 3). Among new users of clopidogrel monotherapy the AOR was 1.28 (0.97-1.69) for duration of treatment shorter than one year and 0.76 (0.57-1.01) for longer durations. The results of the interaction between clopidogrel and low-dose aspirin were as follows: use of low-dose aspirin in monotherapy was observed in 1,682 (10.9%) cases and 6,848 (11.4%) controls yielding to a decreased risk of CRC (AOR=0.83; 0.78-0.88); likewise, use of clopidogrel in monotherapy was observed in 179 (1.2%) cases and 740 (1.2%) controls, yielding to a decreased risk of CRC (AOR=0.75; 0.63-0.89); finally, use of DAPT was observed in 60 cases (0.4%) and 261 (0.4%) controls, also resulting in a risk reduction of CRC; AOR=0.71; 0.53-0.95 (Supplementary Material, Table 2).

Multiple imputation by chained equations yielded virtually identical results (Supplementary Material, Table 1).

For triflusal, we observed 138 (1.0%) users among cases and 517 (1.0%) among controls leading to a non-significant AOR of 0.92 (0.76-1.12). Among users of daily doses of 600-900 mg we found a trend to a risk reduction (AOR=0.83; 0.62-1.11) which was more pronounced for treatments longer than 1 year (AOR=0.75; 0.53-1.06). No association was observed with daily doses of 300 mg, overall (AOR=0.94; 0.67-1.32) or with duration longer than 1 year (AOR=0.94; 0.63-1.40) (Supplementary Material, Table 3).

DISCUSSION

The results of the present study are compatible with a chemoprotective effect of clopidogrel against CRC, equivalent in magnitude to the one observed for low-dose aspirin. This finding indirectly supports the hypothesis that the chemoprotective effect of low-dose aspirin is mostly mediated through the permanent inactivation of platelet-COX-1[6].

Our study provides two novelties regarding low-dose aspirin. First, the effect appears early over the treatment course, in agreement with a recently published study[4]. Second, our study was performed in a Mediterranean population and its preventive effect on CRC was of similar magnitude to the one observed in other populations with greater cardiovascular comorbidity[3,4,8], which suggests that such an effect is independent from lifestyle factors. Our results also show that the chemoprotective effect is not maintained in recent or past users, a finding compatible with the interference of low-dose aspirin into the progression of cancer being a reversible effect upon discontinuation. Yet, there is paucity of mechanistic evidence either supporting or refuting the maintenance of effect upon stopping low-dose aspirin.

It is known that aberrant expression of COX-2 in stromal and epithelial cells in large bowel precedes the development of CRC[6] and that its inhibition with non-aspirin NSAIDs leads to a reduction of CRC risk and improved survival[16]. Low-dose aspirin has a relatively selective pre-systemic action on platelet-COX-1, with only a modest and transient systemic action on COX-2[17]. Aspirin can also inhibit the COX-2 in a dose-dependent fashion. Yet, the typical duration of its COX-2-dependent effects is brief,

391 because of its short half-life (20 minutes) and rapid *de novo* synthesis of COX-2 in
392 nucleated cells. An increasing body of evidence suggests a key role of platelets in the
393 CRC environment. Activated platelets release a wide repertoire of prostanoids
394 (thromboxane A_2, prostaglandin E_2), angiogenic factors, and growth factors that can
395 contribute to COX-2 induction in adjacent nucleated cells of the intestinal mucosa,
396 which in turn increases the risk of CRC[6]. In addition, platelets form aggregates
397 surrounding cancer cells, hampering the action of the immune system and thus
398 facilitating the invasiveness of cancer cells to other locations[18,19]. All these data together
399 further substantiate that the chemoprotective effect of low-dose aspirin is mediated, at
400 least in part, by its antiplatelet effect[19]. This hypothesis would be reinforced if other
401 antiplatelet drugs acting through a mechanism unrelated to COX-inhibition were also
402 associated with a decreased risk of CRC.
403
404 In this study, we show that use of clopidogrel was associated with a duration-dependent
405 decreased risk of CRC of a similar magnitude to that observed with low-dose aspirin.
406 Few studies have addressed the risk of CRC among users of clopidogrel or DAPT.
407 Recently, Leader et al.[9] reported a reduction of CRC risk among users of DAPT for
408 periods longer than 5 years compared to non-users and to low-dose aspirin users.
409 Another study reported a CRC risk reduction close to 30% with clopidogrel
410 monotherapy and DAPT[8] use. In our study, we showed that the decreased risk
411 associated with clopidogrel monotherapy was observed across all subgroups examined
412 and found a reduced risk of similar magnitude among users of DAPT. Of note, in short-
413 term users of clopidogrel we observed an increased risk of CRC (the same pattern, but
414 smaller, was also observed among short-term low-dose aspirin users). In our view, this
415 observation could be partly explained by a detection bias, due to an increased risk of

gastrointestinal bleeding induced by antiplatelet agents that could lead to a greater number of colonoscopies, and as a result, an early cancer diagnosis.

The results of the present study show that the use of low-dose aspirin and/or clopidogrel is associated with a similar chemoprotective effect which supports an important role of their antiplatelet effect in their benefit. However, further mechanistic studies are necessary to clarify the possible contribution of COX-1 inhibition and $P2Y_{12}$-receptor blockage in extra-platelet cells. The $P2Y_{12}$-receptor was originally found to be expressed only by platelets, however, further studies reported that it is functionally present in other cell-types (e.g. cancer cells)[20]. Thus, similarly to low-dose aspirin that can acetylate intestinal COX-1 thus inhibiting rectal mucosa prostaglandin E2 biosynthesis and the phosphorylation of S6[21], it cannot be excluded an extra-platelet component in the chemoprotective effect of clopidogrel.

Recently, some concerns have been raised about an increase of non-cardiovascular and cancer-related mortality associated with long-term ($\geq$ 30 months) DAPT use (low-dose aspirin plus either clopidogrel or prasugrel)[22]. Echoing such concerns, the FDA released a safety note in 2014, which was updated one year later concluding that there was no evidence of an increased risk of overall mortality or on cancer-related death associated with clopidogrel[23].

Regarding other antiplatelet drugs, we only had enough exposure for triflusal, a salicylic-derived agent which incompletely affects platelet-COX-1[13]. In randomized clinical trials, triflusal reported a cardioprotective profile similar to low-dose aspirin when used at daily doses of 600-900 mg[24]. In our study, although we did not reach a

441 statistically significant result, due in part to small number of users, the point estimate, at
442 daily dose of 600-900mg over periods longer than 1 year, was in the range of those
443 observed with low-dose aspirin and clopidogrel. Noteworthy, when triflusal was used at
444 a dose of dubious cardioprotective efficacy (300mg/day, half the authorized), no
445 association was observed.
446
447 Several limitations of our study should be mentioned. First, although we made efforts to
448 validate the CRC diagnosis in BIFAP, a small probability of false positives remains (<
449 5%) which, if non-differential with respect to the exposure (reviewers were blinded to
450 any drug prescription), might have resulted in a minor dilution of the effect of the drugs
451 examined. Second, although the possibility exists that low-dose aspirin can be
452 dispensed over-the-counter, the proportion of non-prescription use is probably low,
453 bearing in mind that it can be obtained almost for free in Spain (for retired patients) and
454 is used long-term by people who are also receiving other prescription-only
455 cardiovascular drugs. In any case, if some misclassification of low-dose aspirin were
456 present it is likely to have resulted in a small underestimation of the chemoprotective
457 effect. Third, colonoscopies were not recorded in a systematic way in the database, so
458 we were unable to analyze our results according to antecedents of colonoscopy. If
459 patients exposed to antiplatelet drugs were more prone to a colonoscopy because of a
460 lower GI bleeding, the consequence would be to increase the short-term detection of
461 CRC (a detection bias), but it could also permit the removal of polyps and, as a result,
462 would decrease the long-term risk of CRC. Although, we did not adjust for colonoscopy
463 we did so for lower GI bleeding. Additionally, we excluded those patients from the
464 analysis and the estimates remained unchanged (not shown). Also, in a recent study[4],
465 the stratification by antecedents of colonoscopy did not materially change the results.

Thus, the impact of not adjusting for colonoscopy is likely to be minor. Finally, as in any other observational study, the possibility of unknown residual confounding cannot be ruled out.

In conclusion, the present study shows that the use of clopidogrel, an antiplatelet drug acting through a COX-independent mechanism, is associated with a protective effect on CRC comparable to low-dose aspirin. This finding reinforces the hypothesis of a platelet-mediated mechanism in CRC developing and that platelet targeting may represent a promising strategy for CRC chemoprotection.

476 **REFERENCES**

477

478 1. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-1502.

479 2. López-Abente G, Núñez O, Pérez-Gómez B, et al. La situación del cáncer en España:

480 Informe 2015. Instituto de Salud Carlos III. Madrid, 2015.

481 3. Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin

482 Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from

483 randomised and observational studies. Lancet. 2007;369(9573):1603-13.

484 4. García Rodríguez LA, Soriano-Gabarró M, Bromley S, et al. New use of low-dose

485 aspirin and risk of colorectal cancer by stage at diagnosis: a nested case-control study in

486 UK general practice. BMC Cancer. 2017;17(1):637.

487 5. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the

488 primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive

489 Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(12):836-

490 45.

491 6. Patrignani P, Patrono C. Aspirin and Cancer. J Am Coll Cardiol. 2016;68(9):967-76.

492 7. Hicks BM, Murray LJ, Hughes C, et al. Clopidogrel use and cancer-specific

493 mortality: a population-based cohort study of colorectal, breast and prostate cancer

494 patients. Pharmacoepidemiol Drug Saf. 2015;24(8):830-40.

495 8. Cea Soriano L, Soriano-Gabarró M, García Rodríguez LA. The protective effect

496 of low-dose aspirin against colorectal cancer is unlikely explained by selection

497 bias: results from three different study designs in clinical practice. PLoS One.

498 2016;11(7): e0159179.

499 9. Leader A, Zelikson-Saporta R, Pereg D, et al. The effect of combined aspirin and

500 clopidogrel treatment on cancer incidence. Am J Med. 2017;130(7):826-32.

10. BIFAP. Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria. www.bifap.org. Accessed April 4, 2018

11. Abbing-Karahagopian V, Kurz X, de Vries F, et al. Bridging differences in outcomes of pharmacoepidemiological studies: design and first results of the PROTECT project. Curr Clin Pharmacol. 2014; 9:130-8.

12. Gil MJ, Rodríguez-Miguel A, Montoya-Catalá H, et al. Validation study of colorectal cancer diagnosis in the Spanish primary care database, BIFAP. Pharmacoepidemiol Drug Saf. 2018; doi: 10.1002/pds.4686

13. Patrono C, Baigent C, Hirsh J, et al. Antiplatelet drugs: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133(Suppl 6):199S-233S.

14. Groenwold RH, White IR, Donders AR, et al. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ. 2012;184(11):1265-9.

15. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ. 2003;326(7382):219

16. Rostom A, Dubé C, Lewin G, et al. U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):376-89.

17. Patrono C, García Rodríguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med. 2005;353(22):2373-83.

18. Contursi A, Sacco A, Grande R, et al. Platelets as crucial partners for tumor metastasis: from mechanistic aspects to pharmacological targeting. Cell Mol Life Sci. 2017;74(19):3491-3507.

19. Xu XR, Yousef GM, Ni H. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents. Blood. 2018 Apr 19;131(16):1777-89.

20. Ballerini P, Dovizio M, Bruno A, et al. P2Y(12) Receptors in tumorigenesis and metastasis. Front Pharmacol. 2018;9:66.

21. Patrignani P, Sacco A, Sostres C, et al. Low-Dose Aspirin acetylates cyclooxygenase-1 in human colorectal mucosa: implications for the chemoprevention of colorectal cancer. Clin Pharmacol Ther. 2017. doi: 10.1002/cpt.639

22. Kotronias RA, Kwok CS, Wong CW, et al. Cancer Event Rate and Mortality with Thienopyridines: A Systematic Review and Meta-Analysis. Drug Saf. 2017; 40(3):229-40.

23. FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix® (clopidogrel) does not change risk of death. Available for download at: https://www.fda.gov/Drugs/DrugSafety/ucm471286.htm. Accessed September 7, 2018.

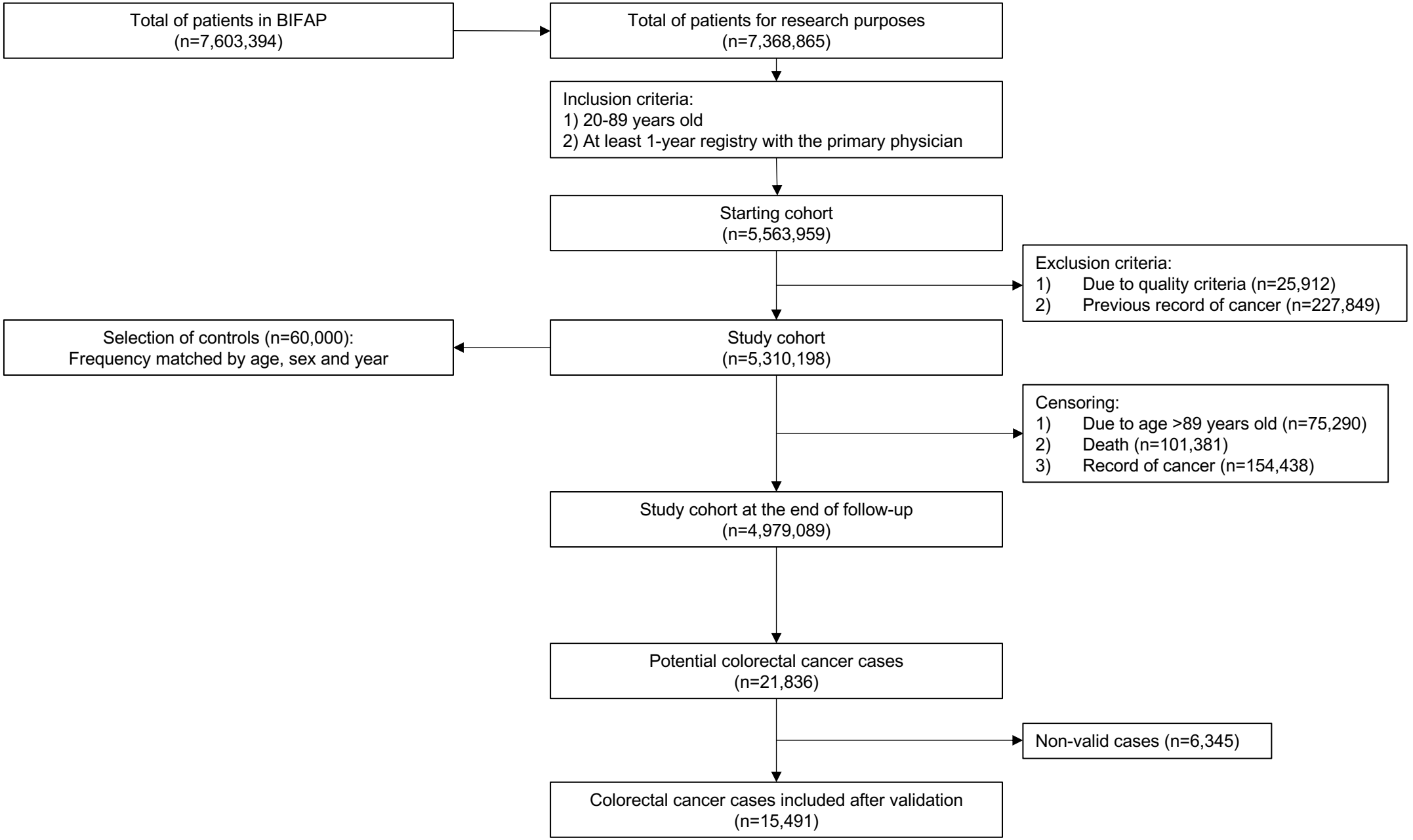
24. Cruz-Fernández JM, López-Bescós L, García-Dorado D, et al. Randomized comparative trial of triflusal and aspirin following acute myocardial infarction. Eur Heart J. 2000;21(6):457-65.

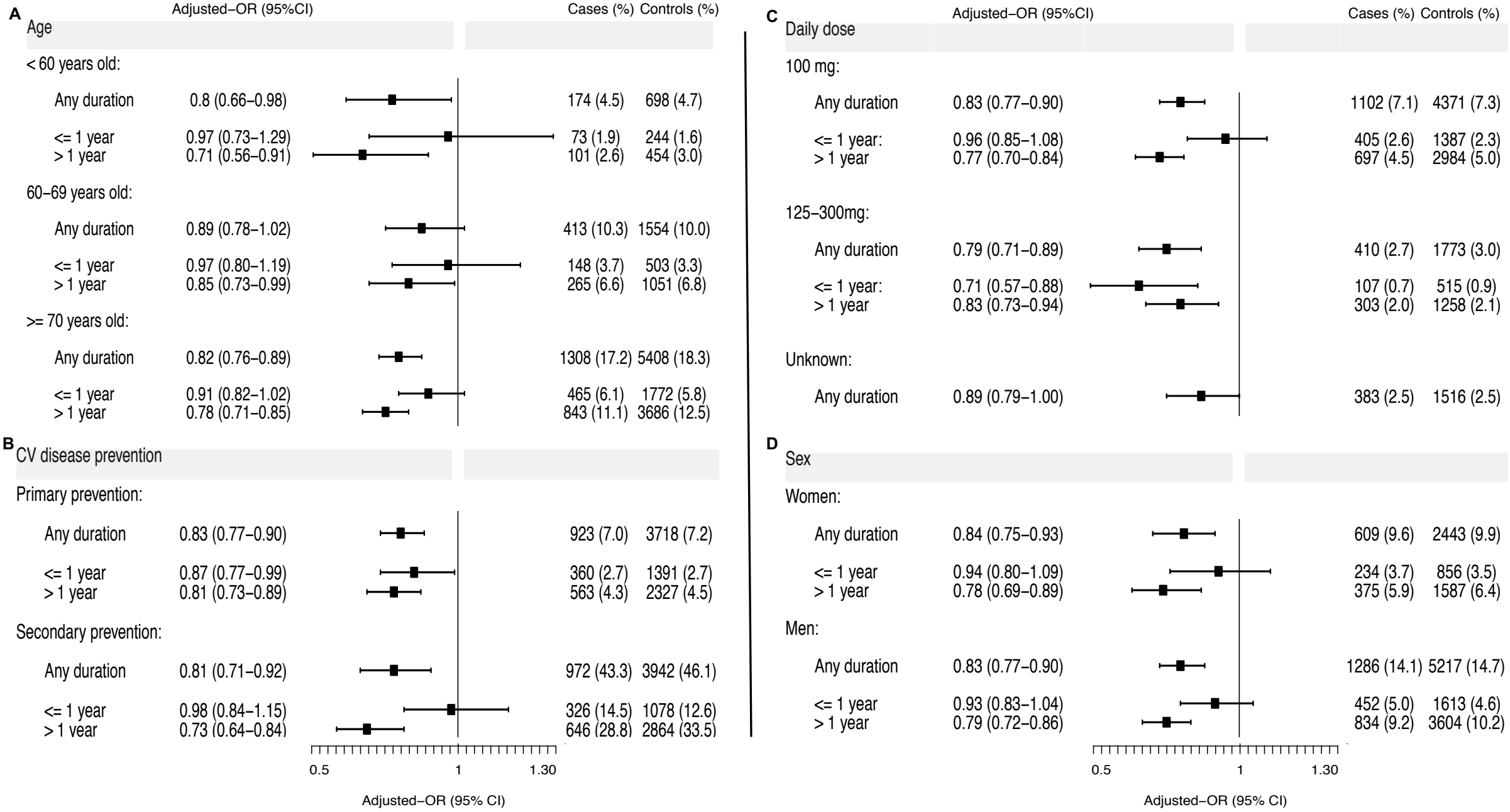
FIGURE TITLES

Figure 1. Flowchart

Figure 2. Use of low-dose aspirin and risk of colorectal cancer, by subgroups

Figure 3. Use of clopidogrel and risk of colorectal cancer, by subgroups (concomitant use of low-dose aspirin excluded)


