TESIS DOCTORAL

“Precisión diagnóstica del test inmunológico cuantitativo para la detección de sangre oculta en heces y su utilidad en la detección del cáncer colorrectal en el paciente con síntomas digestivos”

Noel Pin Vieito

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EIDO
Escola Internacional
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Dirigida por el doctor:

Joaquín Cubiella Fernández

2022

El principito y el aviador (alamy)

“Cuando el misterio es demasiado grande, es imposible desobedecer”

El aviador,

«El Principito» (Capítulo 2)

Antoine de Saint-Exupèry (1943)

Universidade Vigo

Escola Internacional de Doutoramento

Joaquín Cubiella Fernández

FAI CONSTAR que o presente traballo, titulado “Precisión diagnóstica del test inmunológico cuantitativo para la detección de sangre oculta en heces y su utilidad en la detección del cáncer colorrectal en el paciente con síntomas digestivos”, que presenta Noel Pin Vieito para a obtención do título de Doutor, foi elaborado baixo a súa dirección no programa de doutoramento en Metodoloxía e Aplicacións en Ciencias da Vida.

Ourense, 4 de Xaneiro de 2022.

O Director da tese de doutoramento

Dr. Joaquín Cubiella Fernández

Agradecimientos

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no es fácil encontrar una persona que combine un criterio sólido con capacidad de escucha activa. Gracias por tu enorme capacidad de trabajo y pronta respuesta útil, y especialmente por intentar enseñarme a no perder el foco entre tantos rompecabezas con los que la medicina nos desafía cada día. Gracias también al resto de coautores de los diferentes trabajos, a mi tutor Emilio Gil, al coordinador del programa de doctorado Juanjo Pasantes y a nuestra secretaria Mary Riádigos. Sin su trabajo y aclaraciones, imprescindibles a lo largo de diferentes puntos en este proceso, no hubiera podido llevar a término esta tesis doctoral.

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servicio de oncología pediátrica del hospital universitario de St Jude y participar con él en mi primera publicación científica.

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RESUMEN

El National Institute for Health and Care Excellence (NICE) ha recomendado el uso en atención primaria de los test para la detección de sangre oculta en heces que utilizan el método inmunológico cuantitativo (SOH-i) como ayuda para valorar el origen de síntomas digestivos de nueva aparición, cuyas características no los hagan tributarios de derivación preferente a consulta especializada (p.ej. presencia de sangrado o masa rectal). Para ello debería determinarse la concentración de hemoglobina (Hb) en una única muestra fecal utilizando el punto de corte de 10 microgramos de hemoglobina por gramo de heces (µg Hb / g heces).

Esta recomendación NICE, fundamentada en la elevada precisión de SOH-i para detectar cáncer colorrectal (CCR), se dirige específicamente a pacientes con síntomas de bajo riesgo en atención primaria. Sin embargo, la mayor parte de estudios utilizados para avalar su uso han sido realizados en el entorno de atención especializada, en poblaciones con un porcentaje significativo de pacientes con síntomas de alto riesgo. Esta discordancia en el espectro clínico de los pacientes puede implicar también un comportamiento de SOH-i distinto al esperado. Además, se ha descrito que su precisión está influida por características como el sexo o la edad, mientras que NICE recomienda el uso de un único punto de corte independientemente de las características demográficas de cada paciente.

Por otra parte, a pesar de que la existencia de una concentración de Hb fecal por encima del umbral de 10 µg Hb/g de heces se asocia a una elevada probabilidad de existencia en el colon de neoplasia avanzada, en numerosas ocasiones no se identifican lesiones tras la realización de una colonoscopia de calidad indicada por un resultado positivo de SOH-i, sin que exista información sobre el pronóstico de estos pacientes.

El objetivo de este trabajo es conocer la precisión de SOH-i para detectar CCR en aquellos pacientes que consultan por la aparición de síntomas digestivos en el

entorno específico de atención primaria, y obtener información acerca del pronóstico de aquellos pacientes con un falso positivo de esta prueba.

Para ello inicialmente realizamos una revisión de la literatura con metaanálisis de aquellos trabajos que han estudiado la precisión de SOH-i en pacientes con síntomas digestivos independientemente de su lugar de reclutamiento, apreciando que SOH-i mantiene una sensibilidad elevada y una especificidad moderada para la detección de CCR en pacientes con síntomas, al igual que sucede en el entorno de cribado.

Posteriormente, comprobamos que la precisión estimada en este metaanálisis es equiparable a la calculada a partir de datos de práctica real en centros de atención primaria de nuestro entorno, obtenidos con carácter retrospectivo a partir de las bases de datos del laboratorio de análisis clínicos y de documentación clínica de las provincias de Ourense y San Sebastián. Nuestro análisis confirma la elevada precisión diagnóstica de SOH-i para la detección de CCR en atención primaria independientemente del centro, edad, sexo o indicación. Además, en comparación con el uso del umbral recomendado por NICE, si utilizamos el umbral de 20 μg Hb/g de heces, menos de un paciente con CCR adicional dejaría de ser identificado por cada 1000 pacientes evaluados, mientras que usando el umbral de 10 μg Hb / g heces sería preciso realizar aproximadamente 1.3 veces más colonoscopias para identificar un paciente con CCR en comparación con el uso del umbral menor para cualquier subgrupo evaluado.

Paralelamente, hemos estimado el pronóstico de aquellos pacientes sintomáticos con una colonoscopia de calidad que descarta CCR sin apreciar que el resultado de SOH-i suponga un factor de riesgo significativo para ser diagnosticado o fallecer por una neoplasia localizada en el tracto gastrointestinal proximal al colon. Sin embargo, los pacientes con un resultado de SOH-i $\geq$ 20 μg/g de heces mostraron un mayor riesgo de desarrollar CCR de intervalo.

También evaluamos en estos pacientes la incidencia y la mortalidad por cáncer de cualquier origen asociada a la presencia de niveles séricos elevados de antígeno carcinoembrionario (CEA), apreciando que un nivel sérico de CEA > 3 ng/dL supone un aumento moderado del riesgo de detección de cáncer durante el primer año, especialmente si existe anemia en ausencia de sangrado rectal.

Con el fin de discutir nuestros hallazgos con la literatura, actualizamos la información existente sobre la precisión de SOH-i para detectar CCR en pacientes con síntomas digestivos mediante una nueva revisión sistemática con metaanálisis de aquellos trabajos desarrollados específicamente en el entorno de atención primaria. Los resultados obtenidos en este metaanálisis también confirman que el test de SOH-i es la prueba de elección para evaluar pacientes que consultan en su centro de salud por la aparición de síntomas digestivos compatibles con un cáncer colorrectal.

Abreviaturas y acrónimos

AUC *- Área bajo la curva*

CEA *- Antígeno carcinoembrionario*

CCR *- Cáncer colorrectal*

CMBD *- Base de datos de documentación clínica*

DOR *- Razón de probabilidades de diagnóstico*

Hb *- Hemoglobina*

Hb-f *- Hemoglobina fecal*

HSROC *– Hierarchical Summary Receiver Operating Characteristic*

HR *– Hazard ratio*

LCS *- Lesión de colon significativa*

NICE *- National Institute for Health and Care Excellence*

NNS *– Número de colonoscopias necesarias para encontrar un cáncer de colon*

NNT *- Número necesario a tratar*

OMS *- Organización Mundial de la Salud*

OR *– Odds ratio*

Ou *- Ourense*

QUADAS *- Quality Assessment of Diagnostic Accuracy Studies*

RR *- Riesgo relativo*

SOH *- Test de sangre oculta en heces*

SOH-i *- Test de sangre oculta en heces inmunológico*

sROC *– Summary Receiver Operating Characteristic Curve*

SS *- San Sebastián*

TTGI *- Tumor del tracto gastrointestinal*

Índice

INTRODUCCIÓN

Epidemiología del cáncer colorrectal

El cáncer colorrectal (CCR) es una de las causas más frecuentes de muerte en los países occidentales. En España se ha calculado una tasa de incidencia y mortalidad estandarizada por edad a la población mundial de 35.8 y 11.5 por cada 100,000 habitantes respectivamente (**Figura 1**). La información epidemiológica específica de cada país se encuentra disponible a través de la base de datos GLOBOCAN de la *Organización Mundial de la Salud* (OMS) [1].

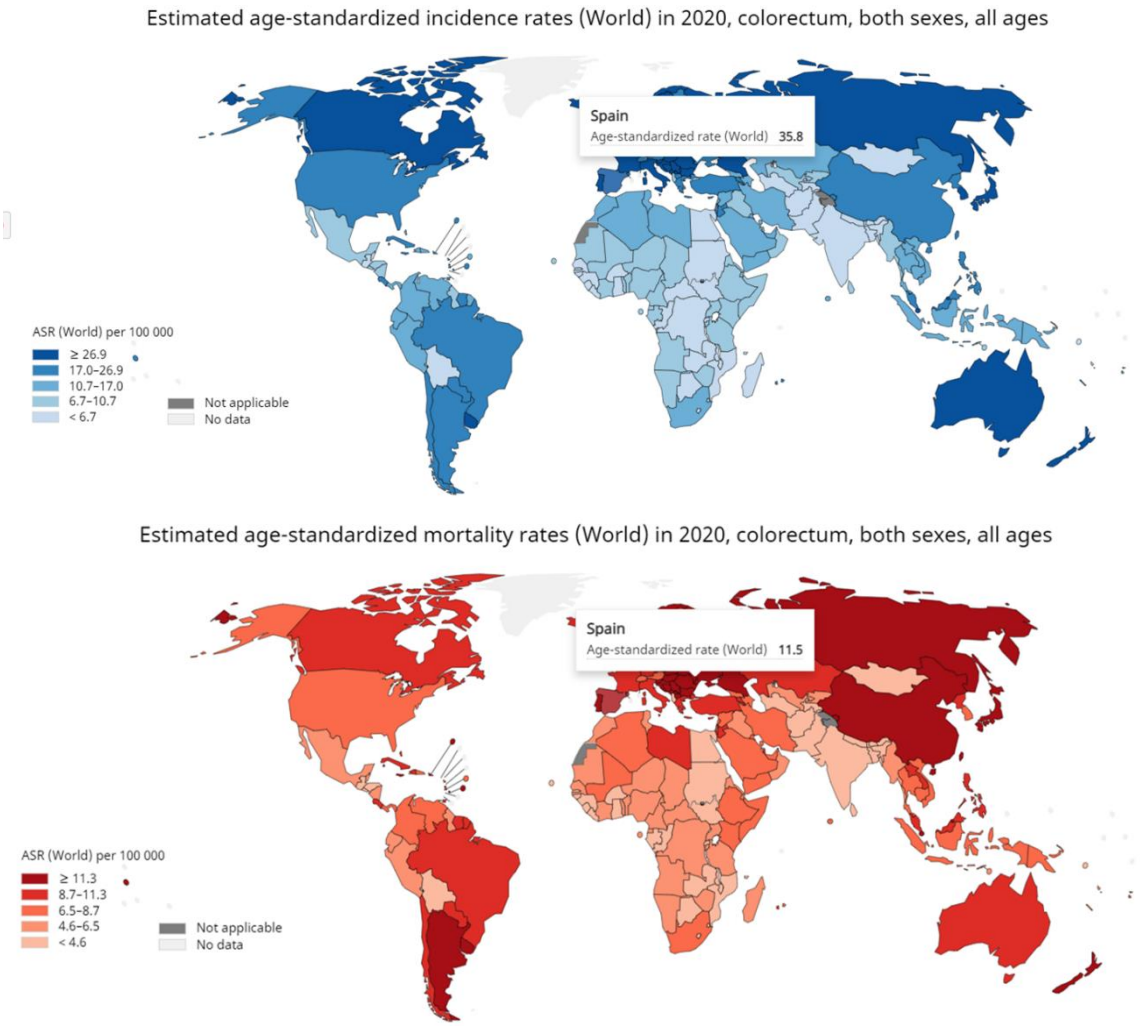

Figura 1. Tasas de incidencia y mortalidad de CCR estandarizadas por edad para ambos sexos en España. Fuente: Globocan 2020

Además, en nuestro entorno existe información adicional disponible a través de la *Red Española de Registros de Cáncer* (REDECAN). Esta base de datos se desarrolló en el año 2010 con el fin de conocer con precisión datos sobre la incidencia, supervivencia y prevalencia de los diversos tipos de cáncer en España. A partir de esta fuente, se estimó que en el año 2021 se diagnosticarían un total de 43,581 nuevos casos (29,372 de colon y 14,209 de recto) (**Figura 2**), de los cuales más del 40% fallecerían debido a esta enfermedad [2].