Total of patients in BIFAP
(n=7,603,394)
Total of patients for research purposes
(n=7,368,865)
Inclusion criteria:
1) 20-89 years old
2) At least 1-year registry with the primary physician
Starting cohort
(n=5,563,959)
Exclusion criteria:
1) Due to quality criteria (n=25,912)
2) Previous record of cancer (n=227,849)
Selection of controls (n=60,000):
Frequency matched by age, sex and year
Study cohort
(n=5,310,198)
Censoring:
1) Due to age >89 years old (n=75,290)
2) Death (n=101,381)
3) Record of cancer (n=154,438)
Study cohort at the end of follow-up
(n=4,979,089)
Potential colorectal cancer cases
(n=21,836)
Non-valid cases (n=6,345)
Colorectal cancer cases included after validation
(n=15,491)


A
Adjusted–OR (95%CI)
Cases (%) Controls (%)
Age
< 60 years old:
Any duration 0.8 (0.66–0.98) 174 (4.5) 698 (4.7)
<= 1 year 0.97 (0.73–1.29) 73 (1.9) 244 (1.6)
> 1 year 0.71 (0.56–0.91) 101 (2.6) 454 (3.0)
60–69 years old:
Any duration 0.89 (0.78–1.02) 413 (10.3) 1554 (10.0)
<= 1 year 0.97 (0.80–1.19) 148 (3.7) 503 (3.3)
> 1 year 0.85 (0.73–0.99) 265 (6.6) 1051 (6.8)
>= 70 years old:
Any duration 0.82 (0.76–0.89) 1308 (17.2) 5408 (18.3)
<= 1 year 0.91 (0.82–1.02) 465 (6.1) 1772 (5.8)
> 1 year 0.78 (0.71–0.85) 843 (11.1) 3686 (12.5)
B
CV disease prevention
Primary prevention:
Any duration 0.83 (0.77–0.90) 923 (7.0) 3718 (7.2)
<= 1 year 0.87 (0.77–0.99) 360 (2.7) 1391 (2.7)
> 1 year 0.81 (0.73–0.89) 563 (4.3) 2327 (4.5)
Secondary prevention:
Any duration 0.81 (0.71–0.92) 972 (43.3) 3942 (46.1)
<= 1 year 0.98 (0.84–1.15) 326 (14.5) 1078 (12.6)
> 1 year 0.73 (0.64–0.84) 646 (28.8) 2864 (33.5)
0.5
1
1.30
Adjusted–OR (95% CI)
C
Adjusted–OR (95%CI)
Cases (%) Controls (%)
Daily dose
100 mg:
Any duration 0.83 (0.77–0.90) 1102 (7.1) 4371 (7.3)
<= 1 year: 0.96 (0.85–1.08) 405 (2.6) 1387 (2.3)
> 1 year 0.77 (0.70–0.84) 697 (4.5) 2984 (5.0)
125–300mg:
Any duration 0.79 (0.71–0.89) 410 (2.7) 1773 (3.0)
<= 1 year: 0.71 (0.57–0.88) 107 (0.7) 515 (0.9)
> 1 year 0.83 (0.73–0.94) 303 (2.0) 1258 (2.1)
Unknown:
Any duration 0.89 (0.79–1.00) 383 (2.5) 1516 (2.5)
D
Sex
Women:
Any duration 0.84 (0.75–0.93) 609 (9.6) 2443 (9.9)
<= 1 year 0.94 (0.80–1.09) 234 (3.7) 856 (3.5)
> 1 year 0.78 (0.69–0.89) 375 (5.9) 1587 (6.4)
Men:
Any duration 0.83 (0.77–0.90) 1286 (14.1) 5217 (14.7)
<= 1 year 0.93 (0.83–1.04) 452 (5.0) 1613 (4.6)
> 1 year 0.79 (0.72–0.86) 834 (9.2) 3604 (10.2)
0.5
1
1.30
Adjusted–OR (95% CI)

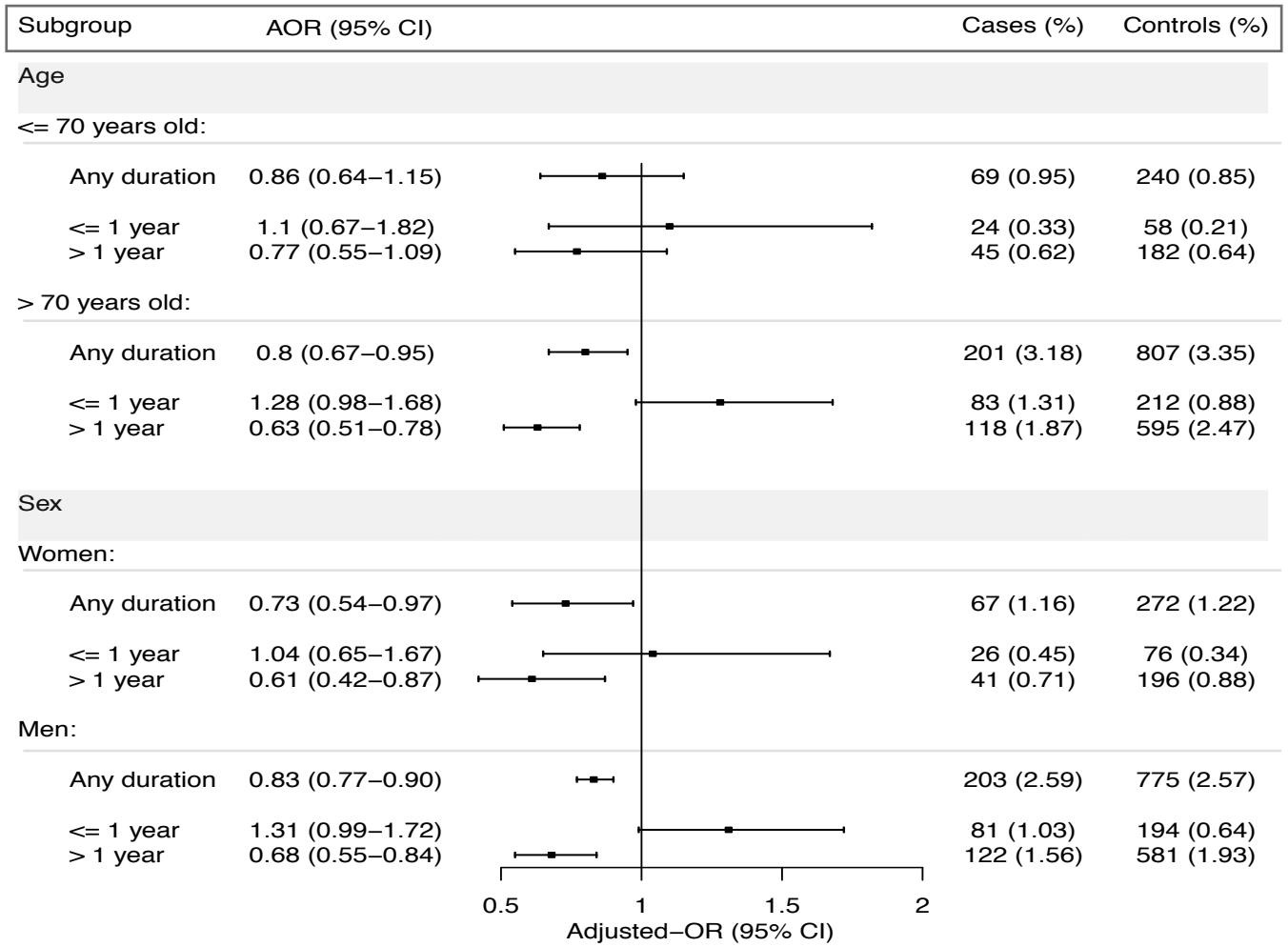

Subgroup
AOR (95% CI)
Cases (%)
Controls (%)
Age
<= 70 years old:
Any duration 0.86 (0.64–1.15) 69 (0.95) 240 (0.85)
<= 1 year 1.1 (0.67–1.82) 24 (0.33) 58 (0.21)
> 1 year 0.77 (0.55–1.09) 45 (0.62) 182 (0.64)
> 70 years old:
Any duration 0.8 (0.67–0.95) 201 (3.18) 807 (3.35)
<= 1 year 1.28 (0.98–1.68) 83 (1.31) 212 (0.88)
> 1 year 0.63 (0.51–0.78) 118 (1.87) 595 (2.47)
Sex
Women:
Any duration 0.73 (0.54–0.97) 67 (1.16) 272 (1.22)
<= 1 year 1.04 (0.65–1.67) 26 (0.45) 76 (0.34)
> 1 year 0.61 (0.42–0.87) 41 (0.71) 196 (0.88)
Men:
Any duration 0.83 (0.77–0.90) 203 (2.59) 775 (2.57)
<= 1 year 1.31 (0.99–1.72) 81 (1.03) 194 (0.64)
> 1 year 0.68 (0.55–0.84) 122 (1.56) 581 (1.93)
0.5
1
1.5
2
Adjusted–OR (95% CI)

Table 1. Baseline characteristics of cases and controls

	CASES n=15,491	CONTROLS n=60,000	Non-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Age, mean (SD), years	68.6 (±11.8)	68.6 (±11.8)	Matched	Matched
Men, No. (%)	9,115 (58.8)	35,307 (58.9)	Matched	Matched
Number of visits within the last year, No. (%)				
<6	3,248 (21.0)	19,508 (32.5)	1 (Ref.)	1 (Ref.)
6-10	3,639 (23.5)	13,357 (22.3)	1.71 (1.62 – 1.80)	1.81 (1.71 – 1.91)
11-20	5,298 (34.2)	17,118 (28.5)	2.01 (1.91 – 2.11)	2.19 (2.07 – 2.31)
>20	3,306 (21.3)	10,017 (16.7)	2.23 (2.11 – 2.37)	2.45 (2.28 – 2.63)
BMI, No. (%), $kg.m^{-2}$				
<24,99	2,123 (13.7)	7,635 (12.7)	1 (Ref.)	1 (Ref.)
25-30	4,933 (31.8)	18,108 (30.2)	0.98 (0.93 – 1.04)	0.97 (0.92 – 1.03)
> 30	3,652 (23.6)	13,421 (22.4)	0.98 (0.92 – 1.04)	0.95 (0.89 – 1.01)
Missing	4,783 (30.9)	20,836 (34.7)		
Smoking, No. (%)				
Non-smoker	4,904 (31.7)	18,016 (30.0)	1 (Ref.)	1 (Ref.)
Current smoker	2,384 (15.4)	8,960 (14.9)	0.98 (0.92 – 1.04)	1.02 (0.97 – 1.08)
Past smoker	1,217 (7.86)	3,821 (6.37)	1.18 (1.09 – 1.27)	1.18 (1.10 – 1.27)
Missing	6,986 (45.1)	29,203 (48.7)		

Table 1. Baseline characteristics of cases and controls (cont'd)

History of, No. (%):	CASES n=15,491	CONTROLS n=60,000	Non-adjusted OR[*] (95% CI)	Adjusted OR[†] (95% CI)
Alcohol abuse[‡]	552 (3.56)	1,578 (2.63)	1.38 (1.25 – 1.52)	1.25 (1.13 – 1.38)
Diabetes	3,067 (19.8)	10,344 (17.2)	1.19 (1.14 – 1.25)	1.05 (0.97 – 1.14)
Hyperuricemia (non-gout)	984 (6.35)	3,829 (6.38)	1.01 (0.93 – 1.08)	0.91 (0.84 – 0.98)
Gout	718 (4.63)	2,363 (3.94)	1.19 (1.09 – 1.30)	1.11 (1.02 – 1.22)
Hypertension	7,527 (48.6)	28,051 (46.8)	1.09 (1.05 – 1.13)	0.93 (0.89 – 0.97)
Dyslipidemia	6,462 (41.7)	24,505 (40.8)	1.04 (1.00 – 1.08)	1.01 (0.95 – 1.07)
Peripheral artery disease	466 (3.01)	1,420 (2.37)	1.28 (1.15 – 1.43)	1.16 (1.04 – 1.30)
Acute myocardial infarction	502 (3.24)	2,213 (3.69)	0.88 (0.79 – 0.97)	0.83 (0.74 – 0.92)
Angina pectoris	467 (3.01)	1,600 (2.67)	1.13 (1.02 – 1.26)	1.06 (0.95 – 1.19)
Stroke[§]	559 (3.61)	2,249 (3.75)	0.96 (0.87 – 1.06)	0.89 (0.80 – 0.98)
Transient ischemic attack	281 (1.81)	1,109 (1.85)	0.98 (0.86 – 1.12)	0.95 (0.82 – 1.09)
Chronic gastritis	154 (0.99)	604 (1.01)	0.99 (0.83 – 1.18)	0.84 (0.70 – 1.01)
Gastroesophageal reflux	1,866 (12.1)	6,896 (11.5)	1.05 (1.00 – 1.11)	0.93 (0.87 – 0.98)
Inflammatory bowel disease	51 (0.33)	238 (0.40)	0.83 (0.61 – 1.12)	0.42 (0.30 – 0.58)
Irritable bowel syndrome	238 (1.54)	941 (1.57)	0.98 (0.85 – 1.13)	0.85 (0.73 – 0.99)
Constipation	1,601 (10.3)	5,424 (9.04)	1.16 (1.10 – 1.24)	0.89 (0.83 – 0.96)
Anorectal pathology[‖]	1,995 (12.9)	5,741 (9.57)	1.40 (1.32 – 1.48)	1.23 (1.16 – 1.30)
Upper GI disorders:				
Complicated[¶]	459 (2.96)	1,062 (1.77)	1.73 (1.55 – 1.94)	1.41 (1.26 – 1.59)
*Non-complicated***	1,103 (7.12)	3,889 (6.48)	1.14 (1.06 – 1.22)	1.02 (0.95 – 1.10)
Dyspepsia	1,797 (11.6)	6,549 (10.9)	1.10 (1.04 – 1.16)	0.98 (0.92 – 1.04)
Lower GI bleeding	898 (5.80)	1,310 (2.18)	2.76 (2.53 – 3.01)	2.45 (2.24 – 2.68)

[*] *Model adjusted only for matching variables (age, sex and year). The category of reference was "no presence of the specific disease listed".*

[†] *Model adjusted for:*

- Matching variables: age, sex and year

- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricemia and gout.

- Use of drugs: non-aspirin NSAIDs (non-selective and coxibs), corticosteroids, low-dose aspirin, non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs and calcium and vitamin D supplements.

[‡] *When the primary care physician recorded an excessive consumption of alcohol*

[§] *Ischemic and hemorrhagic stroke*

[‖] *Includes hemorrhoids, anal fissure and anorectal abscess*

[¶] *Includes complicated ulcer, gastritis or duodenitis with bleeding and upper GI bleeding*

** *Includes non-bleeding or non-complicated ulcer, gastritis or duodenitis*

Table 2. Use of low-dose aspirin and risk of CRC

	CASES n=15,491	CONTROLS n=60,000	Non-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Non-use	12,548 (81.0)	48,614 (81.0)	1 (ref.)	1 (ref.)
Recency of use, in days:				
Current (0-90)	1,895 (12.2)	7,660 (12.8)	0.96 (0.91 – 1.01)	0.83 (0.78 – 0.89)
Recent (91-365)	380 (2.45)	1,265 (2.11)	1.16 (1.03 – 1.31)	1.00 (0.88 – 1.13)
Past (>365)	668 (4.31)	2,461 (4.10)	1.05 (0.96 – 1.15)	0.96 (0.88 – 1.06)
Continuous duration among current users:				
≤ 1 year:	686 (4.42)	2,469 (4.11)	1.08 (0.99 – 1.17)	0.93 (0.85 – 1.02)
<91 days	307 (1.98)	945 (1.57)	1.26 (1.10 – 1.43)	1.12 (0.98 – 1.29)
91-180 days	151 (0.97)	602 (1.00)	0.97 (0.81 – 1.16)	0.85 (0.70 – 1.02)
181-365 days	228 (1.47)	922 (1.54)	0.96 (0.83 – 1.11)	0.79 (0.68 – 0.92)
> 1 year:	1,209 (7.80)	5,191 (8.66)	0.90 (0.84 – 0.96)	0.79 (0.73 – 0.85)
1 – 3 years	659 (4.25)	2,985 (4.98)	0.85 (0.78 – 0.93)	0.73 (0.67 – 0.80)
>3 years	550 (3.55)	2,206 (3.68)	0.96 (0.88 – 1.06)	0.87 (0.78 – 0.96)
Excluding non-aspirin NSAID users‡:				
In the prior 1 year:	**n=10,721**	**n=40,323**		
Current use (any duration)	1,275 (11.9)	4,862 (12.1)	0.98 (0.91 – 1.05)	0.83 (0.77 – 0.89)
Continuous duration, among current users:				
≤ 1 year	465 (4.34)	1,571 (3.90)	1.11 (0.99 – 1.23)	0.92 (0.83 – 1.03)
> 1 year	810 (7.56)	3,291 (8.16)	0.92 (0.84 – 0.99)	0.78 (0.71 – 0.85)
In the prior 3 years:	**n=7,651**	**n=29,109**		
Current use (any duration)	882 (11.5)	3,421 (11.8)	0.97 (0.90 – 1.06	0.82 (0.75 – 0.90)
Continuous duration, among current users:				
≤ 1 year	339 (4.42)	1,179 (4.05)	1.09 (0.96 – 1.23)	0.90 (0.79 – 1.03)
> 1 year	543 (7.09)	2,242 (7.70)	0.91 (0.83 – 1.01)	0.78 (0.70 – 0.87)

**Model adjusted for the matching variables only (age, sex and year).*

†Model adjusted for:

- Matching variables: age, sex and year

- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricemia and gout.

- Use of drugs: non-aspirin NSAIDs (non-selective and coxibs), corticosteroids, non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs and calcium and vitamin D supplements.

‡ COX-2 selective and non-selective non-aspirin NSAIDs

Table 3. Use of clopidogrel (concomitant users of low-dose aspirin excluded) and risk of CRC

	CASES n=13,596	CONTROLS n=52,340	No-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Non-use	13,197 (97.1)	50,869 (97.2)	1 (ref.)	1 (ref.)
Recency of use, in days:				
Current (0-90)	270 (1.99)	1,047 (2.00)	0.99 (0.86 – 1.13)	0.80 (0.69 – 0.93)
Recent (91-365)	39 (0.29)	132 (0.25)	1.13 (0.79 – 1.62)	0.92 (0.63 – 1.34)
Past (>365)	90 (0.66)	292 (0.56)	1.18 (0.93 – 1.50)	1.08 (0.84 – 1.38)
Continuous duration, among current users:				
≤1 year:	107 (0.78)	270 (0.52)	1.52 (1.21 – 1.90)	1.22 (0.97 – 1.55)
<91 days	52 (0.38)	97 (0.19)	2.06 (1.47 – 2.88)	1.73 (1.21 – 2.46)
91-180 days	26 (0.19)	67 (0.13)	1.49 (0.95 – 2.34)	1.19 (0.75 – 1.90)
181-365 days	29 (0.21)	106 (0.20)	1.05 (0.70 – 1.58)	0.82 (0.54 – 1.25)
>1 year:	163 (1.20)	777 (1.49)	0.80 (0.68 – 0.95)	0.65 (0.55 – 0.78)
1 – 3 years	83 (0.61)	444 (0.85)	0.72 (0.57 – 0.91)	0.57 (0.45 – 0.73)
>3 years	80 (0.59)	333 (0.64)	0.92 (0.72 – 1.18)	0.76 (0.59 – 0.99)
Excluding non-aspirin NSAID‡ and/or low-dose aspirin users:				
In the prior 1 year:	**n=9,175**	**n=34,558**		
Current use (any duration)	182 (1.99)	695 (2.01)	0.97 (0.83 – 1.15)	0.80 (0.67 – 0.95)
Continuous duration, among current users:				
≤1 year	74 (0.81)	170 (0.49)	1.62 (1.23 – 2.14)	1.37 (1.02 – 1.83)
>1 year	108 (1.18)	525 (1.52)	0.77 (0.62 – 0.94)	0.62 (0.50 – 0.77)
In the prior 3 years:	**n=6,400**	**n=24,352**		
Current use (any duration)	120 (1.87)	476 (1.95)	0.94 (0.77 – 1.16)	0.77 (0.62 – 0.96)
Continuous duration, among current users:				
≤1 year	50 (0.78)	121 (0.49)	1.55 (1.11 – 2.16)	1.36 (0.95 – 1.93)
>1 year	70 (1.09)	355 (1.46)	0.74 (0.57 – 0.96)	0.59 (0.45 – 0.78)

* *Model adjusted only for matching variables (age, sex and year).*

† *Model adjusted for:*

- Matching variables: age, sex and year

- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricemia and gout.

- Use of drugs: non-aspirin NSAIDs (non-selective and coxibs), corticosteroids, low-dose aspirin, rest of non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs, and calcium and vitamin D supplements.

‡ *COX-2 selective and non-selective non-aspirin NSAIDs*

SUPPLEMENTARY MATERIAL

Methods 1. Case-finding algorithm and strategies to minimize false positives

All potential cases identified by the case-finding algorithm were allocated into homogeneous subgroups according to their registration characteristics. Random samples of 100 cases per group were obtained and electronic health records were manually reviewed by two independent researchers blinded to drug prescriptions. Positive predictive values (PPVs) were calculated for each group and for the whole sample considering the stratified sampling. The resulting PPV was of 87.3% (95%CI: 83.3%-90.4%). Additionally, we improved the PPV by using the following two-step strategy:

1. Manual review of all the electronic health records from groups that resulted in a PPV lower than 50% in the initial validation (n=1,474). The overall PPV raised to 91.0%.

2. Construction of text mining algorithms based on patterns identified after the study of the electronic health records from confirmed false positives in the initial validation. These semantic patterns included dates (e.g.: prevalent cases, date of diagnosis or date of surgery), keywords indicating high probability to be a false positive (e.g.: colorectal cancer of a relative, screening or colonoscopy without colorectal cancer diagnosis) or string-text search identifying hereditary colorectal cancer (an exclusion criteria). The final number of electronic health records meeting these criteria that were manually reviewed was 1,289. This allowed increase the PPV to 95.7%

Table 1. Main analysis comparing multiple imputation by chained equations (MICE) against missing-indicator method

Low-dose aspirin		
	MICE Adjusted[*] OR (95% CI)	**Missing-indicator Adjusted[*] OR (95% CI)**
Recency of use, in days:		
Current (0-90)	0.83 (0.78 – 0.89)	0.83 (0.78 – 0.89)
Recent (91-365)	1.00 (0.88 – 1.13)	1.00 (0.88 – 1.13)
Past (>365)	0.96 (0.88 – 1.06)	0.96 (0.88 – 1.06)
Continuous duration, among current users:		
<91 days	1.12 (0.98 – 1.29)	1.12 (0.98 – 1.29)
91-180 days	0.85 (0.70 – 1.02)	0.85 (0.70 – 1.02)
181-365 days	0.79 (0.68 – 0.92)	0.79 (0.68 – 0.92)
1-3 years	0.73 (0.66 – 0.80)	0.73 (0.67 – 0.80)
>3 years	0.86 (0.78 – 0.96)	0.87 (0.78 – 0.96)
Clopidogrel monotherapy		
	MICE Adjusted[†] OR (95% CI)	**Missing-indicator Adjusted[†] OR (95% CI)**
Recency of use, in days:		
Current (0-90)	0.80 (0.69 - 0.92)	0.80 (0.69 – 0.93)
Recent (91-365)	0.92 (0.63 – 1.34)	0.92 (0.63 – 1.34)
Past (>365)	1.08 (0.84 – 1.38)	1.08 (0.84 – 1.38)
Continuous duration, among current users:		
<91 days	1.72 (1.21 – 2.45)	1.73 (1.21 – 2.46)
91-180 days	1.19 (0.75 – 1.90)	1.19 (0.75 – 1.90)
181-365 days	0.81 (0.53 – 1.24)	0.82 (0.54 – 1.25)
1-3 years	0.57 (0.45 – 0.73)	0.57 (0.45 – 0.73)
>3 years	0.76 (0.59 – 0.98)	0.76 (0.59 – 0.99)

[*]*Model adjusted for:*
- Matching variables: age, sex and calendar year
- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricemia and gout.
- Use of drugs: non-aspirin NSAIDs (non-selective and cox-2 selective), corticosteroids, non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs and calcium and vitamin D supplements.

[†]*Model adjusted for:*
- Matching variables: age, sex and calendar year
- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricemia and gout.
- Use of drugs: non-aspirin NSAIDs (non-selective and cox-2 selective), corticosteroids, low-dose aspirin, rest of non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs and calcium and vitamin D supplements.

Table 2. Interaction between low-dose aspirin and clopidogrel

	CASES n=15,491	CONTROLS n=60,000	Non-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Non-use of any	12,293 (79.4)	47,697 (79.5)	1 (Ref.)	1 (Ref.)
Single low-dose aspirin use:				
Current use (any duration)	1,682 (10.9)	6,848 (11.4)	0.95 (0.90 – 1.01)	0.83 (0.78 – 0.88)
Continuous duration, among current users:				
≤ 1 year	601 (3.9)	2,200 (3.7)	1.06 (0.97 – 1.16)	0.92 (0.83 – 1.01)
> 1 year	1,081 (7.0)	4,648 (7.8)	0.90 (0.84 – 0.97)	0.78 (0.73 – 0.85)
Single clopidogrel use:				
Current use (any duration)	179 (1.2)	740 (1.2)	0.94 (0.80 – 1.11)	0.75 (0.63 – 0.89)
Continuous duration, among current users:				
≤ 1 year	64 (0.4)	169 (0.3)	1.47 (1.10 – 1.96)	1.16 (0.86 – 1.57)
> 1 year	115 (0.7)	571 (1.0)	0.78 (0.64 – 0.96)	0.63 (0.51 – 0.77)
Low-dose aspirin and clopidogrel use (DAPT):				
Current use (any duration)	60 (0.4)	261 (0.4)	0.89 (0.67 – 1.18)	0.71 (0.53 – 0.95)
Continuous duration, among current users:				
≤ 1 year	33 (0.2)	145 (0.2)	0.88 (0.60 – 1.29)	0.66 (0.45 – 0.97)
> 1 year	27 (0.2)	116 (0.2)	0.90 (0.59 – 1.37)	0.78 (0.51 – 1.20)
Rest of combinations	1,277 (8.2)	4,454 (7.4)	1.11 (1.04 – 1.19)	0.97 (0.91 – 1.05)

* *Model adjusted for the matching variables only (age, sex and year).*
† *Model adjusted for:*
- Matching variables: age, sex and year
- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricemia and gout.
- Use of drugs: non-aspirin NSAIDs (non-selective and coxibs), corticosteroids, rest of non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs and calcium and vitamin D supplements.

Table 3. Use of triflusal and risk of CRC, current use of low-dose aspirin excluded

	CASES n=13,596	CONTROLS n=52,340	Non-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Non-use	13,372 (98.4)	51,497 (98.4)	1 (ref.)	1 (ref.)
Recency of use, in days:				
Current users (0-90)	138 (1.0)	517 (1.0)	1.02 (0.85 – 1.24)	0.92 (0.76 – 1.12)
Recent users (91-365)	19 (0.1)	79 (0.2)	0.92 (0.56 – 1.52)	0.86 (0.51 – 1.43)
Past users (>365)	67 (0.5)	247 (0.5)	1.04 (0.79 – 1.36)	1.00 (0.76 – 1.32)
By daily dose:				
300 mg:				
Current use (any duration)	44 (0.3)	162 (0.3)	1.04 (0.75 – 1.45)	0.94 (0.67 – 1.32)
Continuous duration, among current users:				
≤1 year	12 (0.1)	46 (0.1)	1.00 (0.53 – 1.89)	0.94 (0.49 – 1.80)
>1 year	32 (0.2)	116 (0.2)	1.06 (0.71 – 1.56)	0.94 (0.63 – 1.40)
600 - 900 mg:				
Current use (any duration)	57 (0.4)	237 (0.5)	0.92 (0.69 – 1.23)	0.83 (0.62 – 1.11)
Continuous duration, among current users:				
≤1 year	16 (0.1)	45 (0.1)	1.36 (0.77 – 2.41)	1.15 (0.64 – 2.06)
>1 year	41 (0.3)	192 (0.4)	0.82 (0.58 – 1.15)	0.75 (0.53 – 1.06)
Unknown:	37 (0.3)	118 (0.2)	1.20 (0.83 – 1.74)	1.08 (0.74 – 1.59)

**Model adjusted for the matching variables only (age, sex and year).*
†Model adjusted for:
- Matching variables: age, sex and year
- Comorbidities and risk factors: number of visits within the last year, BMI, alcohol abuse, smoking, chronic gastritis, reflux, inflammatory bowel disease, irritable bowel syndrome, constipation, anorectal pathology, upper GI disorders, lower GI bleeding, hyperuricaemia and gout.
- Use of drugs: non-aspirin NSAIDs (non-selective and coxibs), corticosteroids, low-dose aspirin, rest of non-aspirin antiplatelet drugs (cilostazol, dipyridamole, ditazole, prasugrel, ticagrelor, ticlopidine and clopidogrel), analgesic opioids, oral anticoagulants, insulin, oral glucose-lowering drugs, antidepressants, anti-H2 acid suppressors, proton pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, SYSADOAs and calcium and vitamin D supplements.

8.3. Estudio 3

Rodríguez-Miguel A, García-Rodríguez LA, Gil M, Barreira-Hernández D, Rodríguez-Martín S, de Abajo FJ. Population-based case-control study: chemoprotection of colorectal cancer with non-aspirin non-steroidal anti-inflammatory drugs and other drugs for pain control. ***Aliment Pharmacol Ther 2019. Aceptado para publicación el 13 de mayo de 2019.***

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Dear Professor de Abajo

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Editor

POPULATION-BASED CASE-CONTROL STUDY: CHEMOPROTECTION OF COLORECTAL CANCER WITH NON-ASPIRIN NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND OTHER DRUGS FOR PAIN CONTROL

Running title: NSAIDs and chemoprotection of colorectal cancer

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Abbreviations list:

AOR: adjusted odds ratio

BIFAP: base de datos para la investigación farmacoepidemiológica en atención primaria

BMI: body mass index

CI: confidence interval

COX: cyclooxygenase

CRC: colorectal cancer

GI: gastrointestinal

H2: type-2 histamine receptor

ICPC: international classification in primary care

ICD: international classification of diseases

NSAID: non-steroidal anti-inflammatory drugs

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs

OR: odds ratio

PGE_2: prostaglandin-E_2

PPI: proton-pump inhibitors

SD: standard deviation

SYSADOA: symptomatic slow-acting drugs for osteoarthritis

USPSTF: United States Preventive Services Task Force

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Author contributions: Francisco J. de Abajo and Luis A. García Rodríguez performed the study design and supervised the whole study, including data extraction, analysis and interpretation. Also, they made a critical revision of the manuscript for important intellectual content.

Antonio Rodríguez-Miguel performed the acquisition, analysis and interpretation of data and wrote the first draft.

Miguel Gil performed the acquisition of data and critical revision of the manuscript for important intellectual content.

Sara Rodríguez-Martín and Diana Barreira-Hernández performed the acquisition and interpretation of data.

SUMMARY

Background

Inflammation and overexpression of cyclooxygenase-2 have been described to play a key role in the progression from non-pathologic intestinal mucosa to colorectal cancer (CRC).

Aims

To assess the chemoprotective effect of non-aspirin NSAIDs (NA-NSAIDs) under different patterns of use in a Mediterranean population and to explore the potential effect of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs; chondroitin sulfate and glucosamine) and metamizole (or dipyrone), also reported to influence COX-2 activity.

Methods

We performed a case–control study nested in a cohort extracted from the primary care database, BIFAP. From 2001 to 2014, we included 15,491 incident cases and 60,000 random controls. To estimate the association between the drugs of interest and CRC, we built logistic regression models to compute the adjusted-odds ratios (AOR) and 95% confidence intervals (CI).

Results

NA-NSAIDs use was associated with a reduced risk of CRC (AOR=0.67;95%CI: 0.63–0.71) and increased linearly with duration of treatment (p for trend<0.001). The effect diminished upon discontinuation but persisted statistically significant up to one year after. All individual NA-NSAIDs examined showed a decreased risk. The concomitant use of proton-pump inhibitors (PPI) had no impact on the protective effect of NA-NSAIDs;

$AOR_{PPI+NSAID}$=0.64;0.58–0.71. SYSADOA use was associated with a reduced risk (0.79; 0.69–0.90) but disappeared after the exclusion of NSAID users during the previous 1 or 3 years (0.85;0.70–1.04 and 1.00;0.76–1.31, respectively). Metamizole did not show a chemoprotective effect.

Conclusions

NA-NSAID use is associated to a duration-dependent risk reduction of CRC not shared by SYSADOAs and metamizole.

Keywords: colon cancer, chemoprevention, COX-2 inhibitors, analgesic drugs

Word count: 250

INTRODUCTION

Colorectal cancer (CRC) is the most prevalent type among men and women in western lifestyle countries[1,2]. Although overall 5-year survival has reached up to 65% in these countries, in part associated to efficient strategies of prevention and treatment, their effectiveness can vary drastically depending on the stage at diagnosis[1,3]. About 70-80% of all CRC diagnosed are sporadic forms[4,5]. Apart from sex, age or family history of CRC, other risk factors are known to be involved in the tumorigenesis of CRC, as inflammatory status[3,4] to which some metabolic disorders like diabetes or visceral obesity could contribute to[6]. To this day, several drugs have been reported to show a protective effect against CRC[7], placing chemoprotection as another factor to be considered in prevention strategies. In fact, in 2016, the U.S. Preventive Services Task Force (USPSTF) endorsed the use of low-dose aspirin for primary prevention of cardiovascular diseases and CRC in a specific group of population[8]. Recently, new results from three randomised clinical trials assessing the efficacy of low-dose aspirin in primary prevention of cardiovascular diseases, have been published concluding that risks may outweigh the benefits[9-11]. Although non-aspirin NSAIDs (NA-NSAIDs) have shown a remarkable reduction in the incidence of colonic adenomas and CRC in a large number of observational studies and randomised clinical trials[12-14], their use for that indication, at present, is not supported due to cardiovascular and gastrointestinal harms[12]. Thus, it would be necessary to gather updated evidence on the chemoprotective effect of NA-NSAIDs under different patterns of use (dose, duration, treatment persistence, concomitant use with proton-pump inhibitors, or the influence of sex and age) in order to gauge how to optimise the benefit-risk ratio, and perhaps, reconsider them as suitable chemoprotective agents for the prevention of CRC. On the other hand, the evidence at individual drug level is still scarce,

mostly due to the limited number of users included in previous studies[14]; hence, we need more data to assess whether all individual NA-NSAIDs share the same effect or not. Other agents with allegedly anti-inflammatory actions, like systemic slow-acting drug for osteoarthritis (SYSADOAs)[15,16], have also been reported to reduce the risk of CRC[17-21], but these data need to be replicated in other studies and populations. Finally, metamizole (or dipyrone), an analgesic, antipyretic and spasmolytic drug widely used in Spain and other countries, has been reported to inhibit peripheral COX enzymes[22] and then could also be potentially useful as a chemopreventive agent.

METHODS

Data source

The present study was conducted using the population-based database BIFAP ("Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria"). BIFAP contains anonymised electronic health records from primary care of the 9 Spanish Regions participating in it (out of 17)[23]. BIFAP is representative of the Spanish population with respect to age and sex, and was successfully compared to other well-known European databases validated for pharmacoepidemiological research[23,24]. BIFAP includes information on demographics, diagnoses, specialist referrals, drug prescriptions and other additional health data that can also be enriched by linked free-text clinical notes. Information on drug prescriptions includes: product name, date, quantity, dosage and indication. Over the study period, BIFAP included 7.6 million patients (38.6 million person-years) and followed-up over 5.1 years on average.

189 ***Study design***

190 We performed a case-control study nested in a primary cohort selected from BIFAP. Over
191 the period January 1, 2001 to December 31, 2014, individuals aged 20 to 89 without
192 history of cancer entered the study cohort, once they completed at least one-year record
193 with their primary care physician. Members of the study cohort (n=5,310,198) were
194 followed-up from the date of entry in the study (the start date) until the earliest occurrence
195 of an incident CRC or other cancer diagnosis, 90 years old, death or end of the study,
196 whichever came first.