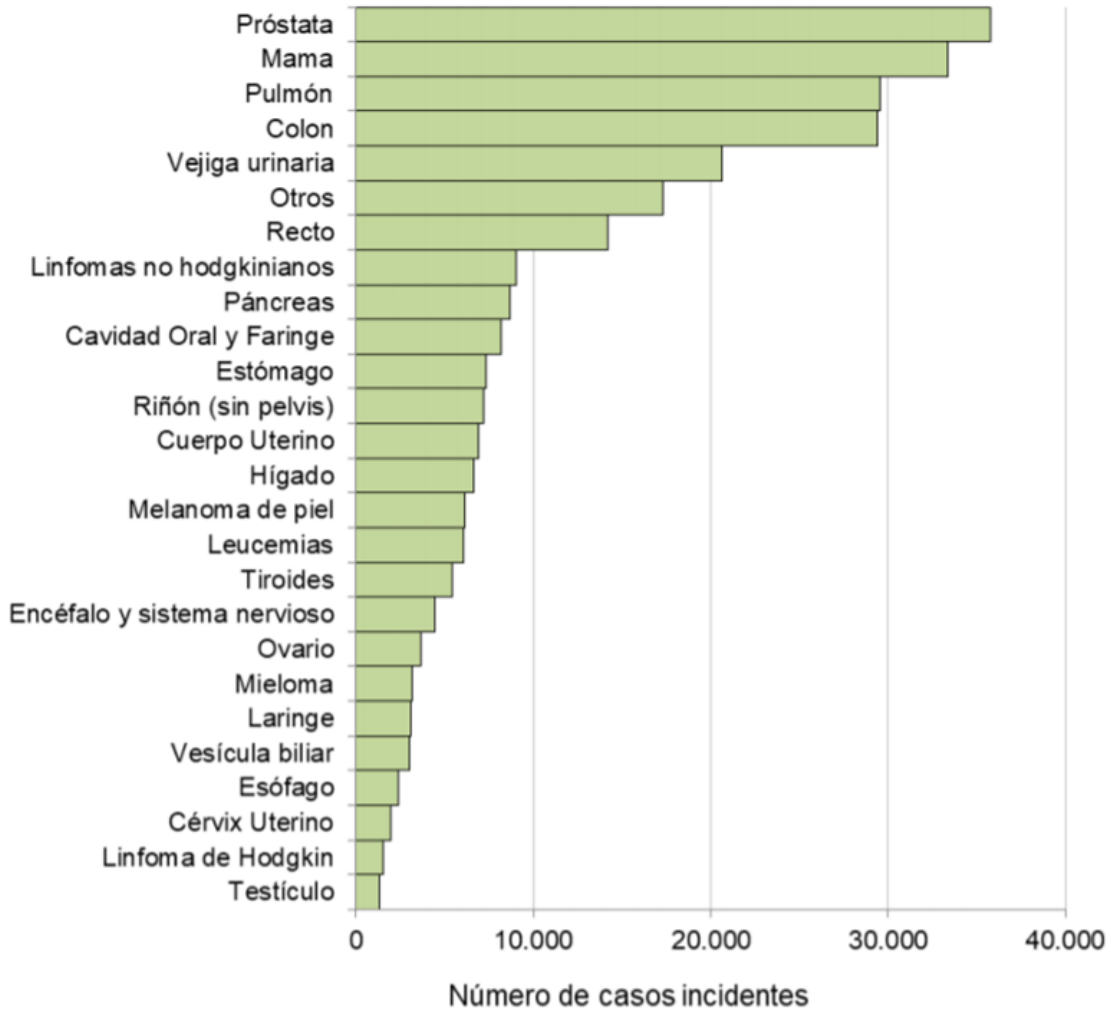

Figura 2. Número estimado de casos incidentes de cáncer en España por tipo tumoral, 2021. Ambos sexos. Fuente: Red Española de Registros de Cáncer

Aunque la mortalidad por CCR ha disminuido de forma progresiva desde la década de los 90 en un porcentaje variable entre el 1.6 - 2.0% al año (**Figura 3**) [3], esta enfermedad todavía constituye la segunda causa más común de mortalidad por cáncer en España por detrás del cáncer de pulmón en el caso de los hombres, y la tercera por detrás del cáncer de mama y de pulmón en el caso de las mujeres.

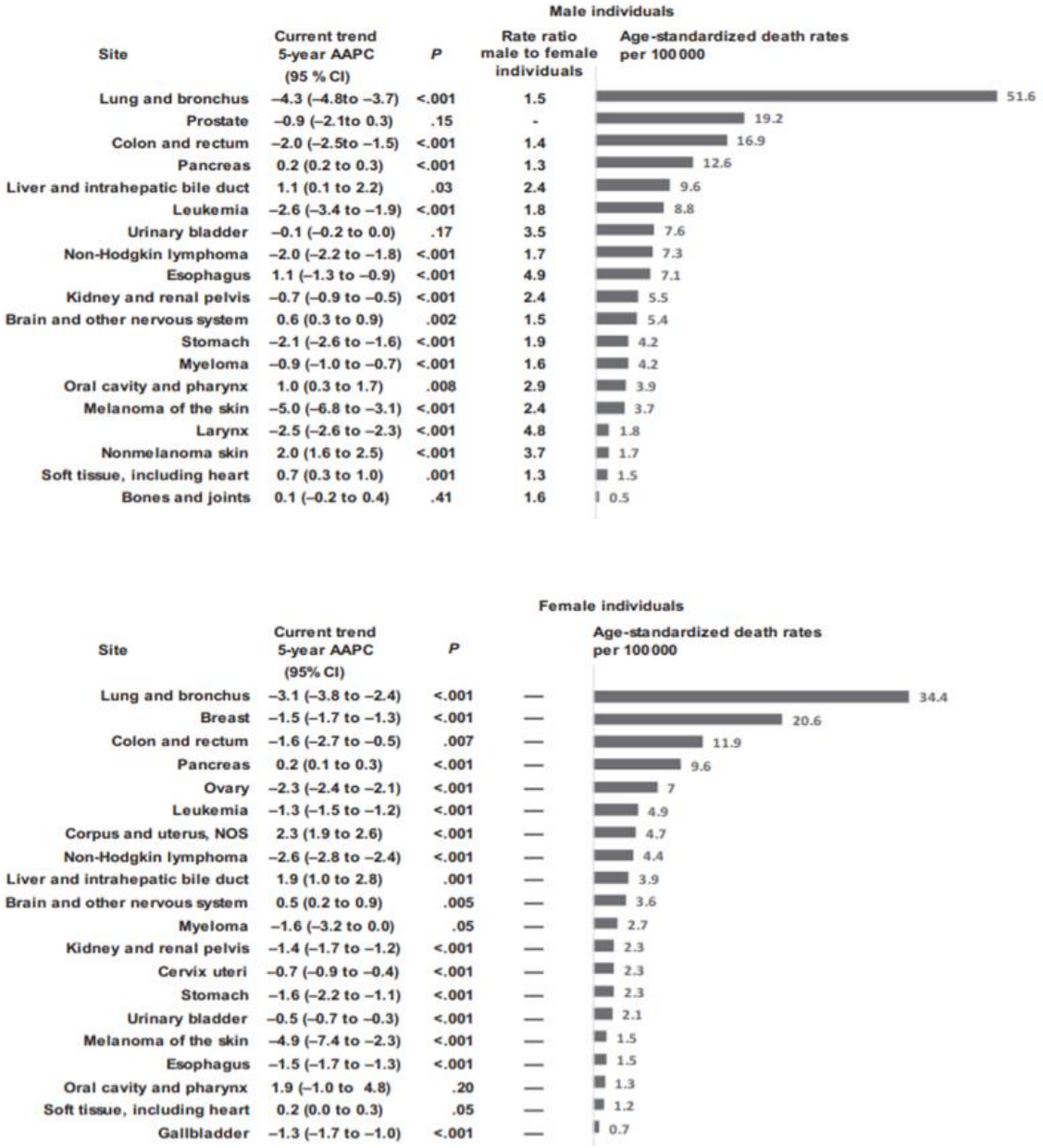

Figura 3. Tasas de mortalidad estandarizada por edad y tendencia (2012-2016) para los tipos de cáncer más comunes en el sexo masculino y femenino. Fuente: Ward EM, et al [3].

En contraste con este descenso en la mortalidad, se ha apreciado un aumento de la incidencia de CCR en sujetos menores de 50 años de ambos sexos de aproximadamente un 2.1% anual entre los años 1992 y 2012 que ha mantenido esta tendencia desde entonces [4]. Este aumento está relacionado principalmente con aquellas lesiones localizadas en el colon izquierdo en general y en concreto a las localizadas en el recto (3.9% anual) [5].

Aunque el CCR en los pacientes menores de 50 años supone aproximadamente el 2.5-5% del total de CCR prevalentes, más del 86% de estos pacientes presentan síntomas en el momento del diagnóstico, lo que se asocia con estadios más avanzados y peor pronóstico [6].

A pesar de ello, la mayoría de las guías de práctica clínica actuales sugieren iniciar programas de detección precoz de CCR a la edad de 50 años, excepto ante la presencia de situaciones como un síndrome hereditario predisponente, el antecedente de enfermedad inflamatoria intestinal o tratamiento con radioterapia en el área abdominal o la presencia de antecedentes familiares de CCR. Para todas ellas se han desarrollado recomendaciones específicas de detección precoz.

Otros documentos de consenso son todavía más conservadores en algunos grupos demográficos. Las recomendaciones del *United States Preventive Services Task Force* aceptan la posibilidad de utilizar como edad de inicio de cribado los 45 años en algunas situaciones [7]. En el caso de la *American Cancer Society* se recomienda esa misma edad en cualquier grupo demográfico [8], lo cual ha supuesto un punto de controversia con respecto a la eficiencia en el uso de recursos [9].

Presentación clínica del cáncer colorrectal

Los pacientes con CCR pueden presentarse de tres formas: a) por la aparición de síntomas y/o signos de sospecha, b) a través de los programas de detección precoz en sujetos asintomáticos y c) por el desarrollo de complicaciones que implican la necesidad de asistencia inmediata hospitalaria como la perforación y obstrucción intestinales o la hemorragia gastrointestinal aguda.

En la mayoría de los pacientes con CCR en estadios precoces no existen síntomas de sospecha, por lo que este tipo de pacientes sólo se diagnostican como resultado de un examen de detección precoz. Aunque la creciente aceptación de la implantación de los programas poblacionales de cribado del CCR ha conducido a un aumento progresivo del porcentaje de casos diagnosticados en fases asintomáticas de la enfermedad, la mayor parte de CCR (aproximadamente el 70-90%) son detectados a partir del desarrollo de síntomas (**Figura 4**) [10,11].

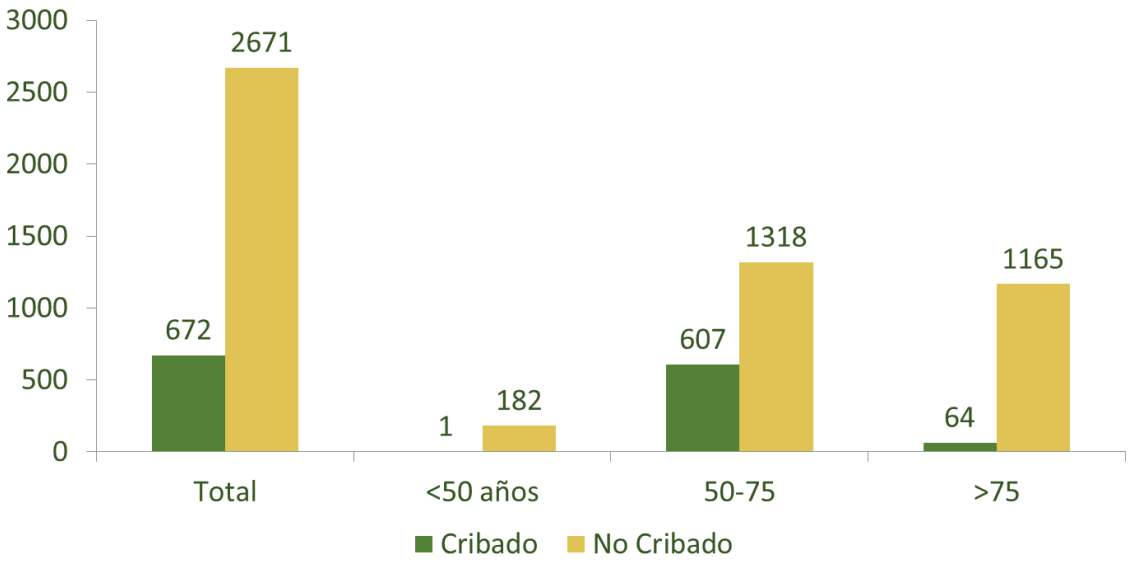

Figura 4. Diagnóstico del cáncer colorrectal (era post-cribado). Fuente: Mansouri D, et al [11].