197

198 ***Case-finding algorithm and selection of cases***

199 Previously, a validation study of the CRC diagnosis in BIFAP was conducted and
200 published[25]. In the primary healthcare systems of 8 regions, diseases are coded using the
201 International Classification of Primary Care, version 2 (ICPC-2) while the other region
202 uses the International Classification of Diseases, version 9 - clinical modification (ICD-
203 CM). Diagnoses in both dictionaries are identified with an alphanumeric code and a text
204 descriptor. A case-finding algorithm for CRC diagnosis was constructed based on code
205 searches plus text-mining strategies (supporting information, Methods 1). The potential
206 cases detected were considered valid when, additionally to an incident CRC record, we
207 found one or more of the following information items: hospital or specialist referral,
208 diagnostic procedures, accurate location, histopathology, staging, treatment (surgery,
209 chemotherapy or radiotherapy) or cancer-related death, supporting the CRC diagnosis.
210 The index date for all cases was the first CRC record in the database. Inherited forms of
211 CRC, as familial adenomatous polyposis or Lynch syndrome were searched using
212 dictionary codes and specific string-texts ("inherited cancer", "Lynch", "familial" or
213 "genetic") and excluded.

214 ***Selection of controls***

215 Controls were selected from the study cohort using the incidence density sampling
216 method[26]; briefly, a random date within the study period was allocated to all subjects of
217 the study cohort and, if the random date fell within the period of follow-up, the subject
218 was considered as an eligible control. This way the probability of being sampled is
219 proportional to the person-time each subject contributed to. Finally, from the pool of
220 eligible controls, we sampled 60,000 subjects, frequency-matched to cases by age, sex
221 and year of index date. The random date allocated previously was considered the index
222 date for controls.

223

224 ***Exposure definition***

225 Cases and controls were categorised as *current users* when the last prescription ended
226 between 0 to 90 days from the index date; as *recent users* when the supply finished
227 between 91 and 365 days before the index date; as *past users* when the supply finished
228 more than 365 days before the index date and, finally, as *nonusers* when there was no
229 recorded prescription ever.

230

231 The drugs studied were: 1) NA-NSAIDs (COX-2 selective and non-selective) as a group
232 and individually. 2) SYSADOAs (chondroitin sulphate and glucosamine)[16] and, 3)
233 metamizole (or dypirone), an analgesic, antipyretic and spasmolytic drug with weak anti-
234 inflammatory effect[22].

235

236 The effect of daily dose was analysed among current users of NA-NSAIDs and
237 metamizole. To this end, we created two categories; low-moderate and high (supporting
238 information, Table 1). For SYSADOAs only one daily dose was used; 800mg for

239 chondroitin sulphate and 1,500mg for glucosamine. We also evaluated the effect of
240 accumulated duration among current users. Accumulated duration was calculated as the
241 sum of the duration of all prescriptions regardless they were consecutive or not. We also
242 assessed, among current users, the effect of the regularity of NA-NSAID use approached
243 through the treatment persistence rate, calculated by dividing the accumulated duration
244 by the total number of days since the first prescription ever until the finalization of the
245 last one. To avoid the influence of very short durations, normally associated with high
246 treatment persistence rates, we only included in this analysis the subjects with at least 1
247 year of accumulated duration. Finally, we created three levels of treatment persistence
248 (<51%, 51-75% and >75%).
249
250 ***Potential confounding variables***
251 We based the selection of potential confounding variables in expert knowledge not in
252 data-driven methods as stepwise. We ascertained the history of the following
253 comorbidities and risk factors any time before the index date: chronic gastritis, gastro-
254 oesophageal reflux, inflammatory bowel disease, irritable bowel syndrome, complicated
255 upper gastrointestinal (GI) disorders (including upper GI bleeding or perforation), non-
256 complicated upper GI disorders (including non-bleeding or non-complicated ulcer,
257 gastritis or duodenitis), dyspepsia, lower GI bleeding, constipation, anorectal pathology
258 (including haemorrhoids, anal fissure and anorectal abscess), alcohol abuse, smoking
259 (current smokers, ex-smokers and non-smokers), BMI (<24,99, 25-30, >30 kg/m^2),
260 diabetes (users of glucose-lowering drugs), hyperuricaemia and gout. Number of visits to
261 the primary care physician (<6, 6-10, 11-20, >20) was ascertained in the year before the
262 index date. Also, we analysed as potential confounders the use of the following drugs:
263 corticosteroids, analgesic opioids, oral anticoagulants, H2-receptor antagonists, proton-

pump inhibitors (PPI), antidepressants, anti-diarrheal drugs, drugs for constipation, statins, low-dose aspirin, non-aspirin antiplatelet drugs, calcium supplements with or without vitamin D, NA-NSAIDs and SYSADOAs.

Statistical analysis

We calculated crude and adjusted-odds ratios (AORs) and their 95% confidence intervals (95%CI) between the drug of interest and CRC through an unconditional logistic regression that included only the matching variables for the crude model and the matching variables plus the potential confounders (described above) for the fully adjusted model. The method of selection of controls ensures that the odds ratio obtained was an unbiased estimate of the incidence rate ratio in the underlying cohort[26].

Covariates "smoking" and "BMI" had missing values. We applied for all analyses the missing-indicator method as the distribution of missing values is similar across the exposure[27]. As a consistency test, we also constructed a multiple imputation by chained equations model for the main analyses.

We explored the existence of an interaction between NA-NSAIDs and several factors (age, sex and concomitant use of PPIs) in a multiplicative scale by comparing the AORs associated with NA-NSAIDs across different strata of the potential interacting variable[28]. For age, we took as reference the categories of the USPSTF report[8]; <60, 60-69, $\geq$70 years. We also explored the interaction in the additive scale for the concomitant use of PPIs and NA-NSAIDs creating a new variable with 5 levels: non-use of any, current use of NA-NSAIDs alone, current use of PPIs alone, current use of both and rest of combinations (past or recent users of either NA-NSAIDs or PPIs).

Two sensitivity analyses were carried out; (i) excluding users of low-dose aspirin and clopidogrel (and also NA-NSAIDs users when SYSADOAs or metamizole were studied) within 1 or 3 years before the index date; and (ii) restricting the analysis to new users, defined as those with no recorded prescription of the drug of interest before the entry in the study cohort.

The level of statistical significance was set at $p<0.05$. Statistical analyses were performed using STATA/SE, v.14.2 (Statacorp LLC. Texas, USA) and R (RStudio, Inc. Boston, USA, v.1.1.423) with "tidyverse" and "forestplot" packages.

Ethics review

The scientific committee of BIFAP approved the study protocol (#10/2015) on September 10, 2015. The investigators only accessed fully anonymised data so, according to the Spanish law, no Institutional Review Board approval was required.

RESULTS

15,491 incident CRC cases and 60,000 controls were included. Cases and controls were correctly matched for age, sex and year of index date. Their baseline characteristics are shown in Table 1. A positive association was observed between CRC and alcohol abuse, gout and acute digestive diseases (anorectal pathology, complicated upper GI disorders and lower GI bleeding), whereas a negative association was found with history of constipation and chronic digestive diseases (chronic gastritis, inflammatory bowel disease and irritable bowel syndrome).

313 The number of current users of NA-NSAIDs was lower among cases (2,168; 14.0%) than
314 among controls (9,817; 16.4%) leading to an AOR=0.67; 95%CI: 0.63-0.71 (Table 2).
315 Similar risk reduction was observed when this category was splitted into COX-2
316 selective, non-selective and switchers (Table 2). The reduced risk gradually disappeared
317 upon discontinuation but some effect remained until 1 year after (Figure 1). Risk
318 reduction was already observed with an accumulated duration shorter than 181 days;
319 AOR=0.70; 0.65-0.75, increasing linearly up to more than 4 years (AOR=0.43; 0.27-0.70)
320 (p for trend < 0.001) (Figure 1). No relevant differences were observed by dose, sex, age
321 (Figure 2) or stratifying by PPI use; AOR for NSAID current users was 0.68 (0.62-0.75)
322 among PPI users and 0.70 (0.63-0.77) among PPI non-users (Table 3). We also examined
323 the potential effect modification by PPI use in the additive scale and found no effect
324 (Table 3). Risk reduction was dependent on treatment persistence but still observed in
325 patients with a treatment persistence rate as low as 50% (Figure 2). Sensitivity analyses
326 (excluding users of low-dose aspirin and clopidogrel within 1 or 3 years before the index
327 date and new user analysis) showed no impact (supporting information, Tables 2 and 3).
328 Results by individual NA-NSAIDs are shown in Figure 3. All of them showed a decreased
329 risk with some differences in the point estimates, but with confidence intervals that
330 greatly overlapped.
331
332 Current use of SYSADOAs was lower among cases (298; 1.9%) than among controls
333 (1,418; 2.4%) leading to an AOR=0.79 (95%CI:0.69-0.90) (Table 4). Of note, risk
334 reduction was observed only among short-term users ($AOR_{\leq 1 year}$=0.69; 0.58-0.83), and
335 disappeared when concomitant and former users of NA-NSAID were excluded (Table 4).
336

The number of current users of metamizole was 1,012 (6.5%) among cases and 3,080 (5.1%) among controls leading to an increased risk of CRC (AOR=1.12; 1.04-1.22), which was particularly relevant at short-term and when used at high doses (supporting information, Table 4). A moderate reduction of risk, but not statistically significant, was observed for an accumulated duration longer than 1 year; AOR=0.88; 0.71-1.08 (supporting information, Table 4).

DISCUSSION

The results of the present study show a statistically significant chemoprotective effect against CRC of NA-NSAIDs ranging from 30% to 60%, depending on the duration of treatment. No significant differences by COX-2 selectivity or by individual drugs were observed. Conversely, our data do not support an independent chemoprotective effect associated to the use of either SYSADOAs or metamizole.

NA-NSAIDs are known to exert their anti-tumor effects by inhibition of COX-2-derived prostanoids[3]. COX-2 is usually absent in non-pathological intestinal cells, being an early-response enzyme rapidly inducible by a wide variety of pro-inflammatory agents[29]. Induced COX-2 in intestinal epithelial and stromal cells leads to production of high levels of PGE_2[29,30]. High concentrations of PGE_2 in epithelial cells are supposed to be involved in the immune system attenuation[31] and, also, in anti-apoptotic, proliferation, migration and angiogenesis effects[5,29,32], promoting ultimately an environment that facilitates the neoplastic transformation of the intestinal mucosa[29,30].

In this study, we show that the most important factor associated with chemoprotection of CRC induced by NA-NSAIDs is the duration of treatment, which is consistent with other studies[12]. Nevertheless, also according with other studies[33], a protective effect is already observed in the first 180 days of treatment. This could be explained if NSAIDs not only prevent the development of pre-tumoral lesions (adenomas), but if they also have an anticancer effect by delaying or stopping the malignant transformation of pre-existing pre-tumoral lesions, as it has been reported[34,35]. Our results show that, as far as chemoprotection is concerned, COX-2 selectivity is not a determinant feature. We examined the effect of 12 individual NA-NSAIDs and found that all of them showed a similar protection with overlapping confidence intervals. Our study provides several novelties that should be emphasised. First, the chemoprotective effect of NA-NSAIDs progressively diminished upon discontinuation but it was still present up to 1 year after stopping treatment; also, the chemoprotective effect decreased as long as treatment persistence rate decreased, though it was still observed at levels of 50% or lower; both findings point to a long-lasting chemoprotective effect of NA-NSAIDs and suggest that short interruptions in treatment may still translate into an effective CRC protection. Our results are consistent with those of Yang et al[33] who also showed an effective CRC protection with COX-2 selective NSAIDs when medication possession ratios were as low as 10-40%. Second, the effect was still observed at low-moderate daily doses. And third, the chemoprotective effect of NA-NSAIDs on CRC is not modified by the concomitant use of PPIs. In our view, these findings might be clinically important as low doses, less frequent administration and the concomitant use of PPIs could help to reduce the burden of adverse events associated with NA-NSAIDs while maintaining an effective CRC chemoprotection[36,37]. If, under these conditions, the benefits outweigh the risks and NA-NSAIDs could be recommended as an adequate chemoprotective intervention, should be

386 explored further in longitudinal studies. Finally, our study was performed in a
387 Mediterranean population, where there is scarcity of studies[14]. In a previous study we also
388 showed a chemoprotective effect for low-dose aspirin in the same population[38].
389
390 In a recent meta-analysis, Tomić T et al[14] assessed the chemoprotective effect of NA-
391 NSAIDs against CRC in people aged 40 or older. They pooled 23 epidemiological studies
392 (cohort and case-control), including more than 13,000 CRC cases, and estimated an OR
393 of 0.74, very similar to the one we found. It is important to note that our study is larger
394 than the meta-analysis and powered enough to assess the effect of individual patient
395 variables, such as age, dose, treatment persistence, discontinuation, or concomitant PPI
396 use as well as the effect of individual NA-NSAIDs, while the meta-analysis did not
397 provide this information. Of note, Tomić et al concluded that there was only evidence for
398 an effective chemoprotection of NA-NSAIDs in women and with high doses. On the
399 contrary, we found a similar protection in both, men and women, and with both low-
400 moderate and high doses. In addition, there is only one small study performed in Spain,
401 so gathering solid new evidence in this population was needed.
402
403 SYSADOAs are prescription-only drugs in Spain authorised for treatment of symptoms
404 of osteoarthritis and usually taken once-daily in monotherapy or combined. Although, the
405 clinical utility of these drugs has been a matter of controversy[39], in recent randomised
406 clinical trials they have shown to be as effective as celecoxib[40] and superior to placebo[41].
407 Also, several studies have reported a risk reduction of CRC associated with their use[17-21].
408 These drugs have been reported to inhibit the production of some inflammatory mediators
409 such as NF-kB[15,16], a cell transcription factor capable to upregulate COX-2[15]. Thus, its
410 inhibition would lead to an anti-inflammatory effect by lowering the expression of COX-

411 2. This action would presumably explain their analgesic effect on osteoarthritis and the
412 suggested CRC protection. In our study, we observed a reduced risk of CRC among users
413 of SYSADOAs within the first year of treatment but the effect did not persist with
414 prolonged treatment and, most importantly, completely vanished after the exclusion of
415 previous NSAID users. This finding suggests that the risk reduction observed with
416 SYSADOAs is mostly explained by a residual effect of previously used NSAIDs. In fact,
417 a recently published study[17] reported a protective effect against CRC among users of
418 SYSADOAs but the adjustment for NSAID use led to a loss of statistical significance,
419 which is consistent with our results.
420
421 Metamizole (or dypirone) is an analgesic, antipyretic and spasmolytic drug with a weak
422 anti-inflammatory effect that is commonly used to relieve post-operative, visceral or
423 neoplastic-associated pain, as well as in spastic states like colics[22]. At present, it is not
424 marketed in some countries like USA, Japan, UK or Australia, due to myelotoxic severe
425 adverse events as agranulocytosis[42] but, conversely, is available in other countries (as
426 Spain, Italy, Germany and many Latino-american countries) because of their lower risk
427 of upper GI complications as compared to NSAIDs[43]. Its mechanism of action is complex
428 and has not been elucidated yet[22]. In our study, we observed no chemoprotective effect
429 among users of metamizole. On the contrary, we observed a small increased risk during
430 a short period after treatment initiation and at daily doses greater than 1,725 mg. This
431 observation could be explained by a confounding by indication as metamizole, especially
432 at high dose, is used to treat visceral pain that could be the first symptom of a CRC. Yet,
433 a small risk reduction after a treatment duration longer than 1 year cannot be ruled out.
434

435 Some limitations of our study should be mentioned. First, although we performed a
436 validation study of CRC diagnosis in BIFAP[25], a small probability of misclassification
437 exists (< 5%) which, if non-differential with respect to the exposure (researchers who
438 validated CCR diagnosis were blinded to all drug prescriptions), might have resulted in a
439 minor underestimation of the chemoprotective effect. Second, NA-NSAIDs, SYSADOAs
440 or metamizole are prescription-only drugs but sometimes dispensed over-the-counter, so
441 misclassification of the exposure might have occurred. In that case, if present but non-
442 differential with respect to CRC, it would have resulted, again, in a small underestimation
443 of the main association (meaning that the true protective effect would be greater). Thirdly,
444 as in any other observational study, the possibility of unknown residual confounding or
445 selection bias cannot be ruled out. Finally, in this study the risks associated with NA-
446 NSAIDs were not evaluated and thus a proper benefit-risk evaluation could not be done.
447
448 In conclusion, our study shows that the use of NA-NSAIDs, both COX-2 selective and
449 non-selective, are associated to a statistically significant chemoprotective effect against
450 CRC. However, their adverse gastrointestinal and cardiovascular harms may outweigh
451 the potential benefits. The finding that the chemoprotective effect is observed at low-
452 moderate doses and with low treatment persistence should be explored further as this may
453 open the possibility to improve the benefit-risk ratio, in addition to the concomitant use
454 of PPIs. In contrast, our results do not support the hypothesis that either SYSADOAs or
455 metamizole have a chemoprotective effect against CRC.
456

Statement of interests

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REFERENCES

1. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-1502.

2. López-Abente G, Núñez O, Pérez-Gómez B, et al. La situación del cáncer en España: Informe 2015. Instituto de Salud Carlos III. Madrid, 2015.

3. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 2010;29(6):781-8.

4. Binefa G, Rodríguez-Moranta F, Teule A, et al. Colorectal cancer: from prevention to personalized medicine. World J Gastroenterol. 2014;20(22):6786-808.

5. Moreira L, Castells A. Cyclooxygenase as a target for colorectal cancer chemoprevention. Curr Drug Targets. 2011;12(13):1888-94.

6. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007;357(24):2482-94.

7. Lang M, Gasche C. Chemoprevention of colorectal cancer. Dig Dis. 2015;33(1):58-67.

8. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(12):836-45.

9. McNeil JJ, Wolfe R, Woods RL, et al. ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509-1518.

10. Bowman L, Mafham M, Wallendszus K, et al; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379(16):1529-1539.

11. Gaziano JM, Brotons C, Coppolecchia R, et al; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of

cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392(10152):1036-1046.

12. Rostom A, Dubé C, Lewin G, et al; U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):376-89.

13. Veettil SK, Lim KG, Ching SM, et al. Effects of aspirin and non-aspirin nonsteroidal anti-inflammatory drugs on the incidence of recurrent colorectal adenomas: a systematic review with meta-analysis and trial sequential analysis of randomized clinical trials. BMC Cancer. 2017;17(1):763.

14. Tomić T, Domínguez-López S, Barrios-Rodríguez R. Non-aspirin non-steroidal anti-inflammatory drugs in prevention of colorectal cancer in people aged 40 or older: A systematic review and meta-analysis. Cancer Epidemiol. 2019;58:52-62

15. Shi G, Li D, Fu J, et al. Upregulation of cyclooxygenase-2 is associated with activation of the alternative nuclear factor kappa B signaling pathway in colonic adenocarcinoma. Am J Transl Res. 2015;7(9):1612-20

16. Bottegoni C, Muzzarelli RA, Giovannini F, et al. Oral chondroprotection with nutraceuticals made of chondroitin sulphate plus glucosamine sulphate in osteoarthritis. Carbohydr Polym. 2014;109:126-38

17. Ibáñez-Sanz G, Díez-Villanueva A, Vilorio-Marqués L, et al. Possible role of chondroitin sulphate and glucosamine for primary prevention of colorectal cancer. Results from the MCC-Spain study. Sci Rep. 2018;8(1):2040

18. Kantor ED, Zhang X, Wu K, et al. Use of glucosamine and chondroitin supplements in relation to risk of colorectal cancer: Results from the Nurses' Health Study and Health Professionals follow-up study. Int J Cancer. 2016;139(9):1949-57.

19. Kantor ED, Lampe JW, Peters U, et al. Use of glucosamine and chondroitin supplements and risk of colorectal cancer. Cancer Causes Control. 2013;24(6):1137-46.

20. Kantor ED, Newton CC, Giovannucci EL, et al. Glucosamine use and risk of colorectal cancer: results from the Cancer Prevention Study II Nutrition Cohort. Cancer Causes Control. 2018;29(3):389-397.

21. Satia JA, Littman A, Slatore CG, et al. Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. Cancer Epidemiol Biomarkers Prev. 2009;18(5):1419-28.

22. Hinz B, Cheremina O, Bachmakov J, et al. Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. FASEB J. 2007:2343-51

23. BIFAP. Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria. www.bifap.org. Accessed December 4, 2018

24. Abbing-Karahagopian V, Kurz X, de Vries F, et al. Bridging differences in outcomes of pharmacoepidemiological studies: design and first results of the PROTECT project. Curr Clin Pharmacol. 2014; 9:130-8.

25. Gil M, Rodríguez-Miguel A, Montoya-Catalá H, et al. Validation study of colorectal cancer diagnosis in the Spanish primary care database, BIFAP. Pharmacoepidemiol Drug Saf. 2019:209-216

26. Rothman K, Greenland S, Lash TS. Case-control studies. In: Rothman K, Greenland S, Lash TS, eds, 3rdedition, Wolter Kluwer/Lippincott, William & Wilkins, 2008, Philadelphia, 2008; pp: 111-127.

27. Groenwold RH, White IR, Donders AR, et al. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. CMAJ. 2012;184(11):1265-9.

537 28. Altman DG, Bland JM. Interaction revisited: the difference between two estimates.
538 BMJ. 2003;326(7382):219
539 29. Dixon DA, Blanco FF, Bruno A, et al. Mechanistic aspects of COX-2 expression in
540 colorectal neoplasia. Recent Results Cancer Res. 2013;191:7-37.
541 30. Guillem-Llobat P, Dovizio M, Alberti S, et al. Platelets, cyclooxygenases, and colon
542 cancer. Semin Oncol. 2014;41(3):385-96.
543 31. Zhang Z, Chen F, Shang L. Advances in antitumor effects of NSAIDs. Cancer Manag
544 Res. 2018;10:4631-4640.
545 32. Wang D, DuBois RN. Pro-inflammatory prostaglandins and progression of colorectal
546 cancer. Cancer Lett. 2008;267(2):197-203.
547 33. Yang YH, Yang YH, Cheng CL, et al. The role of chemoprevention by selective
548 cyclooxygenase-2 inhibitors in colorectal cancer patients – a population-based study.
549 BMC Cancer. 2012;12:582
550 34. Gurpinar E, Grizzle WE, Piazza GA. NSAIDs inhibit tumorigenesis, but how? Clin
551 Cancer Res. 2014;20(5):1104-13
552 35. Patrignani P. Nonsteroidal anti-inflammatory drugs, COX-2 and colorectal cancer.
553 Toxicol Lett. 2000;112-113:493-8
554 36. Mo C, Sun G, Lu ML, et al. Proton pump inhibitors in prevention of low-dose aspirin-
555 associated upper gastrointestinal injuries. World J Gastroenterol. 2015;21:5382-5392.
556 37. Matthews ML. The role of dose reduction with NSAID use. Am J Manag Care.
557 2013;19(14 Suppl):s273-7
558 38. Rodríguez-Miguel A, García-Rodríguez LA, Gil M, et al. Clopidogrel and low-dose
559 aspirin, alone or together, reduce risk of colorectal cancer. Clin Gastroenterol Hepatol.
560 2018. doi: 10.1016/j.cgh.2018.12.012.
561

562 39. Wandel S, Jüni P, Tendal B, et al; Effects of glucosamine, chondroitin, or placebo in
563 patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010; 341: c4675,
564 doi:10.1136/bmj.c4675
565 40. Hochberg MC, Martel-Pelletier J, Monfort J, et al; MOVES Investigation Group.
566 Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a
567 multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum
568 Dis. 2016;75(1):37-44.
569 41. Reginster JY, Dudler J, Blicharski T, et al. Pharmaceutical-grade chondroitin sulfate
570 is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis:
571 the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). Ann Rheum Dis
572 2017; 76:1537-1543; doi:10.1136/annrheumdis-2016-210860.
573 42. Ibáñez L, Vidal X, Ballarín E, et al. Agranulocytosis associated with dipyrone
574 (metamizol). Eur J Clin Pharmacol. 2005;60(11):821-9
575 43. Laporte JR, Ibáñez L, Vidal X, et al. Upper gastrointestinal bleeding associated with
576 the use of NSAIDs: newer versus older agents. Drug Saf. 2004;27(6):411-20
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Table 1. Baseline characteristics of cases and controls

	CASES n=15,491	CONTROLS n=60,000	Crude OR[†] (95% CI)	Adjusted OR[‡] (95% CI)
Age (years, mean±SD)	68.6 (±11.8)	68.6 (±11.8)	Matched	Matched
Men, No. (%)	9,115 (58.8)	35,307 (58.9)	Matched	Matched
Days from start date to index date (median, IQR)	1,113 (518-2,185)	1,021 (478-2,041)	-	-
Number of visits within the last year, No. (%):				
<6	3,248 (21.0)	19,508 (32.5)	1 (Ref.)	1 (Ref.)
6-10	3,639 (23.5)	13,357 (22.3)	1.71 (1.62 – 1.80)	1.81 (1.71 – 1.91)
11-20	5,298 (34.2)	17,118 (28.5)	2.01 (1.91 – 2.11)	2.19 (2.07 – 2.31)
>20	3,306 (21.3)	10,017 (16.7)	2.23 (2.11 – 2.37)	2.45 (2.28 – 2.63)
BMI, No. (%), kg.m^{-2}:				
<24,99	2,123 (13.7)	7,635 (12.7)	1 (Ref.)	1 (Ref.)
25-30	4,933 (31.8)	18,108 (30.2)	0.98 (0.93 – 1.04)	0.97 (0.92 – 1.03)
> 30	3,652 (23.6)	13,421 (22.4)	0.98 (0.92 – 1.04)	0.95 (0.89 – 1.01)
Missing	4,783 (30.9)	20,836 (34.7)		
Smoking, No. (%):				
Non-smoker	4,904 (31.7)	18,016 (30.0)	1 (Ref.)	1 (Ref.)
Current smoker	2,384 (15.4)	8,960 (14.9)	0.98 (0.92 – 1.04)	1.02 (0.97 – 1.08)
Past smoker	1,217 (7.86)	3,821 (6.37)	1.18 (1.09 – 1.27)	1.18 (1.10 – 1.27)
Missing	6,986 (45.1)	29,203 (48.7)		
History of, No. (%):				
Alcohol abuse[§]	552 (3.56)	1,578 (2.63)	1.38 (1.25 – 1.52)	1.25 (1.13 – 1.38)
Diabetes	3,067 (19.8)	10,344 (17.2)	1.19 (1.14 – 1.25)	1.05 (0.97 – 1.14)
Hyperuricaemia (non-gout)	984 (6.35)	3,829 (6.38)	1.01 (0.93 – 1.08)	0.91 (0.84 – 0.98)
Gout	718 (4.63)	2,363 (3.94)	1.19 (1.09 – 1.30)	1.11 (1.02 – 1.22)
Chronic gastritis	154 (0.99)	604 (1.01)	0.99 (0.83 – 1.18)	0.84 (0.70 – 1.01)
Gastro-oesophageal reflux	1,866 (12.1)	6,896 (11.5)	1.05 (1.00 – 1.11)	0.93 (0.87 – 0.98)
Inflammatory bowel disease	51 (0.33)	238 (0.40)	0.83 (0.61 – 1.12)	0.42 (0.30 – 0.58)
Irritable bowel syndrome	238 (1.54)	941 (1.57)	0.98 (0.85 – 1.13)	0.85 (0.73 – 0.99)
Constipation	1,601 (10.3)	5,424 (9.04)	1.16 (1.10 – 1.24)	0.89 (0.83 – 0.96)
Anorectal pathology[¶]	1,995 (12.9)	5,741 (9.57)	1.40 (1.32 – 1.48)	1.23 (1.16 – 1.30)
Upper GI disorders:				
Complicated[‖]	459 (2.96)	1,062 (1.77)	1.73 (1.55 – 1.94)	1.41 (1.26 – 1.59)
Non-complicated[#]	1,103 (7.12)	3,889 (6.48)	1.14 (1.06 – 1.22)	1.02 (0.95 – 1.10)
Dyspepsia	1,797 (11.6)	6,549 (10.9)	1.10 (1.04 – 1.16)	0.98 (0.92 – 1.04)
Lower GI bleeding	898 (5.80)	1,310 (2.18)	2.76 (2.53 – 3.01)	2.45 (2.24 – 2.68)

OR: odds ratio; CI: confidence interval; SD: standard deviation; IQR: interquartile range; BMI: body mass index; GI: gastrointestinal

[†]*Model adjusted only for the matching variables (age, sex and year of index date).*
[‡]*Model adjusted for the matching variables, comorbidities and risk factors shown in the table (the category of reference was no presence of the specific disease or risk factor listed) and use of the following drugs: NA-NSAIDs, SYSADOAs, corticosteroids, analgesic opioids, antidepressants, oral anticoagulants, H2-receptor antagonists, proton-pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, low-dose aspirin, non-aspirin antiplatelet drugs and calcium supplements with or without vitamin D.*
[§]*When the primary care physician recorded an excessive consumption of alcohol*
[¶]*Includes haemorrhoids, anal fissure and anorectal abscess*
[‖]*Includes complicated ulcer, gastritis or duodenitis with bleeding and upper GI bleeding*
[#]*Includes non-bleeding or non-complicated ulcer, gastritis or duodenitis*

Table 2. Colorectal cancer risk and use of NA-NSAIDs

	CASES n=15,491	CONTROLS n=60,000	Crude OR[†] (95% CI)	Adjusted OR[‡] (95% CI)
Non-users	5,820 (37.6)	22,636 (37.7)	1 (Ref.)	1 (Ref.)
Current use:	2,168 (14.0)	9,817 (16.4)	0.86 (0.81 – 0.91)	0.67 (0.63 – 0.71)
Only non-selective	1,843 (11.9)	8,167 (13.6)	0.88 (0.83 – 0.93)	0.68 (0.64 – 0.73)
Only COX-2 selective	29 (0.2)	146 (0.2)	0.77 (0.52 – 1.15)	0.63 (0.42 – 0.94)
Switchers[§]	296 (1.9)	1,506 (2.5)	0.77 (0.67 – 0.87)	0.59 (0.52 – 0.68)
Recent use	2,602 (16.8)	9,860 (16.4)	1.03 (0.97 – 1.08)	0.84 (0.79 – 0.89)
Past use	4,901 (31.6)	17,687 (29.5)	1.08 (1.03 – 1.13)	1.01 (0.97 – 1.06)

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs; OR: odds ratio; CI: confidence interval; COX-2: cyclooxygenase-2

[†]*Model adjusted only for the matching variables (age, sex and year of index date).*
[‡]*Model adjusted for the matching variables, comorbidities and risk factors shown in Table 1 and use of following drugs: SYSADOAs, corticosteroids, analgesic opioids, antidepressants, oral anticoagulants, H2-receptor antagonists, proton-pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, low-dose aspirin, non-aspirin antiplatelet drugs and calcium supplements with or without vitamin D.*
[§]*Recorded use of both non-selective NA-NSAID and COX-2 selective within the current-use time window.*

Table 3. Evaluation of the potential interaction between NA-NSAIDs and proton-pump inhibitors on colorectal cancer risk

	CASES n=15,491	CONTROLS n=60,000	Crude OR[†] (95% CI)	Adjusted OR[‡] (95% CI)
PPI use (multiplicative scale):				
PPI current users:				
NA-NSAID non-use	1,308 (27.4)	3,994 (24.8)	1 (Ref.)	1 (Ref.)
NA-NSAID current use	1,227 (25.7)	5,251 (32.6)	0.69 (0.63 – 0.75)	0.68 (0.62 – 0.75)
NA-NSAID recent and past use	2,247 (47.0)	6,871 842.6)	0.99 (0.91 – 1.07)	0.99 (0.91 – 1.08)
PPI non-users:				
NA-NSAID non-use	3,823 (57.4)	15,965 (56.9)	1 (Ref.)	1 (Ref.)
NA-NSAID current use	520 (7.8)	2,534 (9.0)	0.86 (0.78 – 0.95)	0.70 (0.63 – 0.77)
NA-NSAID recent and past use	2,318 (34.8)	9,546 (34.0)	1.01 (0.95 – 1.07)	0.91 (0.86 – 0.97)
PPIs and NSAIDs (additive scale):				
Non-use of any	3,823 (24.7)	15,965 (26.6)	1 (Ref.)	1 (Ref.)
Current use of NA-NSAIDs alone	520 (3.4)	2,534 (4.2)	0.86 (0.77 – 0.95)	0.70 (0.63 – 0.78)
Current use of PPIs alone	1,308 (8.4)	3,994 (6.7)	1.38 (1.28 – 1.48)	0.94 (0.85 – 1.04)
Current use of NA-NSAIDs and PPIs	1,227 (7.9)	5,251 (8.8)	0.98 (0.91 – 1.05)	0.64 (0.58 – 0.71)
Other combinations (past or recent use of any)	8,613 (55.6)	32,256 (53.8)	1.12 (1.07 – 1.17)	0.93 (0.87 – 0.98)

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs; OR: odds ratio; CI: confidence interval; PPI: proton-pump inhibitors

[†]*Model adjusted only for the matching variables (age, sex and year of index date).*
[‡]*Model adjusted for the matching variables, comorbidities and risk factors shown in Table 1 and use of following drugs: SYSADOAs, corticosteroids, analgesic opioids, antidepressants, oral anticoagulants, H2-receptor antagonists, anti-diarrheal drugs, drugs for constipation, statins, low-dose aspirin, non-aspirin antiplatelet drugs and calcium supplements with or without vitamin D.*

Table 4. Colorectal cancer risk and use of SYSADOAs

	CASES n=15,491	CONTROLS n=60,000	Crude OR† (95% CI)	Adjusted OR‡ (95% CI)
Non-users	14,362 (92.7)	55,293 (92.2)	1 (Ref.)	1 (Ref.)
Recency of use, in days:				
Current use	298 (1.9)	1,418 (2.4)	0.81 (0.71 – 0.92)	0.79 (0.69 – 0.90)
Recent use	201 (1.3)	804 (1.3)	0.96 (0.82 – 1.12)	0.93 (0.79 – 1.09)
Past use	630 (4.1)	2,485 (4.1)	0.97 (0.89 – 1.07)	0.95 (0.87 – 1.04)
Accumulated duration, among current users:				
≤1 year	152 (1.0)	827 (1.4)	0.71 (0.59 – 0.84)	0.69 (0.58 – 0.83)
>1 year	146 (0.9)	591 (1.0)	0.95 (0.79 – 1.14)	0.92 (0.76 – 1.11)
SYSADOA current use, excluding NSAID users:				
In the previous year	127 (1.2)	494 (1.21)	0.96 (0.79 – 1.17)	0.85 (0.70 – 1.04)
In the previous 3 years	70 (0.9)	249 (0.9)	1.08 (0.82 – 1.41)	1.00 (0.76 – 1.31)

SYSADOA: symptomatic slow-acting drugs for osteoarthritis; OR: odds ratio; CI: confidence interval; NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs;

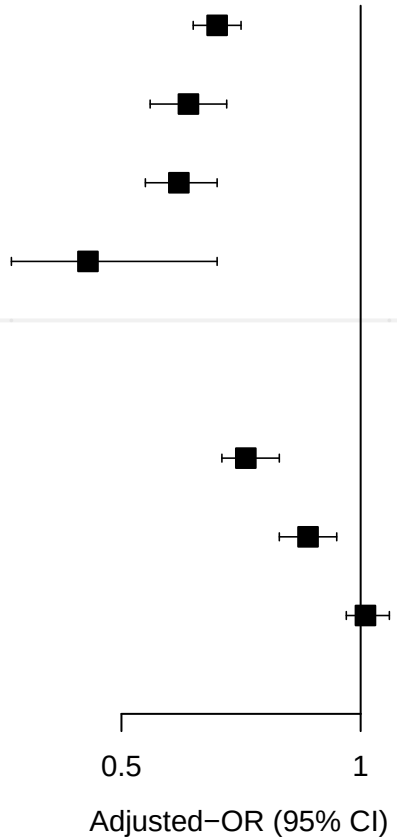
†*Model adjusted only for the matching variables (age, sex and year of index date).*
‡*Model adjusted for the matching variables, comorbidities and risk factors shown in Table 1 and use of following drugs: NA-NSAIDs, corticosteroids, analgesic opioids, antidepressants, oral anticoagulants, H2-receptor antagonists, proton-pump inhibitors, anti-diarrheal drugs, drugs for constipation, statins, low-dose aspirin, non-aspirin antiplatelet drugs and calcium supplements with or without vitamin D.*