La forma de presentación del CCR es amplia y la frecuencia de los síntomas varía según cada estudio. Así, mientras que la alteración del hábito intestinal se ha descrito hasta en un 74% de los pacientes diagnosticados en un reciente estudio retrospectivo [12], En otro trabajo que recoge los síntomas que se han asociado con mayor frecuencia a la existencia de CCR, se incluye la presencia de sangre con las deposiciones en forma de hematoquecia o melenas (37%) como síntoma más común, seguida del desarrollo de dolor abdominal (34%) o la presencia de anemia por déficit de hierro (23%), mientras que en este trabajo sólo un 1.3% de los diagnósticos estaba asociado a la presencia de alteración del hábito intestinal [13]. Otra forma de presentación menos habitual incluye el desarrollo de distensión abdominal, náuseas y vómitos, que aun constituyendo síntomas inespecíficos que aunque pueden ser justificables en la mayor parte de los pacientes por patología benigna, también pueden indicar una obstrucción intestinal incipiente.

Por todo ello, probablemente sea más útil desde un punto de vista clínico conocer cuál es el riesgo de padecer CCR a partir de un determinado síntoma. A ese respecto, un metaanálisis de 15 estudios apreció que tanto el valor predictivo positivo como el negativo de síntomas individuales como la aparición de un cambio en el hábito intestinal, pérdida de peso, masa abdominal o anemia, son limitados. Una excepción es la presencia de una masa abdominal o un sangrado rectal rojo oscuro que mostraron una especificidad superior al 95% para la detección de CCR (**Figura 5**) [14].

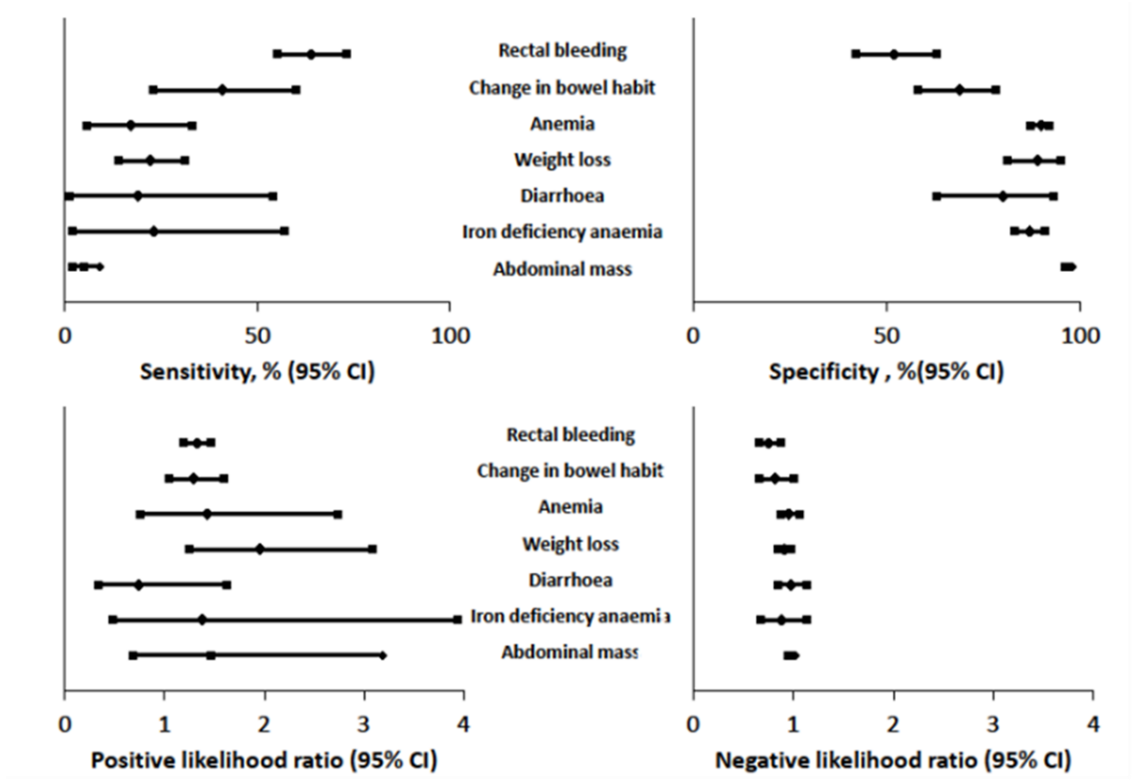

Figura 5. Precisión de los síntomas para el diagnóstico de cáncer colorrectal. Fuente: Ford AC, et al [14].

En otra revisión sistemática de 62 estudios que evalúan la asociación entre el desarrollo de síntomas y el CCR se utilizó la razón de probabilidades de diagnóstico (DOR = [sensibilidad / (1-sensibilidad)] / [(1-especificidad) / especificidad]) como medida resumida de precisión diagnóstica para cada síntoma. La presencia de un DOR elevado indica una alta correlación entre el síntoma y la enfermedad, mientras que un DOR con valor igual a 1 implica que la presencia de síntomas no es mejor que el azar a la hora de discriminar entre pacientes sanos y enfermos. En este trabajo, sólo el sangrado rectal y la pérdida de peso mostraron asociación con la presencia de CCR, e incluso estos dos síntomas presentaron una DOR baja [15].

Otros síntomas del CCR se asocian con la presencia de enfermedad diseminada ya que aproximadamente el 20% de los pacientes diagnosticados de CCR tienen metástasis a distancia en el momento de la presentación [4].

El CCR puede diseminarse por vía linfática y hematógena, además de por contigüidad. La afectación más común es a través de los ganglios linfáticos regionales [16]. Por otra parte, dado que el drenaje venoso del tracto intestinal es llevado a cabo a través del sistema portal, el primer sitio de diseminación hematógena suele ser el hígado, seguido de los pulmones, los huesos y otras localizaciones como el cerebro. Sin embargo, los tumores originados en recto distal pueden metastatizar inicialmente en los pulmones debido a que la vena rectal inferior drena hacia la vena cava inferior en lugar de hacia el sistema venoso portal. Así, los pacientes podrán presentar signos o síntomas atribuibles a cualquiera de estas áreas además de síntomas relacionados con el peritoneo, que también puede afectarse cuando el CCR se extiende por contigüidad. La presencia de dolor en el cuadrante superior derecho, saciedad precoz, distensión abdominal, adenopatía supraclavicular o nódulos periumbilicales, cuando están provocados por un CCR, suelen indicar enfermedad a distancia [17]. Aparte de ello, se han descrito también en la literatura una gran variedad de presentaciones atípicas [18-20]. Por último, el CCR puede diagnosticarse a partir de la detección incidental de metástasis hepáticas o pulmonares durante la realización de ecografía abdominal o una tomografía axial computarizada. El 6% de los adenocarcinomas de origen desconocido dan lugar al diagnóstico de CCR (**Figura 6**) [21,22].

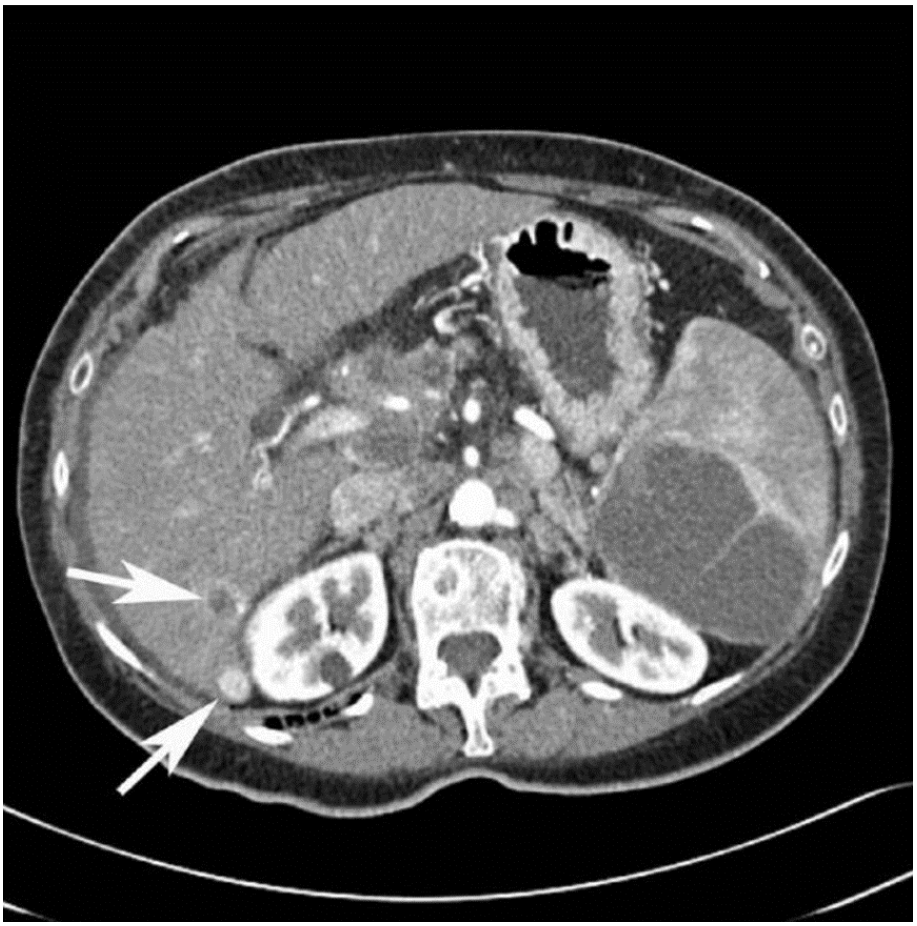

Figura 6. Lesiones hepáticas hipo e hipervasculares en relación con metástasis de adenocarcinoma de colon. Fuente: Schima W, et al [22].

Relación entre síntomas, estadio y pronóstico del cáncer colorrectal

Tanto la presencia como el tipo de síntomas que desarrollan los enfermos de CCR se asocian al pronóstico de esta enfermedad. Esto se debe a que aquellos sujetos que presentan síntomas en el momento del diagnóstico suelen tener una enfermedad más avanzada que conlleva un peor pronóstico.

Por ello, los pacientes diagnosticados fuera de programa de cribado poseen un riesgo mayor de presentar un estadio avanzado (≥T3: riesgo relativo [RR] 1.96), afectación ganglionar (RR 1.92) y metástasis al diagnóstico (RR 3.37). Además, estos pacientes poseen mayor mortalidad (RR 3.02), recurrencia de enfermedad (RR 2.19), y una menor supervivencia e intervalo libre de enfermedad [23].

Por otra parte, el número total de síntomas está inversamente relacionado con la supervivencia del cáncer de colon (excepto en las lesiones localizadas en el recto) [24]. En cuanto a la duración de los síntomas, existe controversia sobre su influencia en el pronóstico. Esto podría ser debido a la inespecificidad de los síntomas digestivos, cuya presencia en relación con enfermedades crónicas de carácter benigno en un paciente concreto podría generar dificultad a la hora de valorar el tiempo de evolución de aquellos síntomas realmente asociados con CCR en ese paciente. Del mismo modo, algunos pacientes con síntomas asociados a la presencia de enfermedad grave podrían diagnosticarse antes, empeorando el pronóstico del grupo con menor duración de síntomas hasta el diagnóstico (**Figura 7**) [25-27].