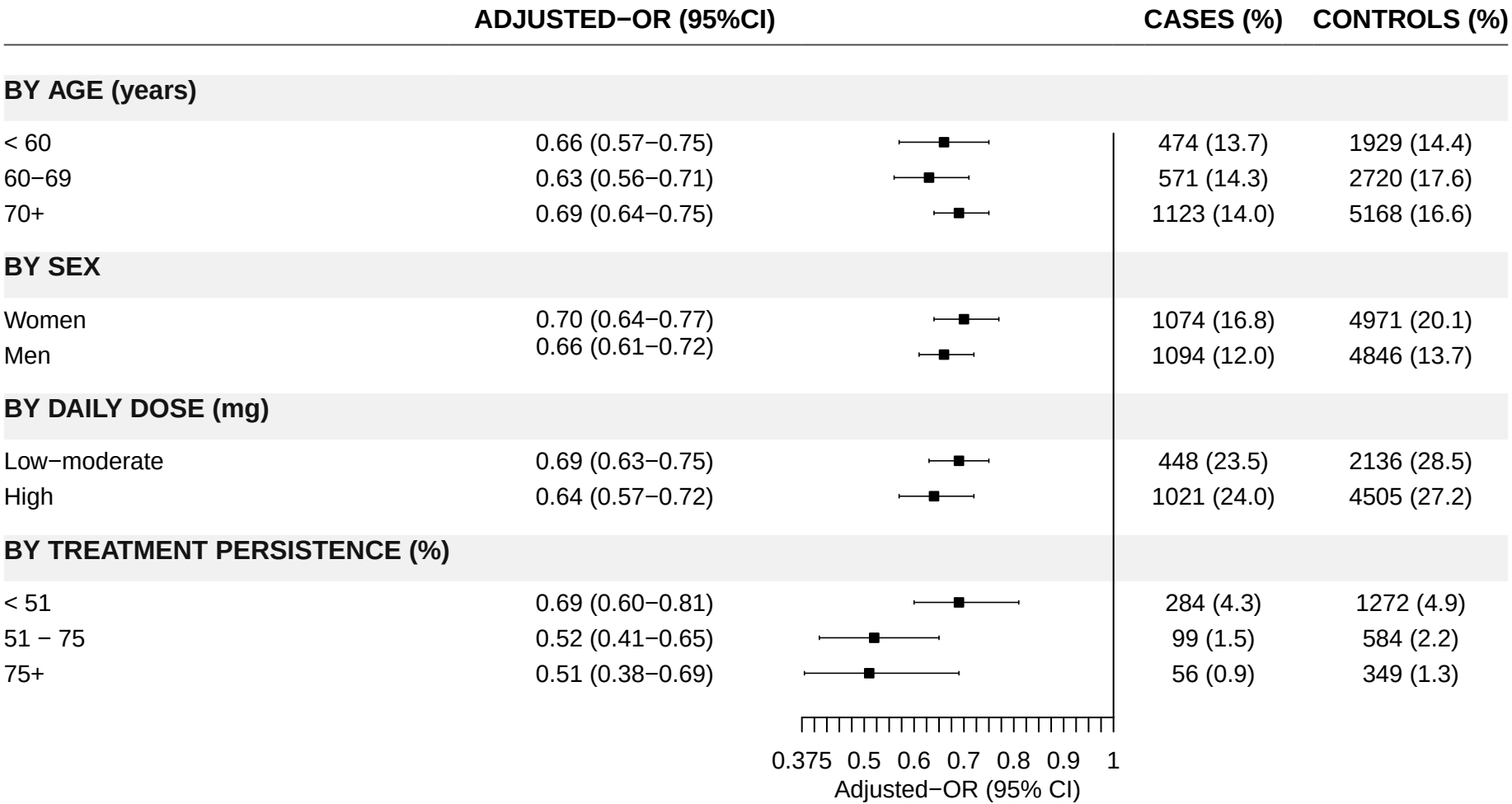
Figure 1. Effect of duration of treatment with NA-NSAIDs (among current users) and time elapsed from treatment discontinuation on colorectal cancer risk

Figure 2. Evaluation of the effect of NA-NSAIDs use on colorectal cancer risk, by different subgroups

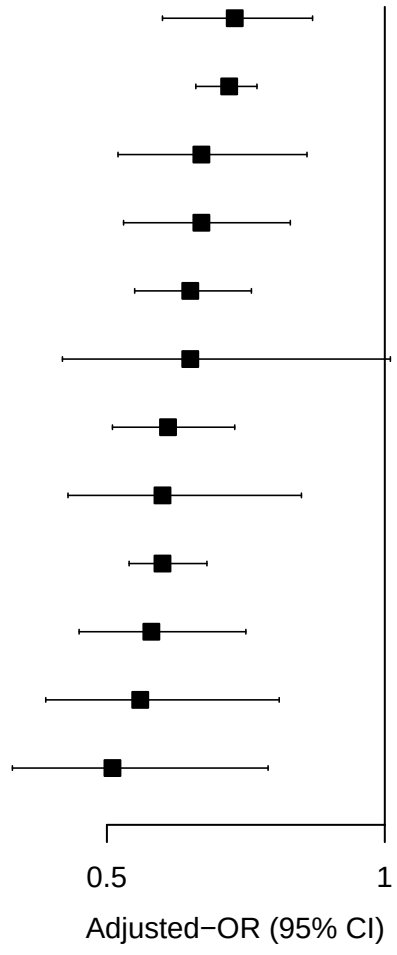
Figure 3. Individual NA-NSAIDs use and colorectal cancer risk

	ADJUSTED−OR (95%CI)	CASES (%)	CONTROLS (%)
CURRENT USERS ACCUMULATED DURATION			
< 181 days	0.70 (0.65−0.75)	1385 (8.9)	6021 (10.0)
181 − 365 days	0.64 (0.56−0.72)	344 (2.2)	1603 (2.7)
1 − 4 years	0.62 (0.55−0.70)	419 (2.7)	2049 (3.4)
4+ years	0.43 (0.27−0.70)	20 (0.1)	144 (0.2)
TIME ELAPSED FROM DISCONTINUATION			
< 181 days	0.76 (0.71−0.83)	1009 (6.5)	4106 (6.8)
181 − 365 days	0.89 (0.83−0.95)	1593 (10.3)	5754 (9.6)
> 1 year	1.01 (0.97−1.06)	4901 (31.6)	17687 (29.5)




ADJUSTED−OR (95%CI)
CASES (%)
CONTROLS (%)
BY AGE (years)
< 60
0.66 (0.57−0.75)
474 (13.7)
1929 (14.4)
60−69
0.63 (0.56−0.71)
571 (14.3)
2720 (17.6)
70+
0.69 (0.64−0.75)
1123 (14.0)
5168 (16.6)
BY SEX
Women
0.70 (0.64−0.77)
1074 (16.8)
4971 (20.1)
Men
0.66 (0.61−0.72)
1094 (12.0)
4846 (13.7)
BY DAILY DOSE (mg)
Low−moderate
0.69 (0.63−0.75)
448 (23.5)
2136 (28.5)
High
0.64 (0.57−0.72)
1021 (24.0)
4505 (27.2)
BY TREATMENT PERSISTENCE (%)
< 51
0.69 (0.60−0.81)
284 (4.3)
1272 (4.9)
51 − 75
0.52 (0.41−0.65)
99 (1.5)
584 (2.2)
75+
0.51 (0.38−0.69)
56 (0.9)
349 (1.3)
0.375 0.5 0.6 0.7 0.8 0.9 1
Adjusted−OR (95% CI)

	ADJUSTED−OR (95%CI)	CASES (%)	CONTROLS (%)
CURRENT USE			
Naproxen	0.73 (0.60−0.87)	151 (1.0)	616 (1.0)
Ibuprofen	0.72 (0.66−0.77)	1106 (7.1)	4725 (7.9)
Meloxicam	0.67 (0.52−0.86)	77 (0.5)	362 (0.6)
Celecoxib	0.67 (0.53−0.83)	102 (0.7)	477 (0.8)
Dexketoprofen	0.65 (0.55−0.76)	195 (1.3)	877 (1.5)
Lornoxicam	0.65 (0.42−1.01)	26 (0.2)	120 (0.2)
Aceclofenac	0.61 (0.51−0.73)	146 (0.9)	740 (1.2)
Piroxicam	0.60 (0.43−0.85)	41 (0.3)	202 (0.3)
Diclofenac	0.60 (0.54−0.68)	389 (2.5)	1953 (3.3)
Etoricoxib	0.58 (0.45−0.75)	75 (0.5)	394 (0.7)
Indometacin	0.56 (0.39−0.81)	37 (0.2)	186 (0.3)
Dexibuprofen	0.51 (0.33−0.79)	25 (0.2)	151 (0.3)



STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Page	Recommendation
Title and abstract	1	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		5-6	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
			Introduction
Background/rationale	2	7-8	Explain the scientific background and rationale for the investigation being reported
Objectives	3	8	State specific objectives, including any prespecified hypotheses
			Methods
Study design	4	9	Present key elements of study design early in the paper
Setting	5	9	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	9-10	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		9-10	(*b*) For matched studies, give matching criteria and the number of controls per case
Variables	7	10-11	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	12-13	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	12-13	Describe any efforts to address potential sources of bias
Study size	10	NA	Explain how the study size was arrived at
Quantitative variables	11	12-13	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	12-13	(*a*) Describe all statistical methods, including those used to control for confounding
		12-13	(*b*) Describe any methods used to examine subgroups and interactions
		12	(*c*) Explain how missing data were addressed
		9-10	(*d*) If applicable, explain how matching of cases and controls was addressed
		12-13	(*e*) Describe any sensitivity analyses
			Results
Participants	13*	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		NA	(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram

Descriptive data	14*	Table 1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Table 1	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Table 2-4	Report numbers in each exposure category, or summary measures of exposure
Main results	16	Table 2-4 and Figures 1-3	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		Table 1-4	(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Table 3-4 and Figure 2	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	15	Summarise key results with reference to study objectives
Limitations	19	18	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	15-18	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21		Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	3	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

SUPPORTING INFORMATION

Methods 1. Detection of cases

All potential cases retrieved were then segmented into homogenous groups according to their recorded information characteristics. Random samples of 100 potential cases per group were obtained and their electronic health records were manually reviewed by two researchers blinded to drug prescriptions. Positive predictive values (PPVs) were calculated per group and for the whole study population considering the stratified method of sampling. The resulting PPV was of 87.3% (95%CI: 83.3%-90.4%). Additionally, in order to improve the sensitivity, researchers developed the following two-step strategy:

1. We performed a manual review of all the electronic health records from groups that resulted in a PPV lower than 50% (1,474 potential cases additionally reviewed) raising the overall PPV to 91.0%.

2. From confirmed false positives we constructed text mining algorithms based on semantic patterns or keywords identified from their electronic health records (algorithm enhance phase). These semantic patterns included dates (which were more likely to be prevalent cases or to detect dates of diagnosis or surgery), keywords indicating high probability to be a false positive (e.g.: colorectal cancer of a relative, screening or colonoscopy without abnormalities) or string-text search identifying hereditary colorectal cancer (hereditary CRC was excluded). The final number of electronic health records meeting these criteria that were manually reviewed was 1,289. This allowed to increase the PPV to 95.7%.

Table 1. Daily dose cut-off points for NA-NSAIDs, paracetamol and metamizole

ACTIVE PRINCIPLE	HIGH DOSE (mg/day)
NA-NSAIDS	
Aceclofenac	>200
Meclofenamic acid	>300
Mefenamic acid	>1000
Niflumic acid	>750
Celecoxib	>200
Dexketoprofen	>50
Dexibuprofen	> 900
Diclofenac	>100
Etoricoxib	>60
Flurbiprofen	>150
Ibuprofen	≥1800
Indometacine	>75
Ketoprofen	>150
Ketorolac	>30
Lornoxicam	>8
Meloxicam	>7,5
Nabumetone	>1000
Naproxen	>1000
Nimesulide	>100
Piroxicam	>10
Rofecoxib	>25
Sulindac	>200
Tenoxicam	>20
OTHERS	
Paracetamol	>2600
Metamizole	>1725

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs; mg: milligram

Table 2. Colorectal cancer risk and use of NA-NSAIDs, excluding low-dose aspirin and clopidogrel users

	CASES n=15,491	CONTROLS n=60,000	Crude OR[†] (95% CI)	Adjusted OR[‡] (95% CI)
Non-users	5,820 (37.6)	22,636 (37.7)	1 (Ref.)	1 (Ref.)
Excluding low-dose aspirin or clopidogrel users:				
In the previous year:				
NA-NSAID current use	1,800 (13.9)	8,118 (16.2)	0.86 (0.81 – 0.92)	0.66 (0.62 – 0.70)
≤1 year	1,457 (11.3)	6,364 (12.7)	0.89 (0.84 – 0.95)	0.68 (0.63 – 0.73)
>1 year	343 (2.7)	1,754 (3.5)	0.76 (0.67 – 0.86)	0.58 (0.51 – 0.66)
In the previous 3 years:				
NA-NSAID current use	1,756 (14.0)	7,939 (16.39	0.86 (0.81 – 0.91)	0.65 (0.61 – 0.70)
≤1 year	1,419 (11.3)	6,239 (12.8)	0.88 (0.83 – 0.95)	0.67 (0.62 – 0.72)
>1 year	337 (2.7)	1,700 (3.5)	0.77 (0.68 – 0.87)	0.59 (0.51 – 0.67)

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs; OR: odds ratio; CI: confidence interval

[†]*Model adjusted only for the matching variables (age, sex and year of index date).*
[‡]*Model adjusted for the matching variables, comorbidities and risk factors shown in manuscript Table 1 and use of following drugs: corticosteroids, rest of non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, antidepressants, H2-receptor antagonists, proton-pump inhibitors, antidiarrheal drugs, drugs for constipation, statins, low-dose aspirin, SYSADOAs and calcium and vitamin D supplements.*

Table 3. Colorectal cancer risk and new users of NA-NSAIDs

	CASES n=15,491	CONTROLS n=60,000	Crude OR[†] (95% CI)	Adjusted OR[‡] (95% CI)
Non-users	5,820 (37.6)	22,636 (37.7)	1 (Ref.)	1 (Ref.)
Recency of use, in days, among new users:				
Current use	906 (8.8)	3,746 (9.7)	0.94 (0.87 – 1.02)	0.74 (0.68 – 0.81)
Recent use	1,243 (12.1)	4,431 (11.4)	1.09 (1.02 – 1.17)	0.90 (0.84 – 0.97)
Past use	2,302 (22.4)	8,023 (20.7)	1.12 (1.06 – 1.18)	1.06 (1.00 – 1.13)
Accumulated duration, among current new users:				
≤1 year	833 (8.1)	3,377 (8.7)	0.96 (0.89 – 1.04)	0.75 (0.69 – 0.82)
>1 year	73 (0.7)	369 (1.0)	0.77 (0.60 – 0.99)	0.62 (0.48 – 0.81)

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs; OR: odds ratio; CI: confidence interval

[†]*Model adjusted only for the matching variables (age, sex and year of index date).*
[‡]*Model adjusted for the matching variables, comorbidities and risk factors shown in manuscript Table 1 and use of following drugs: corticosteroids, non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, antidepressants, H2-receptor antagonists, proton-pump inhibitors, antidiarrheal drugs, drugs for constipation, statins, low-dose aspirin, SYSADOAs and calcium and vitamin D supplements.*

Table 4. Colorectal cancer risk and use of metamizole

	CASES n=15,491	CONTROLS n=60,000	Crude OR† (95%CI)	Adjusted OR‡ (95% CI)
Non-users	10,966 (70.8)	43,700 (72.8)	1 (Ref.)	1 (Ref.)
Recency of use, in days:				
Current use	1,012 (6.5)	3,080 (5.1)	1.31 (1.22 – 1.42)	1.12 (1.04 – 1.22)
Recent use	980 (6.3)	3,478 (5.8)	1.13 (1.05 – 1.21)	0.98 (0.91 – 1.06)
Past use	2,533 (16.4)	9,742 (16.2)	1.04 (0.99 – 1.09)	0.97 (0.92 – 1.03)
Accumulated duration, among current users:				
≤1 year	890 (5.8)	2,596 (4.3)	1.37 (1.27 – 1.48)	1.17 (1.08 – 1.27)
>1 year	122 (0.8)	484 (0.8)	1.01 (0.83 – 1.23)	0.88 (0.71 – 1.08)
By daily dose, among current users:				
Low-moderate	521 (3.4)	1,632 (2.7)	1.28 (1.15 – 1.41)	1.10 (0.99 – 1.23)
High	91 (0.6)	188 (0.3)	1.93 (1.50 – 2.48)	1.62 (1.25 – 2.09)
Non-recorded	400 (2.6)	1,260 (2.1)	1.27 (1.13 – 1.42)	1.08 (0.95 – 1.21)

NA-NSAID: non-aspirin non-steroidal anti-inflammatory drugs; OR: odds ratio; CI: confidence interval

†*Model adjusted only for the matching variables (age, sex and year of index date).*
‡*Model adjusted for the matching variables, comorbidities and risk factors shown in manuscript Table 1 and use of following drugs: NA-NSAIDs, corticosteroids, non-aspirin antiplatelet drugs, analgesic opioids, oral anticoagulants, antidepressants, H2-receptor antagonists, proton-pump inhibitors, antidiarrheal drugs, drugs for constipation, statins, low-dose aspirin, SYSADOAs and calcium and vitamin D supplements.*

9. RESULTADOS

9.1. Resultados del estudio 1

Se detectaron 17.008 casos potenciales de cáncer colorrectal. De éstos, el 78,9% tenían un primer registro como diagnóstico (DI), con comentarios en texto libre asociados y, además, con información adicional en texto libre que reforzara el diagnóstico.

En el estudio de validación general se revisaron de forma manual 760 historias clínicas. El valor predictivo positivo (VPP) global fue del 87,3% (IC 95%: 83,3% - 90,4%). De los 8 grupos creados, en el que se obtuvo el mayor VPP fue en el que se tenía el primer registro como episodio diagnóstico (DI) con comentarios asociados en texto libre (VPP = 92,1%, IC 95%; 87,1% - 95,3%). El valor más bajo se obtuvo en el grupo con un primer registro como episodio de antecedente personal (NT) o condicionante (CN) sin un registro como episodio diagnóstico (DI) en otro momento posterior (VPP = 30,1%, IC 95%; 24,5% - 36,3%).

De las 100 historias clínicas seleccionadas aleatoriamente entre los sujetos que no fueron identificados como potencial caso por el algoritmo, todos fueron clasificados como no casos de cáncer colorrectal, alcanzándose un valor predictivo negativo (VPN) del 100% (IC 95%: 96,3% - 100%).

La información adicional que se encontró con más frecuencia fue la localización del cáncer (colon, recto y sigma), en el 94% de los casos validados, y el tratamiento quirúrgico (81,1%), ambos porcentajes ponderados por el peso de cada grupo.

La tasa de incidencia ajustada por la edad europea fue de 77,7 por 100.000 años-persona en hombres (IC 95%: 76,1 – 79,3) y de 38,1 por 100.000 años-persona en mujeres (IC 95%: 37,1 – 39,2), en el periodo 2001 – 2014. La tasa de incidencia estandarizada por la edad europea reportada por REDECAN, para el año 2012, fue de 65,6 por 100.000 años-persona (IC 95% no publicado) en hombres y 35,3 por 100.000 años-persona (IC 95% no publicado) en mujeres y, para el año 2015, se estimaron las siguientes tasas de incidencia; 77,8 por 100.000 años-persona en hombres (IC 95%: 69,8 – 86,8) y de 42,0 por 100.000 años-persona en mujeres (IC 95%: 38,1 – 46,7).

9.2. Resultados de la validación específica para los estudios 2 y 3

El valor predictivo positivo ponderado global, excluyendo los casos de cáncer colorrectal hereditario, fue del 85,5% (IC 95%: 84,9% – 86,1%).

En tres grupos de los ocho se obtuvo un valor predictivo positivo menor del 50% en la validación general. El número total de historias clínicas sin revisar en estos tres grupos fue de 1.274. Todas ellas fueron validadas de forma manual por los mismos revisores anteriores. Tras esta validación, el número de casos de cáncer colorrectal incluido descendió a 16.136, mientras que el VPP ponderado aumentó al 91%.