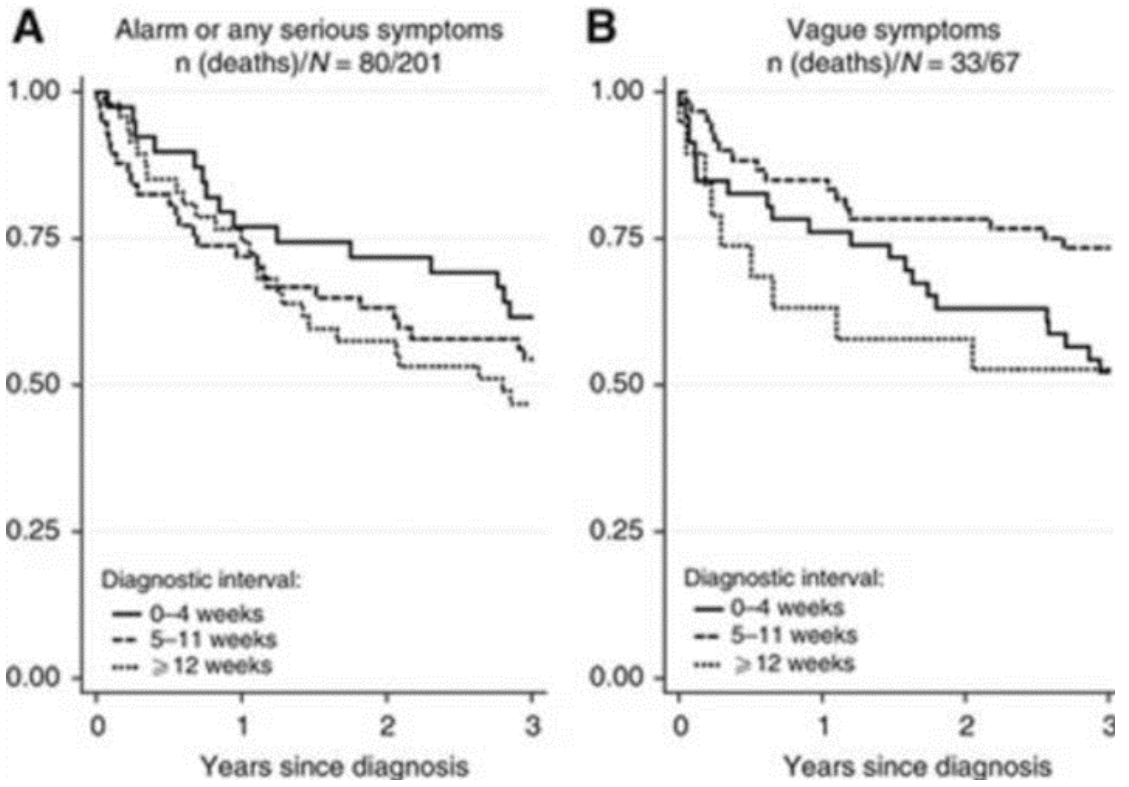

Figura 7. Supervivencia del cancer colorrectal con relación a la duración de los síntomas hasta el diagnóstico. (A) síntomas de alarma asociados a cáncer o enfermedad grave y (B) síntomas vagos o inespecíficos no asociados directamente a la presencia de enfermedad grave. Fuente: Tørring ML, et al [27].

Finalmente, el desarrollo de complicaciones locales (obstrucción o perforación) son infrecuentes, pero están asociadas a mal pronóstico independientemente del estadio y también pueden influir en la decisión de administrar o no quimioterapia adyuvante [28]. En cambio, los tumores que cursan con sangrado rectal (más frecuentemente los localizados en colon distal y el recto) tienen un mejor pronóstico, muchas veces porque este tipo de síntoma facilita el diagnóstico en una etapa más temprana [29]. Sin embargo, el sangrado no constituye un factor pronóstico independiente de supervivencia del CCR [30].

Dado que el factor pronóstico más influyente en la supervivencia del CCR es el estadio en que se encuentra la enfermedad al diagnóstico [31], las autoridades sanitarias

han desarrollado dos estrategias principales para reducir las consecuencias del CCR: el cribado en poblaciones de riesgo medio y en ocasiones de alto riesgo (historia personal o familiar de adenomas o CCR), y la detección temprana en sintomáticos [32-34].

Cribado del cáncer colorrectal en poblaciones de riesgo medio

Las características del CCR justifican una inversión de recursos en el desarrollo de programas de detección precoz. En primer lugar, la información epidemiológica previamente expuesta demuestra que constituye un importante problema de salud pública. Además, el conocimiento de su fisiopatología ha permitido identificar múltiples factores etiopatogénicos con los que es posible definir grupos de riesgo sobre los que concentrar los recursos de manera eficiente [35]. Finalmente, la historia natural de esta enfermedad posibilita una amplia ventana de oportunidad sobre la que llevar a cabo múltiples procedimientos diagnósticos capaces de identificar tanto lesiones precursoras como CCR en estadio precoz [32].

Existen dos grandes grupos de pruebas diagnósticas que pueden ser utilizadas en el cribado del CCR [36]. Las pruebas estructurales, permiten la visualización del colon por lo que se benefician de una mayor precisión diagnóstica. Además de la colonoscopia o la sigmoidoscopia que tienen como desventaja el tratarse de pruebas más invasivas [37], la colonografía por tomografía computarizada también permite explorar el colon al generar una reconstrucción de este en 2 o 3 dimensiones a partir de la obtención de múltiples imágenes tomográficas (colonoscopia virtual) con la limitación de que esta prueba no permite la toma de muestras o el tratamiento de aquellas lesiones identificadas durante su realización [38].

Otro tipo de pruebas como el test de sangre oculta en heces (SOH) o el análisis de DNA fecal están basadas en la detección en las heces de pequeñas pérdidas de sangre y marcadores genéticos respectivamente, que pueden encontrarse en aquellos sujetos portadores de CCR o sus lesiones precursoras antes de que se manifiesten clínicamente [36]. A través de estos biomarcadores es posible identificar aquellas personas con

mayor riesgo de presentar CCR y restringir con ello la realización de pruebas más molestas e invasivas a situaciones en las que existe mayor beneficio [39].

Finalmente, en los últimos años han surgido nuevas modalidades fundamentadas en la detección de otros biomarcadores presentes en diversos fluidos biológicos, y que podrían contribuir en un futuro cercano al arsenal diagnóstico existente [40,41].

Utilidad del test de sangre oculta en heces en el cribado del CCR

La colonoscopia constituye el patrón oro en el diagnóstico del CCR debido a su elevada precisión diagnóstica, facilidad de obtener muestras histológicas y la posibilidad de realizar procedimientos terapéuticos durante la misma. Sin embargo, también es un procedimiento costoso, molesto para el paciente y no exento de efectos secundarios [42]. Por ello, se han desarrollado múltiples estrategias que priorizan la realización de otro tipo de pruebas menos invasivas dentro de los programas de detección precoz de CCR entre las que SOH es la más evaluada [43].

Se han utilizado dos tipos de metodología para determinar la presencia de SOH. Los métodos tradicionales bioquímicos, emplean un papel impregnado con diversos indicadores como la resina de guayaco, la ortotolidina o la bencidina. El paciente debe distribuir seis muestras de heces obtenidas a partir de tres deposiciones consecutivas (dos muestras por cada deposición) en tres tarjetas destinadas a facilitar su evaluación (cada tarjeta tiene dos pocillos para alojar muestras). En caso de que exista sangre oculta en las muestras distribuidas en las tarjetas, al verter sobre las mismas una solución alcohólica de peróxido de hidrógeno, la presencia de la pseudoperoxidasa de la hemoglobina (Hb) provoca una reacción de oxidación que cambia de color el papel volviéndolo azulado. Si durante el primer minuto la coloración azulada se extiende más de 5 mm en una de las muestras, el resultado se considera positivo. Además, a mayor número de muestras positivas se incrementa la probabilidad de existencia de lesiones (**Figura 8**) [44].

Figura 8. Tarjetas de Hemoccult II Sensa y aplicadores de muestra fecal (Izquierda). Detalle de cómo se visualiza la reacción de oxidación resultante de la presencia de sangre en dos muestras (Derecha).

Aunque este tipo de pruebas han demostrado reducir la mortalidad en ensayos aleatorizados controlados, se han descrito múltiples problemas durante su utilización. En primer lugar, los test más clásicos como el Hemoccult II suelen detectar únicamente concentraciones mayores de 600 µg/Hb por gramo de heces, e incluso variantes desarrolladas posteriormente y mejoradas, como el Hemoccult-SENSA, sólo detectan concentraciones por encima de 300 µg/Hb por gramo de heces por lo que su sensibilidad no es muy elevada. Además, la interpretación del resultado es subjetiva, lo que disminuye el rendimiento de esta prueba cuando es realizada por personal poco entrenado [45].

Otro problema de los test bioquímicos es que tampoco son totalmente específicos para la detección de Hb humana, por lo que determinados alimentos con actividad peroxidasa (p.ej. carnes rojas o vegetales no cocinados) pueden producir falsos positivos si no se retiran de la dieta tres días antes de su utilización [46,47]. A esto último se añade que la existencia de lesiones en el tracto digestivo superior también puede dar lugar a la presencia de Hb en las heces, por lo que también es importante retirar

previamente fármacos antitrombóticos o antiinflamatorios que podrían provocar lesiones benignas potencialmente sangrantes e interferir con ello el resultado [48].

Para finalizar, toda esta rutina que rodea la recogida de muestras (tres deposiciones consecutivas, dieta, retirada farmacológica) conlleva una serie de molestias para los pacientes que contribuyen al descenso de la participación en los programas de detección precoz [49].

A diferencia de los anteriores, los test de SOH inmunológicos (SOH-i) se basan en la reacción de anticuerpos mono o policlonales específicos contra diferentes componentes de la sangre (Hb, albúmina) [50]. Algunos combinan técnicas inmunológicas y químicas para ofrecer resultados de forma cualitativa, al igual que los métodos químicos. Sin embargo, los más utilizados en el momento actual en los programas poblacionales de cribado desarrollados en nuestro país se basan exclusivamente en una reacción antígeno-anticuerpo a través de anticuerpos que reaccionan frente a la globina humana y utilizan métodos de aglutinación en látex: OC-Sensor (*Eiken Chemical Co., Ltd, Japón*) y FOB-Gold (*Sentinel Diagnostics, Milán*). Otro tipo de marcas más utilizadas en otros países, basadas también exclusivamente en el método inmunológico, usan técnicas de enzimoinmunoanálisis (HM-JACKarc, *Hitachi Chemical Diagnostics Systems, Tokyo, Japan*) o de aglutinación con partículas de gelatina magnetizadas (Magstream 1000, *Fujirebio Inc.,Tokyo,Japón*).

Todos ellos poseen una gran ventaja sobre los test de SOH que siguen el método tradicional: la posibilidad de establecer diferentes umbrales de riesgo gracias a su capacidad de cuantificar la concentración de hemoglobina fecal detectada [51]. Se ha demostrado que la precisión diagnóstica del test de SOH está influida por características

de los pacientes como el sexo o la edad, y el uso de test inmunológicos permite el uso de puntos de corte individualizados [52,53].

La siguiente tabla tomada del trabajo de Enrique Quintero resume las características de algunas de las marcas de sangre oculta en heces que han sido aprobadas por la Administración de alimentos y medicamentos en Estados Unidos [54].

Pruebas	Método	Límite de detección (µg de Hb/g de heces)	Lectura
Químicas			
Hemoccult II®	Reacción peroxidasa	600	Visual
Hema-Screen®	Reacción peroxidasa	600	Visual
Hemo-fec®	Reacción peroxidasa	600	Visual
Hemocult-SENSA®	Reacción peroxidasa con revelador sensible	300	Visual
Inmunológicas			
Primera generación			
InmunoCare®	Inmunocromatográfico	300	Visual
FlexSure OBT®*	Inmunocromatográfico	300	Visual
Immudia Hem SP®*	Hemaglutinación	300	Visual
OCHemodia®*	Aglutinación en látex	40	Visual
Monohaem®*	Inmunoquímico	1.000	Visual
Última generación			
Insure Inform®	Inmunocromatográfico	50	Visual
Instant View®	Inmunocromatográfico	300	Visual
Hemeselect®*	Hemaglutinación	300	Visual
Hemoccult-ICT®	Inmunocromatográfico	300	Visual
Clearview Ultra-FOB®	Aglutinación en látex	50	Visual
OCLight®, FOB-Gold®	Aglutinación en látex	20 a 2.000	Automatizado
OC-SENSOR®, OC-MICRO® SENTiFOB®	Aglutinación en látex	20 a 2.000	Automatizado
Immudia RPH (Magstream 1000)®	Aglutinación magnética	100 a 200	Automatizado

Hb: hemoglobina.
*Test retirados del mercado.

Tabla 1. Características de algunas de las marcas de sangre oculta en heces que han sido aprobadas por la Administración de alimentos y medicamentos en Estados Unidos. Fuente: Quintero E [54].

Se ha demostrado por medio de grandes ensayos clínicos aleatorizados con grupo control que los test de SOH bioquímicos reducen la mortalidad por CRC en los programas de detección precoz. Sin embargo, debido a los inconvenientes descritos previamente, este tipo de tests ha sido progresivamente sustituidos por otros más modernos, basados en el método inmunológico [55,56].

Los test inmunológicos permiten un diagnóstico más preciso del CCR en el entorno de cribado [57]. Por una parte, son más específicos no requiriendo restricción farmacológica o la realización de dieta previamente a su uso, ya que no reaccionan con la sangre metabolizada que proviene el tracto gastrointestinal alto ni con otros componentes de la dieta [58]. Además, son capaces de detectar concentraciones de hemoglobina fecal (Hb-f) mucho más bajas que en el caso de los test químicos por lo que su sensibilidad es mayor [59].

Finalmente, en el caso de los test de sangre oculta en heces inmunológicos cuantitativos, no sólo se ha simplificado la recogida y el procesamiento de la muestra, sino que además es posible llevar a cabo un análisis automatizado de las muestras, evitando la interpretación subjetiva [54]. Para ello están disponibles equipos que permiten cuantificar la cantidad de Hb existente en hasta 50 muestras en una hora de forma automatizada, por lo que no sólo se evita el factor subjetivo de la lectura cualitativa sino que se hace posible el análisis masivo de muestras requerido en un programa poblacional de cribado.

La **Figura 9** y la **Tabla 2** resumen las principales ventajas de los test de SOH inmunológicos sobre aquéllos basados en el método químico.

Figura 9. Analizador automático OC-Sensor DIANA para la determinación cuantitativa de sangre oculta en heces (Izquierda) y dispositivo para recoger muestra fecal (Derecha).

	Prueba de SOH-Q	Prueba de SOH-I
Restricción dietética	Recomendable	No
Retirar AINE o aspirina 7 días antes	Sí	No
Falsos positivos para detección de hemoglobina fecal:		
Carnes rojas	Sí	No
Vegetales no cocinados	Sí	No
Sangre del tracto digestivo alto	Sí	No
Falsos negativos para detección de hemoglobina fecal:		
Ingesta de ácido ascórbico	Sí	No
Resecamiento de la muestra	Sí	–
Caducidad del amortiguador	–	Sí
Muestra insuficiente	Sí	Sí
Temperatura del ambiente elevada	Sí	Sí
Deficiente conservación postest (>4 °C)	–	Sí
Tiempo desde recogida de la muestra hasta su lectura	14 días	21 días
Número de muestras necesarias para su lectura	3	1
Efecto prozona*	No	Sí
Lectura subjetiva	Sí	Sí (cualitativo) No (cuantitativo)
Lectura automatizada	No	Sí (cuantitativo)

AINE: antiinflamatorios no esteroideos; SOH-I: test de sangre oculta en heces inmunológico; SOH-Q: test de sangre oculta en heces químico.
*Efecto prozona: en condiciones de exceso del antígeno (hemoglobina superior a 2.000 µg/g de heces) el ensayo lee una concentración de hemoglobina nula o inferior a la presente en la muestra.

Tabla 2. Ventajas e inconvenientes del test de sangre oculta en heces dependiendo del tipo de test empleado. Fuente: Quintero E [54].

Diagnóstico precoz del cáncer colorrectal basado en síntomas

A pesar de la eficacia en términos de reducción de mortalidad que se ha demostrado con el desarrollo de los programas de cribado, la mayor parte de CCR son diagnosticados fuera de los mismos en pacientes con síntomas [11,60]. En un trabajo retrospectivo se demostró que, a pesar de la efectividad del programa nacional de cribado, menos del 12% de CCR se detectaban a través del uso de SOH [61].

Por este motivo, es previsible que la mayoría de los pacientes con CCR se pongan en contacto con el sistema de salud a través de atención primaria [62]. Desafortunadamente, la consulta por sintomatología abdominal persistente es común en ese entorno, y el dolor abdominal, la alteración del hábito intestinal, o el sangrado rectal son síntomas a los que se tienen que enfrentar diariamente los especialistas de medicina de familia [63,64]. En un estudio se ha estimado que el 10% de todas las consultas de atención primaria están relacionadas con problemas digestivos [65]. Sin embargo, la mayor parte de estas molestias van a tener un origen funcional y la prevalencia de lesiones de colon significativas en este tipo de pacientes (LCS) (p.ej. CRC o enfermedad inflamatoria intestinal) es baja, estimándose en aproximadamente el 7% en algún estudio [66]. Por otra parte, en un metaanálisis también se ha comunicado que los síntomas digestivos tienen un valor predictivo positivo muy limitado, de solamente un 3-4% [67].

Esta subjetividad repercute en el manejo de los pacientes por los médicos de atención primaria que se sienten sometidos al doble riesgo de equivocarse: por un lado pudiendo malinterpretar una serie de síntomas digestivos como molestias que no suponen una amenaza aunque limiten la calidad de vida, pero también mostrando excesiva preocupación ante síntomas comunes que podrían estar relacionados con una

enfermedad grave [68,69]. Todo ello afectará el flujo de pacientes entre atención primaria y especializada, que se verá comprometido por un número indeterminado de sujetos que serán objeto de múltiples evaluaciones o exploraciones innecesarias, mientras que otros tardarán sufrirán demoras en el diagnóstico de enfermedades potencialmente graves [34].

Por ejemplo, en el caso concreto de un paciente que consulte por sangrado rectal, que es considerado un síntoma de alarma relacionado con CCR [70], es probable que se genere una consulta rápida al gastroenterólogo o una solicitud de colonoscopia [71]. Sin embargo, este síntoma está presente de manera habitual en la población general y es causado mayormente por patología benigna anal como hemorroides o fisuras sin que sea sencillo determinar a partir de la anamnesis o la exploración física la ausencia de otro tipo de problemas más graves [72-74]. En este tipo de situación, la incertidumbre ante un síntoma potencialmente grave da lugar a que el flujo de pacientes hacia consulta especializada aumente provocando un incremento en el consumo de recursos y el aumento en las listas de espera.

El otro extremo del problema se aprecia en otro tipo de síntomas más inespecíficos considerados de bajo riesgo que no entran en el grupo de "síntomas de alarma". Estos síntomas están formados por un grupo heterogéneo de molestias vagas e inespecíficas que con mayor frecuencia son reflejo de problemas funcionales [75]. Para ellos, los médicos de atención primaria suelen usar una estrategia de "esperar y ver evolución" que puede dar lugar a una demora en el diagnóstico y traducirse en progresión del cáncer y empeoramiento del pronóstico en comparación con aquellos pacientes que tuvieron síntomas de alarma como forma de presentación [27,29,76-78], a pesar de que se ha demostrado que el número de consultas de aquéllos pacientes que

serán diagnosticados de CCR es significativamente mayor que las de aquellos pacientes que presentan síntomas similares que no están relacionados con esta enfermedad [79].

Esta situación ha llevado a intentar protocolizar el flujo de pacientes entre especialistas, identificando una serie de situaciones objetivas que precisan derivación a atención especializada para priorizar la identificación de pacientes con cáncer. Sin embargo, estas iniciativas como la introducción de vías rápidas en Escocia (*Urgent suspicion of cancer*) e Inglaterra (*Two-week-wait referral criteria*) iniciadas en el año 2000 como parte del plan nacional de tratamiento del cáncer [80], únicamente tuvieron como resultado el aumento de la presión asistencial en las consultas especializadas y una mayor demanda de colonoscopias [81], que se acompañó de un discreto aumento en las tasas de detección de cáncer sin producir una mejoría significativa en la supervivencia del mismo [82-85], mientras que sólo un 6-13% de los pacientes derivados mostraba patología relevante del tracto gastrointestinal (**Figura 10**) [86].

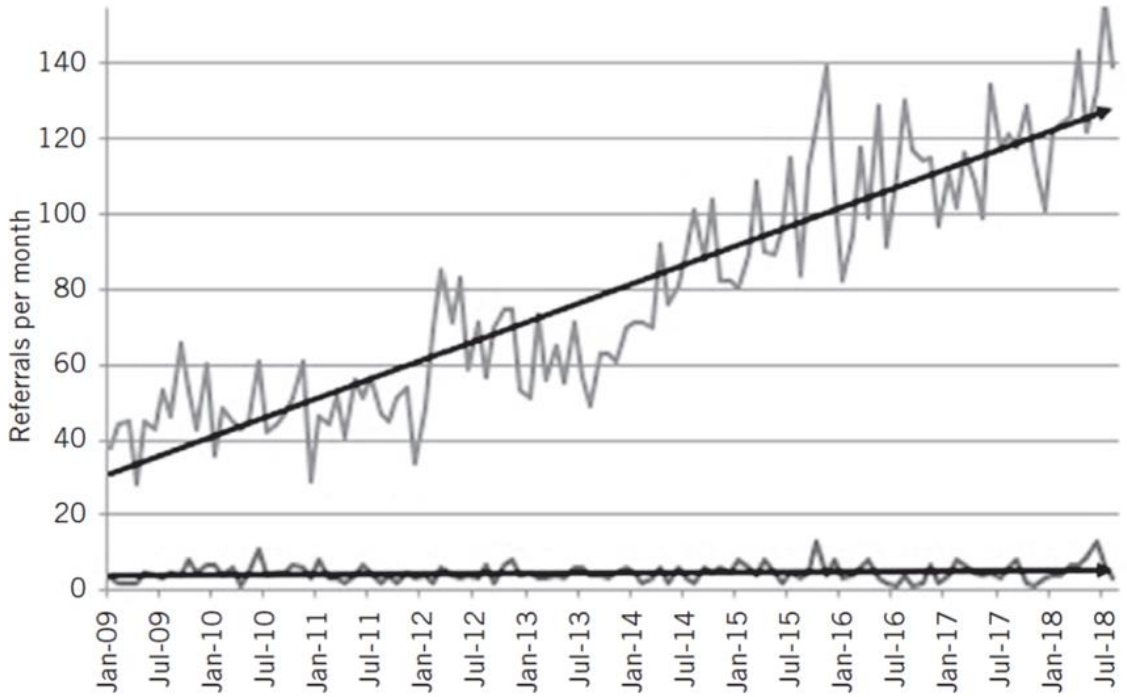

Figura 10. Incremento en la tasa de pacientes derivados a atención especializada (línea superior) en comparación con la estabilidad en el diagnóstico de cáncer colorrectal en esos pacientes (línea inferior) entre enero de 2009 y julio de 2018. Fuente: Maclean W [85].

Utilidad del test de sangre oculta en heces en el estudio de síntomas digestivos: Recomendación NICE

El desarrollo de programas de detección precoz ha permitido demostrar que el uso del test de SOH reduce la mortalidad por CCR, aumentando la proporción de pacientes diagnosticados en fases tempranas de la enfermedad y facilitando la detección y posterior eliminación de lesiones preneoplásicas [87].

Paralelamente, tres metaanálisis han mostrado que síntomas como la rectorragia o los cambios de hábito intestinal se asocian al diagnóstico de CCR. Sin embargo, estos síntomas también son muy prevalentes en personas sin cáncer, por lo que pierden utilidad para los médicos a la hora de evaluar el riesgo que posee un paciente concreto de presentar una enfermedad grave en el tracto intestinal [14,67,70].

Este problema ha conducido a la búsqueda y evaluación de diversas estrategias de mejora de la gestión del flujo de pacientes entre atención primaria y especializada, así como de la eficiencia en el uso de recursos [88-90]. En ese contexto, los test de SOH-i también fueron objeto de múltiples trabajos, destinados a conocer si su precisión para detectar CCR en pacientes sintomáticos era lo suficientemente elevada como para ser utilizado como herramienta de priorización en la práctica clínica diaria.

La primera revisión sistemática que ha valorado el uso del test de SOH-i como prueba de primera línea en la evaluación de pacientes con síntomas se llevó a cabo en el año 2008 [67]. Esta revisión incluye nueve trabajos que analizan la precisión diagnóstica de múltiples marcas comerciales diseñadas para determinar la existencia de Hb fecal a través de diferentes métodos [91-99], y concluye que los test basados en el método inmunológico tienen mayor precisión diagnóstica que los tradicionales basados

en el método del guayaco, sugiriendo además que pueden ser útiles para identificar aquellos pacientes con síntomas con una mayor probabilidad de presentar CCR.

Sin embargo, se encontró un grado de heterogeneidad muy elevado entre los diversos estudios meta analizados, que los autores justifican por el gran número de diferencias metodológicas entre ellos. Las poblaciones analizadas no compartían el mismo espectro clínico, y se utilizaron marcas comerciales con diferentes características, que tampoco coinciden en la manera de transmitir el resultado de la medición de la Hb-f (algunas lo hacen de forma cuantitativa y otras cualitativamente). Todo ello limita las posibilidades de llegar a conclusiones sólidas sobre la precisión del test de SOH-i en esta revisión sistemática.

Mientras tanto, no faltaron trabajos que alertaban sobre el riesgo de que el uso de SOH-i fuera de los programas de cribado pudiese provocar mayores efectos colaterales que beneficio. Sus autores argumentaban que cualquier síntoma debería ser investigado independientemente de la presencia de Hb-f, por lo que aquellos pacientes con un resultado negativo del test podrían sufrir retrasos injustificados en el diagnóstico de enfermedades importantes [100-103].