En 1.097 historias clínicas se encontraron patrones de palabras o cadenas de texto potencialmente identificativas de criterios de exclusión como caso válido (p. ej. palabras que identificasen un posible cáncer hereditario como; “genético”, “hereditario”, “Lynch” o fechas que identificasen un caso no incidente; una fecha anterior a 2001 en un primer registro diagnóstico, entre otros). Todas fueron validadas manualmente por los dos revisores anteriores. Tras ello, el número de casos de cáncer colorrectal descendió a

15.491 y el valor predictivo positivo ponderado aumentó al 95,7%. Estos 15.491 casos de cáncer colorrectal fueron los que finalmente se incluyeron en los estudios 2 y 3.

9.3. Resultados del estudio 2

Se incluyeron 15,491 casos de cáncer colorrectal y 60,000 controles seleccionados aleatoriamente y apareados con los casos por frecuencia de edad, sexo y año de la fecha índice.

Se observó una disminución del riesgo de cáncer colorrectal entre los usuarios actuales de AAS a dosis bajas (OR ajustado = 0,83; IC 95%: 0,78 – 0,89) que no se mantuvo en aquellos sujetos que interrumpieron el tratamiento (OR ajustado = 1,00; IC 95%: 0,88 – 1,13, en usuarios recientes y OR ajustado = 0,96; IC 95%: 0,88 – 1,06, en usuarios pasados). En los usuarios actuales se observó un efecto duración de forma que, con usos de más de un año se obtuvo un OR ajustado de 0,79 (IC 95%: 0,73 – 0,85), resultando estadísticamente significativa esta reducción de riesgo a partir de los primeros 180 días (OR ajustado = 0,79; IC 95%: 0,68 – 0,92). Se obtuvieron estimadores muy similares en los análisis por dosis, sexo, edad y uso para prevención primaria o secundaria cardiovascular.

Entre los usuarios actuales de clopidogrel en monoterapia también se observó una reducción del riesgo de cáncer colorrectal (OR ajustado = 0,80; IC 95%: 0,69 – 0,93), con un claro efecto duración entre los usuarios actuales; el OR ajustado para duraciones de más de un año de uso fue de 0,65 (IC 95%: 0,55 – 0,78), siendo en este momento cuando se observa una reducción de riesgo estadísticamente significativa. La reducción de riesgo asociada a clopidogrel en monoterapia desaparece cuando se interrumpe el tratamiento

(OR ajustado = 0,92; IC 95%: 0,63 – 1,34, en usuarios recientes y OR ajustado = 1,08; IC 95 %: 0,84 – 1,38, en usuarios pasados). No hubo grandes diferencias en los estimadores cuando se hizo el análisis estratificado por edad y sexo. Aunque en pacientes con edad ≤ 70 años el estimador puntual sugiere una protección similar al resto, no alcanza la significación estadística. Entre los usuarios actuales de terapia dual antiagregante con AAS a dosis bajas y clopidogrel no se observó una reducción del riesgo mayor que para cada uno de los fármacos por separado. La prevalencia de uso de triflusal fue baja en esta población lo que no permitió alcanzar la significación estadística en los análisis realizados, pero el estimador puntual sugiere una tendencia hacia la reducción de riesgo en usuarios actuales con duraciones mayores de un año y con dosis diarias mayores o iguales a 600 mg (la dosis diaria recomendada en la ficha técnica).

9.4. Resultados del estudio 3

Se incluyeron 15,491 casos de cáncer colorrectal y 60,000 controles seleccionados aleatoriamente y apareados con los casos por frecuencia de edad, sexo y año de la fecha índice (los mismos casos y controles que para el estudio 2).

Se observó una reducción de riesgo de cáncer colorrectal entre los usuarios actuales de AINE no-AAS (OR ajustado = 0,67; IC 95%: 0,63 – 0,71). Cuando se desglosó el uso actual de AINE según la selectividad COX-2 los estimadores puntuales fueron similares, con IC 95% claramente solapados. Se observó que la reducción de riesgo se mantuvo, aunque en menor medida, hasta un año tras la interrupción del tratamiento (OR ajustado = 0,84; IC 95%: 0.79 – 0.89, en usuarios recientes), pero no más allá (OR ajustado = 1,01; IC 95%: 0,97 – 1,06). Entre los usuarios actuales, se observó un efecto duración que

aumentó con el tiempo de forma lineal hasta más de 4 años de uso (OR ajustado = 0,43; IC 95%: 0,27 – 0,70) y que comenzó a ser estadísticamente significativo en los primeros 180 días de uso. Se observó una mayor reducción del riesgo de cáncer colorrectal con persistencias de tratamiento más altas (OR ajustado = 0,51; IC 95%: 0,38 – 0,69, en persistencia de tratamiento de más del 75%), pero aún observada con persistencias de tratamiento del 50% o menores (OR ajustado = 0,69; IC 95%: 0,60 – 0,81). Se crearon dos categorías de dosis: baja-moderada y alta, no observándose diferencias en el estimador puntual entre ambos. Estratificando por edad y sexo tampoco se observaron diferencias en los estimadores, ni tampoco en el análisis por principio activo.

El uso actual de SYSADOA se asoció a una reducción del riesgo de cáncer colorrectal durante el primer año de uso (OR ajustado = 0,69; IC 95%: 0,58 – 0,83), pero que no se observó con duraciones más prolongadas (OR ajustado = 0,92; IC 95%: 0,76 – 1,11). Cuando se eliminó del análisis a los usuarios actuales y previos de AINE, la reducción de riesgo asociada a SYSADOA desapareció.

El uso actual de metamizol se asoció con un aumento de riesgo de cáncer colorrectal con duraciones de uso de menos de un año y, especialmente, a dosis diarias altas (OR ajustado = 1,62; IC 95%: 1,25 – 2,09). Con duraciones de uso superiores a un año, el estimador puntual sugiere una tendencia hacia la protección, aunque no alcanzó la significación estadística (OR ajustado = 0,88; IC 95%: 0,71 – 1,08).

10. DISCUSIÓN

En estos tres trabajos se ha podido demostrar la idoneidad de la base de datos BIFAP como fuente de información para el estudio farmacoepidemiológico del cáncer colorrectal. Además, hemos confirmado en BIFAP un efecto quimioprotector frente al cáncer colorrectal, entre los usuarios de AAS a dosis bajas, similar al reportado en otras poblaciones y, aportamos evidencia que apoya la idea de que el uso de otros antiagregantes plaquetarios, como clopidogrel, comparten este efecto. El efecto quimioprotector de los AINE no-AAS también se ha confirmado en la población de BIFAP y gracias al gran tamaño del estudio, ha sido posible examinar dicho efecto en diferentes condiciones de uso. En cambio, nuestros resultados no apoyan el efecto quimioprotector postulado por otros investigadores para los SYSADOA, una vez que se excluye a los pacientes con un uso actual o previo de AINE, ni tampoco para metamizol.

10.1. Discusión del estudio 1

En este estudio se ha construido un algoritmo específico y adaptado a las características del registro de información en BIFAP, consiguiéndose un rendimiento bastante alto (VPP = 87,3% y VPN = 100%). Los resultados confirman que el diagnóstico del cáncer colorrectal está adecuadamente registrado en BIFAP, tanto por el VPP alto como por la comparabilidad externa de las tasas de incidencias obtenidas. El diagnóstico de cáncer colorrectal se encontró en mayor proporción registrado como episodio diagnóstico junto con comentarios e información adicional asociados en texto libre, de los que fue posible extraer información adicional del diagnóstico, lo que facilitó su validación. Esta situación, además, es la que tiene un mayor peso en el total de casos detectados y donde se alcanza la mayor proporción de verdaderos positivos. A pesar de tratarse de una base

de datos de atención primaria, la información adicional asociada al diagnóstico también se ha detectado en un porcentaje alto, especialmente en datos de localización específica del tumor y de tratamiento quirúrgico. En los casos en los que el diagnóstico se registra como primer episodio como condicionante o antecedente personal, el rendimiento del algoritmo es menor, sobre todo en ausencia de un registro de un diagnóstico posterior. Además, el registro de un evento como antecedente personal o condicionante, no permite asociar comentarios en texto libre, de forma que la posibilidad de confirmación diagnóstica es menor.

El algoritmo de búsqueda creado obtuvo una tasa baja de falsos positivos, lo que reduce el riesgo de sesgo de clasificación, algo especialmente importante cuando se quieren hacer estudios de estudios de casos y controles, donde es importante confirmar que los casos empleados realmente lo son. Por otra parte, es importante que la tasa de falsos negativos sea también muy baja. En este sentido, el algoritmo de búsqueda obtuvo un valor predictivo negativo del 100%, lo que permite tener plena confianza en la validez del control. Dados los buenos resultados tanto del algoritmo de búsqueda como de la estrategia de validación diseñada, se puede concluir que ambos pueden ser empleados para estudios futuros en los que el evento de interés sea el cáncer colorrectal en BIFAP, sin necesidad de llevar a cabo de nuevo un estudio de validación previo o quizás haciendo mínimos ajustes en cada caso concreto.

La tasa de incidencia de cáncer colorrectal estandarizada por edad (tomando como referencia a la población europea) obtenida en BIFAP es similar a la reportada por REDECAN para el año 2012 (6) y la estimada por la misma red para el año 2015 (57). Nuestras tasas de incidencia, sin embargo, se calcularon para el periodo 2001 – 2014, por

lo que, teniendo en cuenta que la incidencia de cáncer colorrectal ha ido en aumento a lo largo del periodo de estudio (6), es posible que la tasa de incidencia en BIFAP pueda estar ligeramente sobreestimada. Tal vez esto pueda atribuirse al hecho de que la población que visita al médico de atención primaria puede tener una mayor prevalencia de enfermedades y factores de riesgo que la población general. En todo caso, la diferencia es pequeña, por lo que la estimación sigue siendo razonablemente válida.

10.2. Discusión del estudio 2

Los resultados de este estudio confirman en población española (y mediterránea) una reducción de riesgo de cáncer colorrectal asociado al uso de AAS a dosis bajas, de una magnitud similar a la observada en estudios publicados anteriormente en otras poblaciones con diferentes estilos de vida y morbilidad cardiovascular (8). No existen apenas estudios realizados en población mediterránea. Únicamente hemos podido identificar uno publicado en Israel donde solo se estudian duraciones de uso prolongadas (46), de ahí la importancia de replicar, en primer lugar, en nuestra muestra el efecto quimioprotector de AAS a dosis bajas. Una vez confirmado esto, el objetivo fundamental del estudio fue evaluar el posible efecto quimioprotector de clopidogrel en monoterapia frente a cáncer colorrectal, utilizando el AAS a dosis bajas como control interno. El hallazgo más importante de nuestro estudio ha sido que el uso de clopidogrel en monoterapia se asocia con una reducción de riesgo de cáncer colorrectal muy similar a la observada para AAS a dosis bajas, indicando que el mecanismo por el que se produce esta quimioprotección podría estar mediado, en ambos casos, por sus respectivas acciones como antiagregantes plaquetarios. Esta afirmación resulta más consistente al tratarse de dos fármacos cuyos mecanismos de acción a través de los cuales ejercen su actividad

antiagregante son diferentes; el AAS a dosis bajas inhibiendo irreversiblemente la COX-1 plaquetar (29) y el clopidogrel bloqueando el receptor de $P2Y_{12}$ sobre el que actúa el ADP liberado por los gránulos densos de la plaqueta cuando se activa y que actúa amplificando la señal de dicha activación plaquetar (29). Dicho esto, no se puede descartar que el bloqueo del receptor $P2Y_{12}$ tenga una actividad antitumoral extraplaquetaria; así por ejemplo, se ha descrito que dicho receptor se expresa en células tumorales, lo cual podría explicar en parte el efecto observado con clopidogrel (59-61). Sin embargo, no observamos mayor reducción del riesgo al examinar el uso actual de la terapia dual antiagregante con AAS a dosis bajas y clopidogrel, debido, probablemente, a que la duración de uso recomendada de esta terapia suele ser corta (62).

En nuestro estudio no tuvimos suficiente población expuesta a otros antiagregantes plaquetarios, y solo pudimos evaluar, además de clopidogrel, el uso de triflusal. Aunque el mecanismo de acción de triflusal no está totalmente definido, se piensa que su acción antiagregante se produce de manera similar al del AAS a dosis bajas debido a la similitud estructural con ésta (63). Aunque no se llegó a alcanzar la significación estadística, observamos que con dosis de 600 – 900 mg diarios de triflusal, la dosis recomendada y con la que se realizaron los ensayos clínicos de prevención secundaria comparativos con AAS a dosis bajas (64), existía una tendencia hacia la protección, mientras que cuando se usaban dosis de 300 mg la reducción de riesgo de cáncer colorrectal no se observaba. Esto puede deberse, a nuestro parecer, a que, a dosis de 300 mg, triflusal tiene un efecto antiagregante plaquetario insuficiente.

Estos hallazgos, además de la importancia de sugerir la posibilidad de un nuevo fármaco (clopidogrel) como quimioprotector frente al cáncer colorrectal, es también relevante

porque apoya la hipótesis de que la quimioprotección del AAS a dosis bajas es explicada primariamente por su acción antiagregante plaquetaria, lo cual a su vez refuerza la idea de que las plaquetas tienen un papel destacado en el desarrollo del cáncer colorectal (27, 30).

Algunas limitaciones de este estudio deben ser mencionadas. En primer lugar, a pesar de haber realizado un estudio de validación exhaustivo, no se puede descartar la posibilidad de que exista un sesgo de clasificación del cáncer colorrectal, que, en todo caso, debería ser no diferencial respecto a la exposición dado que los revisores que realizaron la validación de los casos estuvieron "cegados" a los tratamientos. Si estuviera presente dicho error de clasificación no diferencial, es probable que tuviera como efecto una cierta dilución de la magnitud de la quimioprotección observada, tanto para el AAS a dosis bajas como para clopidogrel. Por otro lado, también existe la posibilidad de que los fármacos, en particular el AAS a dosis bajas, se adquieran sin prescripción médica en la farmacia comunitaria, aunque parece poco probable, ya que generalmente estos fármacos se utilizan junto a otros como antihipertensivos o estatinas y todos se encuentran financiados por el Sistema Nacional de Salud. En cualquier caso, de existir este error de clasificación es probable que fuera no diferencial (independiente del estatus caso-control), lo que habría resultado en una infraestimación de la asociación entre el fármaco de interés y el cáncer colorrectal, con lo que, de nuevo, el efecto quimioprotector real sería aún mayor. Por último, como en otros estudios observacionales, no se puede descartar la presencia de una confusión residual debida a potenciales factores de confusión no recogidos o insuficientemente medidos.

10.3. Discusión del estudio 3

En este estudio se ha observado que el uso de AINE (excluyendo AAS) reduce de forma significativa y relevante el riesgo de desarrollo de cáncer colorrectal. Este efecto quimioprotector, además, presenta un efecto duración muy destacado, siendo éste el factor más influyente. El efecto quimioprotector duración-dependiente sigue una tendencia lineal estadísticamente significativa que comienza en los primeros 180 días de uso y aumenta hasta duraciones de 4 años o más. Además, el efecto protector permanece, aunque en menor medida, hasta el primer año tras la interrupción del tratamiento.

El mecanismo de acción por el cual los AINE ejercen esta quimioprotección frente al cáncer colorrectal se piensa que está íntimamente relacionado con su capacidad de inhibir la COX-2. La selectividad sobre la inhibición de la COX-2, en cambio, no parece muy relevante dado que ni por subgrupo ni por principio activo, observamos mayores efectos con los fármacos más COX-2 selectivos. Tampoco se observa un gradiente con la dosis diaria de uso. Uno de los hallazgos más novedosos encontrados en el presente estudio, es que el efecto protector se mantiene con persistencias de tratamiento del 50% o menores, siendo coherente este resultado con el publicado en un estudio previo por Yang et al (65), en el que encontraron reducciones de riesgo de cáncer colorrectal con adherencias (*medication possesion ratios*) de entre un 10% y un 40%, con AINE selectivos de la COX-2 (65). Un hallazgo importante de nuestro estudio, nunca antes reportado, es que el uso concomitante con inhibidores de la bomba de protones no modifica el efecto quimioprotector de los AINE. Como el riesgo gastrointestinal y cardiovascular asociado al uso de AINE disminuye si se utilizan a dosis diarias bajas (66), con duraciones cortas y, en el caso del riesgo gastrointestinal, cuando se administran junto con inhibidores de

la bomba de protones (67), es previsible que en estas condiciones, si se mantiene el efecto quimioprotector y disminuyen los efectos adversos, la relación beneficio-riesgo de los AINE para quimioprevención sea más favorable, pero esta hipótesis debería ser comprobada en estudios longitudinales específicos.

En los usuarios de SYSADOA hemos observado que existe una reducción de riesgo de cáncer colorrectal a corto plazo, concretamente durante el primer año de uso. Sin embargo, al excluir a los usuarios previos de AINE durante el año anterior o los tres años previos, se diluye notablemente el efecto (o desaparece) y se pierde la significación estadística, algo que fue confirmado en un estudio previo (13). Esto sugiere que el efecto protector observado podría deberse a un efecto residual de un uso anterior de AINE.

Metamizol es un fármaco con una actividad antiinflamatoria débil del que aún no se ha dilucidado completamente su mecanismo de acción (55). Se ha descrito que podría tener cierta actividad inhibidora COX-2(55) y es por ello por lo que se le podría suponer un potencial efecto quimioprotector frente al cáncer colorrectal similar al observado en los AINE. Sin embargo, observamos que existe un aumento de riesgo de cáncer colorrectal a corto plazo y especialmente, a dosis diarias altas, que probablemente es explicado por una posible confusión por indicación, ya que metamizol suele emplearse para el tratamiento del dolor visceral, síntoma que podría ser debido a un cáncer colorrectal incipiente aún sin diagnosticar. Por otro lado, se observó una tendencia hacia la protección con el uso a largo plazo, pero sin alcanzar la significación estadística.

Algunas limitaciones deben ser consideradas en este estudio. Al igual que en el estudio 2, existe la posibilidad de que haya sucedido un sesgo de clasificación, tanto del evento

como de la exposición, ambos probablemente no diferenciales, lo que, de estar presentes, estarían diluyendo el efecto principal observado.

Por último, es importante destacar la gran potencia que aporta el uso de este tipo de grandes bases de datos como BIFAP, permitiendo la realización de análisis con una precisión que, de otra manera, no serían posibles. Recientemente se ha publicado una revisión sistemática y metanálisis de 23 estudios publicados hasta abril de 2018, sobre el uso de AINE no-AAS y el riesgo de cáncer colorrectal en sujetos de 40 años o más (48). Como fortaleza de este estudio, los autores destacaban el haber podido agrupar a más de 1 millón de sujetos en estudio y haber incluido aproximadamente 13,000 casos de cáncer colorrectal (48). Nuestro estudio incluyó una cohorte de estudio de más de 5 millones de sujetos y la inclusión de 15.491 casos de cáncer colorrectal, consiguiendo una potencia estadística superior a la del metanálisis, lo que nos permitió, además, analizar el efecto en diferentes subgrupos y condiciones de uso, algo que rara vez es posible en un metanálisis que agrega resultados de diferentes estudios. Sólo resta decir que nuestro estudio es el más grande publicado hasta la fecha.