A pesar de las críticas, la investigación sobre este tema siguió adelante. Entre otros trabajos, destacaría un estudio prospectivo multicéntrico desarrollado en dos áreas de salud de nuestro país, en el que se demostró que el uso del test de SOH-i cuantitativo es más preciso en la detección del CCR que el uso de varios criterios de derivación basados en síntomas clínicos, usados habitualmente para valorar la idoneidad de la solicitud de colonoscopias (**Figura 11**) [104]. Trabajos posteriores demostrarían también la utilidad de este tipo de pruebas en la detección de otro tipo de LCS además del CCR [105].

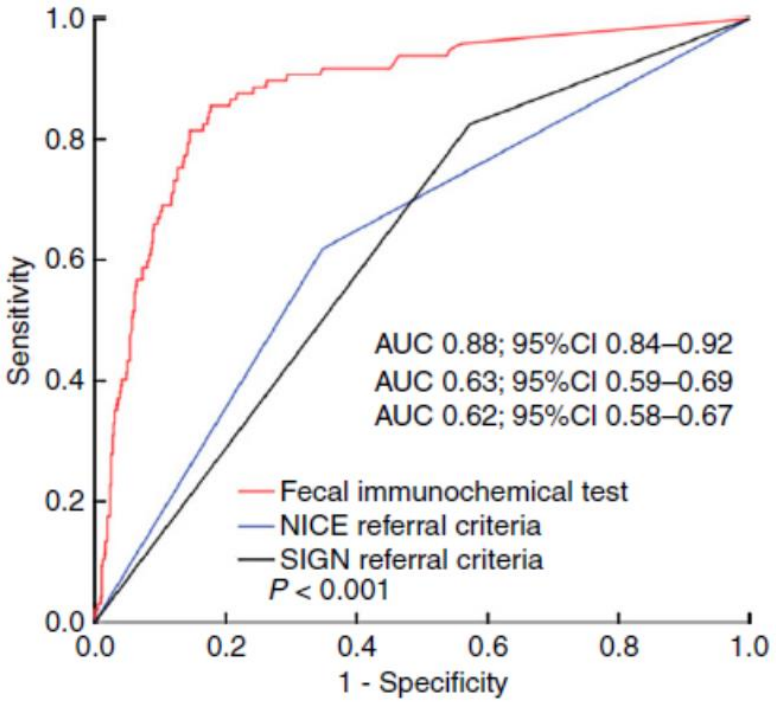

Figura 11. Comparación de la precisión diagnóstica del test de sangre oculta en heces inmunológico cuantitativo en comparación con los criterios de derivación NICE y SIGN basados en síntomas clínicos. AUC, área bajo la curva. Fuente: Cubiella J, et al [104].

Ante esta controversia, el *National Institute for Health and Care Excellence* (NICE), encargó la realización de otra revisión sistemática para resumir la evidencia disponible sobre los test de SOH-i más modernos y poder realizar una recomendación [106].

Esta revisión incluyó nueve estudios [86,104,107-113] y proporcionaría información sobre la precisión diagnóstica de tres marcas comerciales de test de SOH-i cuantitativo, mostrando que cuando el resultado de esta prueba se basa en la evaluación de una única muestra utilizando un punto de corte de 10 μg Hb / g de heces, la sensibilidad para detectar CCR es del 92.1% (Intervalo de confianza-IC del 95%: 86.9-95.3%) y del 100% (IC del 95%: 71.5-100%) para las marcas comerciales OC-Sensor® (*Eiken Chemical Co. Ltd, Tokio, Japón*) y HM-JACKarc® (*Kyowa-Medex Co. Ltd, Tokio, Japón*) respectivamente, sugiriendo que ambas podrían ser útiles para descartar

la presencia de CCR. En esa revisión, se estimó que la especificidad del test era del 85.8% (IC del 95%: 78.3-91.0%) para OC-Sensor® y del 76.6% (IC del 95%: 72.6-80.3%) en el caso de HM-JACKarc®.

Esta revisión incluiría también datos no publicados sobre la precisión diagnóstica de otra marca comercial, FOB Gold® (*Sentinel Diagnostics, Milán, Italia*). Esta información fue proporcionada por el fabricante de forma confidencial para completar una información expuesta previamente en un congreso científico que sería finalmente incluida en la revisión. Según estos datos, la sensibilidad y especificidad para la detección de LCS (hemorragia gastrointestinal, CCR o pólipo de colon) de SOH-i utilizando como punto de corte 9 μg Hb / g de heces es de 45.2%; y 92.3% respectivamente.

Aunque la evaluación de la precisión diagnóstica de Ridascreen® (*R-Biopharm AG, Darmstadt, Alemania*), marca también disponible en el Reino Unido, estaba dentro de los objetivos de esa revisión sistemática, no se identificaron estudios que la utilizaran en pacientes sintomáticos.

En definitiva, a partir de la evidencia disponible, NICE recomendó la determinación de Hb-f por medio de tres marcas comerciales de SOH-i cuantitativa (OC Sensor®, HM-JACKarc® y FOB Gold®) con un umbral de 10 μg Hb / g de heces, para evaluar aquellos pacientes que desarrollasen síntomas de bajo riesgo (sin sangrado rectal) de nueva aparición y sin explicación clara, que no cumpliesen con los criterios de derivación al especialista por sospecha elevada de cáncer (**Figura 12**) [114-115]. Sin embargo, se han señalado varios problemas a la hora de aplicar esta recomendación a la práctica clínica [116].

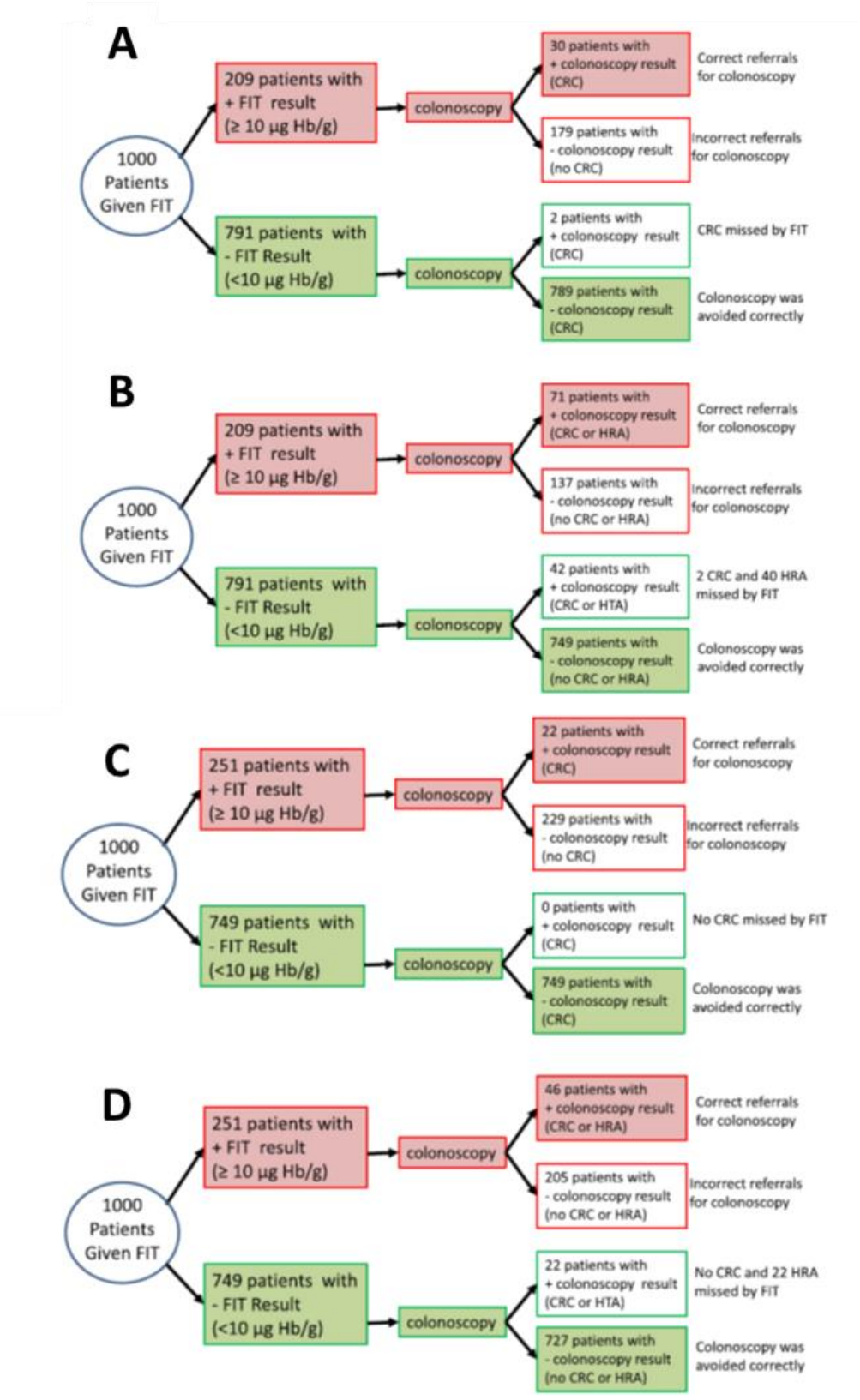

Figura 12. Desenlaces esperados tras someter a 1000 pacientes hipotéticos a una evaluación con OC-Sensor (A y B) HM-JACKarc (C y D) usando un umbral de 10 µg Hb / g en heces y teniendo en cuenta el cáncer colorrectal (A y C) o la neoplasia avanzada (B y D) como objetivo. Fuente: Westwood M [106].

Justificación del trabajo: Incógnitas en la aplicación de la recomendación NICE a la práctica diaria

Aunque los test de SOH-i cuantitativos han demostrado ser una herramienta útil para apoyar al médico de atención primaria en la decisión de solicitar una consulta al especialista o una colonoscopia, la recomendación de NICE (DG30) ha recibido numerosas críticas [116-117].

1. *Aplicabilidad en sujetos con síntomas de bajo riesgo en el entorno de atención primaria*

A pesar de que la recomendación DG30 está dirigida a apoyar la toma de decisiones de los médicos de atención primaria ante la presencia de síntomas de bajo riesgo de CCR, la revisión sistemática que la avala sólo incluye un estudio que reproduce esa situación concreta [86], y en ninguno de los trabajos que la componen y evalúan la precisión de SOH-i cuantitativo se utilizan datos de práctica real.

Esto supone un problema, ya que la precisión de SOH-i para detectar CCR en la práctica diaria llevada a cabo en el entorno de atención primaria, podría ser diferente a la calculada a partir de una muestra de sujetos cuyos síntomas han llevado a la solicitud por su médico de cabecera de que sean valorados por un gastroenterólogo o bien directamente a la realización de una colonoscopia [67].

Aunque las poblaciones de ambos entornos (atención primaria y secundaria) van a estar caracterizadas por poseer distinta prevalencia de CCR, el cambio en el comportamiento de SOH-i entre una hipotética muestra de ambas no tiene por qué estar justificado por esta diferencia [118]. Las neoplasias que producen síntomas, generalmente se asocian a estadios más avanzados [119], que también pueden justificar la presencia de mayores concentraciones de Hb-f [120].

Por otra parte, la presencia de síntomas de alto riesgo estará también asociada a una mayor prevalencia de patología benigna (p.ej. una enteropatía asociada a antiinflamatorios o una enfermedad inflamatoria intestinal), que son más prevalentes que el CCR [121]. Todo ello podría dar lugar a que la sensibilidad y especificidad de estos test para detectar CCR sean distintas en la población de atención primaria (inferior en el caso de la sensibilidad, y superior en el caso de la especificidad) a las estimadas en estudios previos, llevados a cabo con cohortes reclutadas en atención especializada.

Asimismo, estimar de manera fiable las diferencias de comportamiento del test de SOH-i cuantitativo entre sujetos con síntomas digestivos y sujetos asintomáticos puede ser complicado. La existencia de síntomas inespecíficos (que podrían estar o no motivados por la presencia de CCR) no siempre es reflejada por algunos pacientes cuyo médico puede considerar sanos y asintomáticos [122,123], e incluso se ha comprobado que existe una baja concordancia entre la descripción realizada de un síntoma tan relevante y objetivo como el sangrado rectal por parte de los pacientes y sus médicos [68]. En otro estudio se describe que hasta el 65% de los participantes del programa de cribado en Reino Unido presentaban síntomas del tracto gastrointestinal bajo previamente a la realización del test de SOH-i, sin que se apreciasen diferencias en la prevalencia de CCR con respecto a los participantes asintomáticos [124]. Finalmente, se ha comunicado que el porcentaje de lesiones mayores de 9 mm diagnosticadas en pacientes con síntomas inespecíficos es similar al que presentan los sujetos sin síntomas [125].

Por todo ello, es preciso un mayor número de estudios que aporten información sobre la aplicación de SOH-i en atención primaria, ya que es en ese entorno concreto donde la aplicación de esta prueba diagnóstica obtendría el máximo beneficio en la optimización de los recursos del sistema sanitario.

Finalmente, independientemente del impacto que indudablemente tendría el diagnóstico de CCR en cualquier persona, el objetivo de todo médico ante un paciente que desarrolla un nuevo síntoma, pero especialmente el de un médico de atención primaria, no es sólo descartar esta enfermedad, sino que también se debe cuestionar la presencia de otro tipo de problemas que podrían justificar los mismos síntomas. Por ello, también es preciso recopilar más información sobre el comportamiento de SOH-i ante la presencia de cualquier enfermedad significativa de colon.

2. Influencia del punto de corte y el número de muestras en la precisión del test

La recomendación de NICE de utilizar siempre el punto de corte de 10 μg Hb/g de una única muestra de heces para evaluar a cualquier paciente con síntomas digestivos de bajo riesgo, independientemente de su edad o género también ha generado controversia.

Esto es debido a que los test de SOH-i han mostrado poseer, para el mismo punto de corte, una mayor sensibilidad para detectar neoplasias avanzadas en el caso de los hombres, mientras que en el caso de las mujeres su especificidad es mayor [126].

Se han propuesto varias hipótesis para justificar este hallazgo: una mayor incidencia de neoplasia avanzada en hombres [127], el hecho de que los hombres posean una mayor concentración de Hb en el organismo, implicando que sus lesiones también pudiesen estar caracterizadas por una mayor presencia de globina [128], la mayor prevalencia de lesiones derechas en las mujeres, que podrían ser más difíciles de detectar que las localizadas en el colon izquierdo [129], o incluso se ha propuesto que las mujeres podrían tener tiempos de tránsito más lentos que posibilitarían una mayor degradación de la Hb, disminuyendo con ello la posibilidad de su detección en las heces [130]. Por otra parte, la concentración media de Hb-f considerada “normal” varia de manera significativa con la edad [131,132].

A partir de toda esta información, proponer el uso de SOH-i con diferentes umbrales en función del género parece razonable. Sin embargo, la información disponible obtenida a partir de los trabajos realizados en el entorno de cribado es contradictoria, y un metaanálisis reciente no ha mostrado diferencias en la precisión de SOH-i cuantitativo con respecto a edad o género [132].

Además, se ha sugerido que el umbral de 10 μg Hb/g de heces es el más apropiado para la evaluación de pacientes sintomáticos dado que se aproxima al límite de cuantificación documentado por los fabricantes de la mayoría de las marcas comerciales utilizadas (OC-Sensor® and HM-JACKarc®), siendo éste el que proporcionaría una mayor sensibilidad y valor predictivo negativo para la detección de LCS [106].

Con respecto al número de muestras necesarias para asegurar una adecuada precisión de los test, sólo dos trabajos evaluaron si la determinación de la concentración de Hb-f en más de una muestra de heces puede mejorar la precisión del test de SOH-i cuantitativo para detectar neoplasia avanzada (CCR o adenoma avanzado). Los dos trabajos utilizaron una muestra reclutada a partir de la población de pacientes a los que se solicita una colonoscopia para investigar el origen de síntomas digestivos o realizar vigilancia tras resección de pólipos [30,133]. Estos trabajos usaban diferentes marcas comerciales de SOH-i cuantitativo (HM-JACKarc® [30] y FOB-Gold® [133]), pero en ambos la precisión obtenida usando un umbral de 20 μg Hb/g en dos muestras de heces fue similar a la apreciada evaluando una única muestra con el umbral de 10 μg Hb/g de heces. Esto resalta la necesidad de continuar la búsqueda de información para comprobar la eficacia de diferentes estrategias de priorización, no solo enfocadas a la búsqueda de neoplasias avanzadas sino también a cualquier LCS.

3. Actitud ante un resultado positivo en un paciente con colonoscopia normal

A pesar de que la existencia de una concentración de Hb-f por encima del umbral de 10 μg Hb/g de heces se asocia a una elevada probabilidad de existencia en el colon de neoplasia avanzada (adenoma avanzado o cáncer) [134], en numerosas ocasiones no se identifican lesiones tras la realización de una colonoscopia de calidad (con una preparación adecuada e intubación de ciego) indicada por un resultado positivo del test de SOH-i.

En ese sentido, se ha descrito una mayor especificidad de SOH-i para lesiones localizadas en tramos distales del tracto gastrointestinal [135], pero a pesar de ello se desconoce la incidencia posterior de lesiones relevantes proximales al colon durante el seguimiento de estos pacientes. Algunas situaciones, como por ejemplo la alteración del hábito intestinal o el antecedente de gastrectomía previa, podrían justificar la presencia de sangre no metabolizada en el colon proveniente de áreas del tracto gastrointestinal proximales al mismo.

Una revisión sistemática llegó a la conclusión de que no existe evidencia suficiente para establecer una recomendación a favor o en contra de la realización sistemática de una esofagogastroduodenoscopia en aquellos pacientes con un resultado positivo del test de SOH seguido de una colonoscopia normal [136].

Sin embargo, la mayor parte de los estudios incluidos usaban test de SOH basados en el método del guayaco o habían sido desarrollados en entorno de cribado. Por ello, las conclusiones extraídas a partir de esos datos no tienen por qué ser válidas en un paciente con síntomas de reciente aparición y un resultado positivo de SOH-i sin que existan lesiones en el colon que lo justifiquen. Esa situación podría generar incertidumbre sobre la necesidad de continuar la realización de estudios para descartar

otro tipo de lesiones sangrantes localizadas en áreas del tracto gastrointestinal diferentes al colon [137].

Esta posibilidad podría estar avalada por una serie de trabajos en los que se ha apreciado que el riesgo de lesiones situadas en intestino delgado o en el estómago puede ser superior en aquellos pacientes con un test de SOH-i positivo [138-141].

El riesgo de presentar otras lesiones proximales al colon podría valorarse también por medio de otros biomarcadores. Entre ellos, el antígeno carcinoembrionario (CEA) es uno de los marcadores tumorales más ampliamente conocidos. Se trata de una glicoproteína intracelular compleja que es producida en aproximadamente el 90% de CCR. Puede ser detectada en sangre y es empleada de forma mayoritaria en la vigilancia de las recurrencias del CCR tras su resección con intención curativa [142].

No obstante, los niveles séricos de CEA pueden estar elevados en muchos otros tipos de cáncer y su determinación ha demostrado ser útil en situaciones clínicas no relacionadas con la presencia de CCR, en las que el diagnóstico de una nueva lesión en múltiples localizaciones genera incertidumbre sobre su pronóstico debido a que presenta características indefinidas [143-145].

Todo ello ha provocado que muchos médicos de atención primaria incorporasen la determinación de CEA como parte de los exámenes rutinarios de salud en personas asintomáticas. Sin embargo, esta práctica no está recomendada [146]. Los niveles séricos de CEA pueden estar elevados en el seno de múltiples patologías benignas (p.ej., hepatopatía crónica, enfermedad inflamatoria intestinal) o incluso en personas fumadoras, en quienes el tabaco puede llegar a justificar incrementos por encima del doble de la concentración de CEA medida en sujetos sanos [147]. Además, la incidencia de otro tipo de neoplasias gastrointestinales que podrían justificar la elevación de los

niveles de CEA es baja. Por último, este marcador tiene una sensibilidad limitada para detectar cualquiera de estas lesiones en estadios tempranos de su historia natural [148].

Esta situación puede modificarse en el contexto de la presencia de síntomas digestivos. Como se ha comentado anteriormente, el CCR es la neoplasia gastrointestinal más frecuente y uno de los tumores más comunes en todo el mundo [149]. Sin embargo, otros tumores gastrointestinales menos prevalentes podrían ser el origen de una gran variedad de síntomas que inicialmente podrían generan una sospecha de CCR como consecuencia de la inespecificidad de los síntomas ya expuesta, independientemente del resultado de un test de SOH-i cuantitativo. La mayor parte de estos tumores gastrointestinales pueden justificar incrementos de los niveles séricos de CEA [143-145], dando lugar a que su incidencia en conjunto pueda ser lo suficientemente notoria como para que la determinación de los niveles de CEA pueda resultar eficiente en esta situación concreta.

Para intentar resolver estos puntos de controversia, nos hemos propuesto realizar una nueva revisión sistemática con metaanálisis que nos permita evaluar hasta qué punto diversas características que varían en la población de atención primaria y especializada (porcentaje de síntomas de alto riesgo, prevalencia de CCR) pueden influir en la estimación de la precisión de SOH-i cuantitativo, dando lugar a que su comportamiento en el entorno de atención primaria sea distinto al previsto a partir de la información actual obtenida a partir de pacientes reclutados en atención especializada. También pretendemos obtener más información sobre la capacidad de SOH-i para detectar cualquier LCS y no sólo el CCR.

Además, utilizaremos datos obtenidos a través de la práctica clínica real para determinar cuál ha sido la precisión de SOH-i observada en nuestro medio en los

últimos años, así como la influencia del sexo, la edad o la presencia de síntomas sobre la misma para diferentes puntos de corte.

Otro objetivo consistirá en averiguar cuál es el pronóstico de aquellos pacientes con una concentración de Hb-f por encima del umbral recomendado por NICE (10 μg Hb/g de heces), que fueron estudiados mediante la realización de una colonoscopia de calidad, sin que se encontrasen lesiones que justificaran el resultado de SOH-i. También evaluaremos la utilidad de determinar el CEA en aquellos pacientes con síntomas no justificados por la presencia de CCR independientemente del resultado de SOH-i.

Finalmente, concluimos nuestra línea de investigación con la realización de una segunda revisión sistemática de todos aquellos trabajos desarrollados simultáneamente por otros investigadores que compartieron nuestro objetivo de conocer la precisión de SOH-i para detectar CCR en aquellos pacientes que acuden a su centro de salud debido al desarrollo de síntomas digestivos, con el fin de actualizar la información existente y contrastar nuestros resultados.

HIPÓTESIS

Hipótesis

La precisión de SOH-i cuantitativo para detectar CCR puede variar dependiendo de la forma de presentación de esta neoplasia y de las características demográficas de cada enfermo. Como resultado, la precisión de SOH-i cuantitativo para detectar CCR en pacientes que consultan por la aparición de síntomas digestivos en el entorno específico de atención primaria, puede ser inferior a la estimada en la literatura existente para la población global de pacientes con síntomas digestivos.

Los pacientes con síntomas digestivos que poseen una concentración de Hb-f $\geq$ 20 µg Hb / g de heces sin hallazgos que la justifiquen tras la realización de una colonoscopia poseen un mayor riesgo de presentar una neoplasia localizada en el tracto gastrointestinal proximal al colon. El CEA es un biomarcador que puede ayudar a identificar los sujetos con mayor riesgo, quienes podrían ser subsidiarios de exploraciones adicionales.

OBJETIVOS

Objetivos

a) Realizar una revisión sistemática y en caso de ser posible un metaanálisis de todos aquellos trabajos que han estudiado la precisión de SOH-i para detectar CCR en pacientes con síntomas digestivos. Evaluar la influencia de la forma de presentación del CCR en la precisión de SOH-i. Estimar la precisión de SOH-i para detectar cualquier LCS.

Artículo 1: *Pin Vieito N, Zarraquiños S, Cubiella J. High-risk symptoms and quantitative faecal immunochemical test accuracy: Systematic review and meta-analysis. World J Gastroenterol 2019; 25:2383-2401.*

b) Comprobar si la precisión obtenida se corresponde con los resultados en práctica real de nuestro entorno.

Artículo 2: *Pin-Vieito N, García Nimo L, Bujanda L, et al. Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study. United European Gastroenterol J 2021; 9:256-267.*

c) Calcular el riesgo de detección de tumores del tracto gastrointestinal (TTGI) y muerte en pacientes con síntomas digestivos y una determinación de SOH-i positiva (concentración de Hb-f ≥ 20 µg Hb / g de heces) sin CCR.

Artículo 3: *Pin-Vieito N, Iglesias MJ, Remedios D, et al. Risk of gastrointestinal cancer in a symptomatic cohort after a complete colonoscopy: Role of faecal immunochemical test. World J Gastroenterol 2020;26:70-85.*

d) Estimar el riesgo de ser diagnosticado o morir por cáncer en pacientes sintomáticos con un nivel sérico de CEA elevado (> 3 ng/dL) y una colonoscopia normal.