11. CONCLUSIONES

Conclusiones objetivo específico 1. *Construir un algoritmo general de búsqueda de casos de cáncer colorrectal en BIFAP y describir las características del registro de este diagnóstico en la base de datos.*

1) Se construyó un algoritmo de búsqueda general adaptado a las características del registro de cáncer colorrectal en BIFAP, con un rendimiento alto.
2) Aparte del diagnóstico, en un porcentaje alto, se ha encontrado información asociada al mismo en texto libre e información adicional que sirven para mejorar la posibilidad de confirmación del diagnóstico principal.
3) La información adicional registrada más frecuentemente es la localización del tumor y el tratamiento quirúrgico.

Conclusiones objetivo específico 2. *Implementar una estrategia de validación general y estimar los porcentajes de casos válidos y no válidos de cáncer colorrectal, así como su valor predictivo positivo y el valor predictivo negativo*.

1) La estrategia de validación diseñada junto con el buen rendimiento del algoritmo de búsqueda permitieron validar un número alto de potenciales casos de cáncer colorrectal con un consumo de recursos moderado.
2) El rendimiento general de la estrategia de validación y del algoritmo fue alto, con un VPP = 85,5% y un VPN del 100%.
3) El porcentaje de casos válidos y el valor predictivo positivo fueron mayores cuando el evento se registró como primer episodio diagnóstico y cuando, además, se encontró información adicional en texto libre.

4) Los valores más bajos de confirmación del diagnóstico de cáncer colorrectal se dieron cuando éste se registró en primer lugar como antecedente personal o condicionante y sin registro de un episodio diagnóstico posterior.

5) Las búsquedas en texto libre en ausencia de cualquier diagnóstico compatible con cáncer colorrectal también presentaron porcentajes muy altos de falsos positivos, de forma que no se considera una estrategia de búsqueda válida en este momento.

Conclusiones objetivo específico 3. *Implementar una estrategia de validación adicional que permita mejorar el algoritmo de búsqueda y aumentar el valor predictivo positivo, en el contexto de los estudios de casos y controles.*

1) La estrategia adicional de revisión de casos en los grupos con bajo valor predictivo positivo (<50%) y la mejora del algoritmo general incluyendo los patrones de texto que más frecuentemente caracterizaron a los falsos positivos validados, mejoró el rendimiento general, aumentando el VPP hasta el 95,7%.

2) Esta estrategia de validación adicional, por el contrario, resulta menos generalizable ya que fue específicamente adaptada a las características de la población y del diseño de nuestros estudios (casos incidentes y no hereditarios).

Conclusiones objetivo específico 4. *Comparar la tasa de incidencia cruda y estandarizada (tomando la población europea como estándar) de cáncer colorrectal obtenida en BIFAP con la publicada por la Red Española de Registros de Cáncer (REDECAN) para los años 2012 y 2015.*

1) Las tasas de incidencia estandarizadas por la edad europea por 100.000 años-persona en el periodo 2001- 2014 obtenidas en BIFAP, tanto en hombres como en mujeres y en ambos sexos, son similares a la reportadas por la Red Española de Registros de Cáncer para el año 2012 y a la estimada para el año 2015.

Conclusiones objetivo específico 5. *Confirmar el efecto quimioprotector del AAS a dosis bajas frente a cáncer colorrectal en BIFAP y caracterizar este efecto.*

1) El efecto quimioprotector de AAS a dosis bajas frente al cáncer colorrectal observado en la población de BIFAP, en torno a un 20%, es similar al observado en otras poblaciones con diferentes hábitos de vida y morbilidad cardiovascular.
2) El efecto quimioprotector de AAS a dosis bajas frente al cáncer colorrectal comienza a observarse con duraciones de uso superiores a 180 días, siendo, además, duración-dependiente pero no dosis-dependiente (dentro del rango 75-325 mg).
3) El efecto quimioprotector de AAS a dosis bajas está presente mientras permanece la exposición al fármaco, pero desaparece cuando se interrumpe el tratamiento.
4) El efecto quimioprotector de AAS a dosis bajas se observa tanto en hombres como en mujeres y tanto menores como en mayores de 70 años.

5) Los pacientes tratados con AAS a dosis bajas para la prevención de eventos cardiovasculares podrían recibir el beneficio adicional de la protección frente a cáncer colorrectal.

Conclusiones objetivo específico 6. *Evaluar si clopidogrel en monoterapia comparte un efecto quimioprotector frente al cáncer colorrectal similar al reportado para el AAS a dosis bajas y caracterizar su efecto, en la población de BIFAP.*

1) El uso de clopidogrel en monoterapia se asocia con una reducción del riesgo del cáncer colorrectal muy similar en magnitud (20-30%) al observado para AAS a dosis bajas.

2) El efecto quimioprotector observado para clopidogrel en monoterapia es duración dependiente, y desaparece al interrumpir el tratamiento, también de forma similar a lo observado con el AAS a dosis bajas.

3) La exposición a terapia dual antiagregante con AAS a dosis bajas y clopidogrel muestra resultados de quimioprotección similares a los observados para cada fármaco por separado, probablemente debido a que su uso se limita a periodos cortos.

4) El mecanismo biológico que podría explicar el efecto quimioprotector frente a cáncer colorrectal de clopidogrel es su acción antiagregante plaquetaria, pero a través de un mecanismo de acción diferente al de AAS a dosis bajas, reforzando la hipótesis del importante papel de las plaquetas en el desarrollo del cáncer colorrectal.

5) En el análisis estratificado por edad y sexo, no se observan diferencias en los estimadores puntuales, aunque en sujetos con 70 años o menores, este efecto no alcanza la significación estadística.

6) Los pacientes que reciban tratamiento con clopidogrel en monoterapia para la prevención secundaria cardiovascular, podrían recibir el beneficio adicional de la protección frente a cáncer colorrectal.

Conclusiones objetivo específico 7. *Confirmar el efecto quimioprotector de los AINE (excluido el AAS) en BIFAP y caracterizar este efecto en diferentes condiciones de uso (dosis diaria, duración y persistencia del tratamiento) y su posible interacción con otros factores como edad y sexo y uso concomitante con los inhibidores de la bomba de protones (IBP).*

1) El uso de AINE no-AAS presenta una reducción de riesgo frente a cáncer colorrectal de entre un 40% y un 60%, dependiendo de la duración de uso. Este efecto quimioprotector, además, sigue presente hasta un año después tras la interrupción del tratamiento.

2) El efecto quimioprotector observado en AINE no-AAS no parece dosis-dependiente y la selectividad COX-2 no es una característica determinante.

3) El efecto quimioprotector observado en los AINE no-AAS se mantiene con una persistencia de tratamiento igual o inferior al 50%.

4) El efecto quimioprotector observado en AINE no-AAS no es modificado por el uso concomitante de inhibidores de la bomba de protones.

5) El efecto quimioprotector es similar en hombres y en mujeres y tampoco se modifica con la edad.

Conclusiones objetivo específico 8. *Evaluar el efecto quimioprotector de los AINE por principio activo y comprobar si existen diferencias entre ellos o si, por el contrario, se trata de un efecto de clase.*

1) El efecto quimioprotector de los AINE en el análisis por principio activo muestra reducciones de riesgo muy similares entre ellos, con gran solapamiento de sus intervalos de confianza.

2) No se observan diferencias en el efecto quimioprotector, por principio activo, en relación con la selectividad COX-2, lo que indica que el factor determinante en su acción no es la selectividad sino la efectividad para inhibir dicha enzima.

3) Se puede concluir que el efecto quimioprotector asociado al uso de AINE no-AAS es un efecto de clase.

Conclusiones objetivo específico 9. *Evaluar el efecto quimioprotector frente al cáncer colorrectal de los SYSADOA y de metamizol, en BIFAP.*

1) El uso de SYSADOA se asocia a una reducción de cáncer colorrectal durante el primer año, pero no con duraciones más prolongadas.

2) Dicha reducción de riesgo asociado al uso de SYSADOA desaparece cuando se excluyen del análisis a los pacientes que habían recibido un tratamiento previo con AINE, por lo que se concluye que la reducción de riesgo observada podría deberse a un efecto residual de ese tratamiento anterior con AINE.

3) El uso de metamizol se asocia con un aumento de riesgo de cáncer colorrectal a corto plazo y a dosis altas, probablemente debido a una confusión por indicación.

4) Aunque no es estadísticamente significativo, no puede descartarse un efecto quimioprotector a largo plazo en usuarios de metamizol.

12. REFERENCIAS

1. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-1502.

2. World Health Organization. International agency for research on cancer. http://gco.iarc.fr/today/home. Acceso el 17 de mayo de 2019.

3. Fitzmaurice C, Allen C, Barber RM, et al. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3(4):524-548.

4. Binefa G, Rodríguez-Moranta F, Teule A, et al. Colorectal cancer: from prevention to personalized medicine. World J Gastroenterol. 2014;20(22):6786-808.

5. Center MM, Jemal A, Smith RA, et al. Worldwide variations in colorectal cancer. CA Cancer J Clin. 2009;59(6):366-78.

6. López-Abente G, Núñez O, Pérez-Gómez B, et al. La situación del cáncer en España: Informe 2015. Instituto de Salud Carlos III. Madrid, 2015.

7. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. Gastroenterology. 2010;138(6):2029-2043

8. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(12):836-45

9. Rostom A, Dubé C, Lewin G, et al; U.S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):376-89

10. Kubatka P, Kruzliak P, Rotrekl V, et al. Statins in oncological research: from experimental studies to clinical practice. Crit Rev Oncol Hematol. 2014;92(3):296-311.

11. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333.

12. Singh S, Singh AG, Murad MH, et al. Bisphosphonates are associated with reduced risk of colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(3):232-9.e1.

13. Ibáñez-Sanz G, Díez-Villanueva A, Vilorio-Marqués L, et al. Possible role of chondroitin sulphate and glucosamine for primary prevention of colorectal cancer. Results from the MCC-Spain study. Sci Rep. 2018;8(1):2040.

14. Singh S, Singh H, Singh PP, et al. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2013;22(12):2258-68.

15. Wactawski-Wende J, Kotchen JM, Anderson GL, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006;354(7):684-96.

16. Gurpinar E, Grizzle WE, Piazza GA. COX-Independent Mechanisms of Cancer Chemoprevention by Anti-Inflammatory Drugs. Front Oncol. 2013;3:181.

17. Patrignani P. Nonsteroidal anti-inflammatory drugs, COX-2 and colorectal cancer. Toxicol Lett. 2000;112-113:493-8.

18. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 2010;29(6):781-8.

19. Wang D, DuBois RN. Pro-inflammatory prostaglandins and progression of colorectal cancer. Cancer Lett. 2008;267(2):197-203.

20. Bertagnolli MM, Eagle CJ, Zauber AG, et al; APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006;355(9):873-84.

21. Baron JA, Sandler RS, Bresalier RS, et al; APPROVe Trial Investigators. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology. 2006;131(6):1674-82.

22. Arber N, Eagle CJ, Spicak J, et al; PreSAP Trial Investigators. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med. 2006;355(9):885-95.

23. Baron JA, Sandler RS, Bresalier RS, et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet. 2008;372(9651):1756-64.

24. Bresalier RS, Sandler RS, Quan H, et al; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352(11):1092-102.

25. Solomon SD, McMurray JJ, Pfeffer MA, et al; Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352(11):1071-80.

26. Sun SX, Lee KY, Bertram CT, et al. Withdrawal of COX-2 selective inhibitors rofecoxib and valdecoxib: impact on NSAID and gastroprotective drug prescribing and utilization. Curr Med Res Opin. 2007;23(8):1859-66.

27. Guillem-Llobat P, Dovizio M, Alberti S, et al. Platelets, cyclooxygenases, and colon cancer. Semin Oncol. 2014;41(3):385-96.

28. Patrignani P, Patrono C. Aspirin and Cancer. J Am Coll Cardiol. 2016;68(9):967-76.

29. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007;357(24):2482-94.

30. Xu XR, Yousef GM, Ni H. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents. Blood. 2018;131(16):1777-1789.

31. Patrono C, Baigent C, Hirsh J, et al. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):199S-233S

32. Dovizio M, Alberti S, Guillem-Llobat P, et al. Role of platelets in inflammation and cancer: novel therapeutic strategies. Basic Clin Pharmacol Toxicol. 2014;114(1):118-27.

33. Strom BL, Kimmel SE, Hennessy S. Pharmacoepidemiology. 5th edition. UK. Wiley-Blackwell. 2012. Part I, introduction; p. 3-4

34. Real Decreto 577/2013, de 26 de julio, por el que se regula la farmacovigilancia de medicamentos de uso humano.

35. Jick H, Madsen S, Nudelman PM, et al. Postmarketing follow-up at Group Health Cooperative of Puget Sound. Pharmacotherapy. 1984;4(2):99-100.

36. Lo Re V 3rd, Carbonari DM, Forde KA, et al. Validity of diagnostic codes and laboratory tests of liver dysfunction to identify acute liver failure events. Pharmacoepidemiol Drug Saf. 2015;24(7):676-83.

37. Gerstman BB, Lundin FE, Stadel BV, et al. A method of pharmacoepidemiologic analysis that uses computerized Medicaid. J Clin Epidemiol. 1990;43(12):1387-93

38. García Rodríguez LA, Walker AM, Pérez Gutthann S. Nonsteroidal antiinflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. Epidemiology. 1992;3(4):337-42.

39. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ. 1991;302(6779):766-8.

40. Salvador Rosa A, Moreno Pérez JC, Sonego D, et al. The BIFAP project: database for pharmaco-epidemiological research in primary care. Aten Primaria. 2002;30(10):655-61.

41. Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP). http://www.bifap.org. Acceso 21 de mayo de 2019.

42. Abbing-Karahagopian V, Kurz X, de Vries F, et al. Bridging differences in outcomes of pharmacoepidemiological studies: design and first results of the PROTECT project. Curr Clin Pharmacol. 2014; 9:130-8.

43. Afzal Z, Schuemie MJ, van Blijderveen JC, et al. Improving sensitivity of machine learning methods for automated case identification from free-text electronic medical records. BMC Med Inform Decis Mak. 2013;13:30.

44. Afzal Z, Engelkes M, Verhamme KM, et al. Automatic generation of case-detection algorithms to identify children with asthma from large electronic health record databases. Pharmacoepidemiol Drug Saf. 2013;22(8):826-33.

45. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer Res. 1988;48(15):4399-404.

46. Leader A, Zelikson-Saporta R, Pereg D, et al. The effect of combined aspirin and clopidogrel treatment on cancer incidence. Am J Med. 2017;130(7):826-832

47. Vaughan LE, Prizment A, Blair CK, et al. Aspirin use and the incidence of breast, colon, ovarian, and pancreatic cancers in elderly women in the Iowa Women's Health Study. Cancer Causes Control. 2016;27(11):1395-1402.

48. Tomić T, Domínguez-López S, Barrios-Rodríguez R. Non-aspirin non-steroidal anti-inflammatory drugs in prevention of colorectal cancer in people aged 40 or older: A systematic review and meta-analysis. Cancer Epidemiol. 2019;58:52-62.

49. Informe uso de antiulcerosos. AEMPS.https://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/antiulcerosos.pdf. Acceso el 20 de mayo de 2019.

50. Juarranz M, Calle-Purón ME, González-Navarro A, et al. Physical exercise, use of Plantago ovata and aspirin, and reduced risk of colon cancer. Eur J Cancer Prev. 2002;11(5):465-72.

51. Kantor ED, Zhang X, Wu K, et al. Use of glucosamine and chondroitin supplements in relation to risk of colorectal cancer: Results from the Nurses' Health Study and Health Professionals follow-up study. Int J Cancer. 2016;139(9):1949-57.

52. Kantor ED, Lampe JW, Peters U, et al. Use of glucosamine and chondroitin supplements and risk of colorectal cancer. Cancer Causes Control. 2013;24(6):1137-46.

53. Kantor ED, Newton CC, Giovannucci EL, et al. Glucosamine use and risk of colorectal cancer: results from the Cancer Prevention Study II Nutrition Cohort. Cancer Causes Control. 2018;29(3):389-397.

54. Satia JA, Littman A, Slatore CG, et al. Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. Cancer Epidemiol Biomarkers Prev. 2009;18(5):1419-28.

55. Hinz B, Cheremina O, Bachmakov J, et al. Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. FASEB J. 2007:2343-51

56. Waterhouse, J, Muir, C.S, Correa, P, et al. 1976. Cancer Incidence in Five Continents Vol. III, IARC Scientific Publications. IARC, Lyon.

57. Galceran J, Ameijide A, Carulla M, et al; for the REDECAN Working Group. Cancer incidence in Spain, 2015. Clin Transl Oncol. 2017;19:799-825.

58. Rothman K, Greenland S, Lash TS. Case-control studies. In: Rothman K, Greenland S, Lash TS, eds, 3rd edition, Wolter Kluwer/Lippincott, William & Wilkins, 2008, Philadelphia, 2008; pp: 111-127.

59. Ballerini P, Dovizio M, Bruno A, et al. P2Y(12) Receptors in Tumorigenesis and Metastasis. Front Pharmacol. 2018;9:66.

60. Elaskalani O, Falasca M, Moran N, et al. The Role of Platelet-Derived ADP and ATP in Promoting Pancreatic Cancer Cell Survival and Gemcitabine Resistance. Cancers (Basel). 2017;9(10).

61. Wei Q, Costanzi S, Liu QZ, et al. Activation of the P2Y1 receptor induces apoptosis and inhibits proliferation of prostate cancer cells. Biochem Pharmacol. 2011;82(4):418-25.

62. Valgimigli M, Bueno H, Byrne RA, et al; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213-260.

63. de la Cruz JP, Pavia J, Bellido I, et al. Platelet antiaggregatory effect of triflusal in human whole blood. Methods Find Exp Clin Pharmacol. 1988;10(4):273-7.

64. Cruz-Fernández JM, López-Bescós L, García-Dorado D, et al. Randomized comparative trial of triflusal and aspirin following acute myocardial infarction. Eur Heart J. 2000;21(6):457-65.

65. Yang YH, Yang YH, Cheng CL, et al. The role of chemoprevention by selective cyclooxygenase-2 inhibitors in colorectal cancer patients – a population-based study. BMC Cancer. 2012;12:582

66. Matthews ML. The role of dose reduction with NSAID use. Am J Manag Care. 2013;19(14 Suppl):s273-7

67. Mo C, Sun G, Lu ML, et al. Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries. World J Gastroenterol. 2015;21:5382-5392.