Artículo 4: *Pin-Vieito N, Iglesias MJ, Remedios D, et al. Predictive Value of Carcinoembryonic Antigen in Symptomatic Patients without Colorectal Cancer: A Post-hoc Analysis within the COLONPREDICT Cohort. Diagnostics (Basel) 2020;10:1036.*

d) Realizar una revisión sistemática y en caso de ser posible un metaanálisis de aquellos trabajos que han estudiado la precisión de SOH-i en pacientes con síntomas digestivos en el entorno específico de atención primaria.

Artículo 5: *Pin-Vieito N, Tejido-Sandoval C, de Vicente-Bielza N, et al. Faecal immunochemical tests safely enhance rational use of resources during the assessment of suspected symptomatic colorectal cancer in primary care: systematic review and meta-analysis. Gut 2021; gutjnl-2021-324856. Epub ahead of print.*

METODOLOGÍA Y RESULTADOS

Metodología y resultados - Artículo 1

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Objetivo

Realizar una revisión sistemática y en caso de ser posible un metaanálisis de aquellos trabajos que han estudiado la precisión de SOH-i cuantitativo para detectar CCR en pacientes con síntomas digestivos. Evaluar la influencia de la forma de presentación del CCR en la precisión de SOH-i. Estimar la precisión de SOH-i para detectar cualquier LCS.

Métodos

Dos investigadores revisaron de forma independiente las bases de datos MEDLINE y EMBASE, ampliando la búsqueda a la bibliografía y autores de trabajos considerados relevantes [150]. Se incluyeron todos aquellos estudios transversales que evaluaban la precisión diagnóstica de SOH-i para detectar CCR en a) pacientes con síntomas digestivos (incluyendo además datos no publicados del estudio COLONPREDICT) o b) citados de forma consecutiva para realizar colonoscopia si incluían un porcentaje de sujetos sintomáticos. Se clasificaron los estudios por umbral y marca de SOH-i, además de porcentaje de síntomas y prevalencia de CCR.

Se evaluó la calidad de los artículos utilizando la herramienta Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [151]. El sesgo de publicación se valoró por medio de un gráfico de embudo invertido (Funnel plot).

Cuando cuatro o más estudios presentaron suficiente homogeneidad clínica y estadística, se utilizó el software STATA (v14) para aplicar el modelo bivariante y calcular los estimadores de sensibilidad y especificidad, con sus intervalos de confianza al 95% [152]. Además, se generaron curvas resumen de la precisión global siguiendo el modelo jerárquico (HSROC) [153]. Alternativamente, se utilizó un modelo de efectos

aleatorios siguiendo el método de DerSimonian con el software Meta-Disc (v1.4) [154], y se dibujaron curvas resumen (sROC) [155] utilizando el modelo de DerSimonian and Lair's para representar la precisión global mediante el área bajo la curva (AUC) o el índice Q (el punto de la curva en que la sensibilidad iguala la especificidad) [156,157].

Para el estudio de la heterogeneidad, además de la inspección visual de las estimaciones de sensibilidad y especificidad por medio de forest plot, se utilizaron test estadísticos (Q de Cochran y Ji-cuadrado) para valorar la existencia de heterogeneidad, tomando el índice de inconsistencia (I^2) como medida del grado de la misma [158].

El efecto umbral se valoró por medio de la correlación de Spearman ($p<0.1$ se considera significativo), y se utilizaron los espacios ROC para representar la sensibilidad frente 1-especificidad de cada estudio (una "imagen de hombro" sugiere la presencia de efecto umbral).

Resultados

Se incluyeron catorce estudios observacionales analíticos de cohortes prospectivas que cumplieron los criterios de inclusión además de los datos individuales del estudio COLONPREDICT [40,86,104,107,108,110,111,133,134,159-164], acumulando una muestra de 13,073 pacientes (58% mujeres) con un rango de edad media entre 59 y 67 años. La prevalencia de CCR fue variable entre 0.4 y 16.8%.

La sensibilidad global de OC-Sensor® disminuyó a medida que se usaron puntos de corte crecientes desde 98.2% (IC 95% 96.2-99.3%) para el punto de corte por encima del límite de detección de Hb-f hasta 90.3% (IC 95% 86.9-93.0%) a 20 µg Hb/g heces. Por otro lado, la especificidad global de OC-Sensor® aumenta desde 35.8% (IC 95% 34.2-37.3%) para el punto de corte por encima del límite de detección de Hb-f µg Hb /g

heces hasta 83.4% (IC 95% 82.5-84.2%) a 20 µg Hb /g heces. La mejor área bajo la curva se obtiene con los estudios que evalúan el punto de corte de 20 µg Hb/g heces (AUC = 0.93; IC 95% 0.91-0.96).

Se apreció una elevada heterogeneidad entre los diversos estudios, especialmente en las estimaciones de especificidad.

La sensibilidad global estimada para los trabajos que utilizaron OC-Sensor® como marca comercial de SOH-i en el punto de corte de 10 µg Hb/g heces (8 estudios; 10,400 pacientes) fue 89.6% (IC 95% 82.7-94.0%). En el análisis de sensibilidad, la estimación de sensibilidad en aquellos estudios realizados exclusivamente en pacientes sintomáticos (4 estudios; 4,035 pacientes) fue significativamente superior a la estimada en aquellos estudios realizados en cohortes de pacientes con y sin síntomas (4 estudios; 6,365 pacientes) (100% Sintomáticos: 94.1%; IC 95% 90.0-96.6% vs Mixtos: 85.5%; IC 95% 76.5-91.4%; p< 0.01). Sin embargo, no existieron diferencias significativas entre el subgrupo de estudios con prevalencia de CCR < 2.5% con respecto a aquéllos que tenían una prevalencia de CCR ≥ 2.5% (Prevalencia < 2.5%: 84.9; IC 95% 73.4-92.0% vs prevalencia ≥ 2.5%: 91.7%; IC 95% 83.3-96.1%; p=0.25).

Cuando se consideró el diagnóstico de cualquier LCS como objetivo, la sensibilidad global de OC-Sensor® disminuyó desde 91.7% (IC 95% 89.5-93.6%) para el punto de corte por encima del límite de detección de Hb-f hasta 78.6% (IC 95% 75.6-81.4%) usando el umbral de 10 µg Hb/g de heces. Por otro lado, la especificidad global de OC-Sensor® aumenta desde 36.9% (IC 95% 35.0-39.0%) para el punto de corte por encima del límite de detección de Hb-f µg/g hasta 69.8% (IC 95% 67.9-71.6%) si usamos el de 20 µg Hb/g de heces.

Conclusión

Este metaanálisis confirma que la SOH-i presenta una sensibilidad elevada y una especificidad moderada para la detección de CCR en pacientes sintomáticos. La precisión para descartar la presencia de CCR es mayor en aquellos estudios realizados en poblaciones formadas exclusivamente por sujetos con síntomas. La precisión de SOH-i para detectar LCS es moderada.

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META-ANALYSIS

High-risk symptoms and quantitative faecal immunochemical test accuracy: Systematic review and meta-analysis

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Abstract

BACKGROUND

The quantitative faecal immunochemical test for haemoglobin (FIT) has been revealed to be highly accurate for colorectal cancer (CRC) detection not only in a screening setting, but also in the assessment of patients presenting lower bowel symptoms. Therefore, the National Institute for Health and Care Excellence has recommended the adoption of FIT in primary care to guide referral for suspected CRC in low-risk symptomatic patients using a 10 μg Hb/g faeces threshold. Nevertheless, it is unknown whether FIT´s accuracy remains stable throughout the broad spectrum of possible symptoms.

AIM

To perform a systematic review and meta-analysis to assess FIT accuracy for CRC detection in different clinical settings.

METHODS

A systematic literature search was performed using MEDLINE and EMBASE databases from inception to May 2018 to conduct a meta-analysis of prospective studies including symptomatic patients that evaluated the diagnostic accuracy of quantitative FIT for CRC detection. Studies were classified on the basis of brand, threshold of faecal haemoglobin concentration for a positive test result, percentage of reported symptoms (solely symptomatic, mixed cohorts) and CRC prevalence (< 2.5%, ≥ 2.5%) to limit heterogeneity and perform subgroup analysis to assess the influence of clinical spectrum on FIT´s accuracy to detect CRC.

RESULTS

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Fifteen cohorts including 13073 patients (CRC prevalence 0.4% to 16.8%) were identified. Pooled estimates of sensitivity for studies using OC-Sensor at 10 μg Hb/g faeces threshold (n = 10400) was 89.6% [95% confidence interval (CI): 82.7% to 94.0%). However, pooled estimates of sensitivity for studies formed solely by symptomatic patients (n = 4035) and mixed cohorts (n = 6365) were 94.1% (95%CI: 90.0% to 96.6%) and 85.5% (95%CI: 76.5% to 91.4%) respectively (P < 0.01), while there were no statistically significant differences between pooled sensitivity of studies with CRC prevalence < 2.5% (84.9%, 95%CI: 73.4% to 92.0%) and ≥ 2.5% (91.7%, 95%CI: 83.3% to 96.1%) (P = 0.25). At the same threshold, OC-Sensor® sensitivity to rule out any significant colonic lesion was 78.6% (95%CI: 75.6% to 81.4%). We found substantial heterogeneity especially when assessing specificity.

CONCLUSION
The results of this meta-analysis confirm that, regardless of CRC prevalence, quantitative FIT is highly sensitive for CRC detection. However, FIT ability to rule out CRC is higher in studies solely including symptomatic patients.

Key words: Bowel disease; Colorectal cancer; Diagnostic accuracy; Faecal haemoglobin; Faecal immunochemical test; Faecal occult blood test; Inflammatory bowel disease; Significant colonic lesion

Core tip: The quantitative faecal immunochemical test for haemoglobin (FIT) has been recommended to guide referral for suspected colorectal cancer (CRC) in people with unexplained symptoms without rectal bleeding. However, the information regarding its accuracy in different settings is scarce. Our meta-analysis reveals that sensitivity for CRC may change across populations with differences in clinical symptoms, irrespective of CRC prevalence. On the other hand, we should not use this to rule out CRC if its prevalence is high. In addition, FIT is not sensitive enough to exclude other significant colonic diseases.

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INTRODUCTION

The quantitative faecal immunochemical test for haemoglobin (hereinafter referred to as 'FIT') has been revealed to be highly accurate for colorectal cancer (CRC) detection not only in a screening setting, but also in the assessment of patients presenting lower bowel symptoms[1,2]. Therefore, the National Institute for Health and Care Excellence (NICE) has recently recommended adoption of FIT in primary care to guide referral for suspected CRC in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral. Results should be reported using a threshold of 10 micrograms of haemoglobin per gram of faeces (μg Hb/g faeces)[3,4].

However, a clinical concern has been highlighted on transference of research results to clinical practice[3]. The NICE recommendation applies only to patients who present low-risk symptoms. In contrast, most available studies include patients who had symptoms (*e.g.*, rectal bleeding) associated with higher probability of CRC and most were performed in a secondary care setting. Although other population variables could be involved, this difference in the clinical spectrum could account for the high CRC prevalence shown in the meta-analysis used to support this recommendation (range 2.15% to 5.4%), compared to the estimated 1.5% for the relevant symptomatic group used in NICE guidance 'NG12'[5].

Thus, since the prevalence of the target condition may affect estimates of test performance by means of mechanisms other than patient spectrum[6], there is

insufficient information to elucidate whether the presence of high-risk symptoms or another clinical difference involving a higher CRC prevalence in the studies that fitted this meta-analysis inclusion criteria, will affect the expected performance of FIT in primary care. With the aim of assessing the stability of FIT´s accuracy across the broad spectrum of situations we could face outside a screening setting, we decided to perform an additional systematic review expanding upon previous inclusion criteria.

MATERIALS AND METHODS

We designed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct and report our systematic review[7].

Data sources and searches

We included all studies identified by a sensitive search of "FIT for CRC" in MEDLINE (*via* PubMed) and EMBASE (*via* Ovid) databases from inception to 21 May 2018. Data sources were also extended to the reference lists of all articles extracted from the search strategy detailed in Appendix 1.

Study selection

Two authors (NP and SZ) independently reviewed and screened titles and abstracts of articles retrieved and determined final eligibility by means of examination of full texts. Any disagreement was resolved through discussion or by consulting a third author (JC). We regarded studies as suitable for our review if they met all the following inclusion criteria:

Population, setting and study design

We included all prospective cohort studies performed on adult patients out of CRC screening programme setting either including patients: (1) Consulting with a physician for non-acute lower abdominal symptoms; or (2) consecutively scheduled for elective colonoscopy, when at least a fraction of symptomatic patients was included. No language restriction was applied.

Index test

Studies that evaluated the diagnostic accuracy of the quantitative FIT for CRC detection either reporting absolute numbers of true-positive, false-negative, true-negative, and false-positive observations, or data from which sensitivity and specificity could be extrapolated. In the case of studies reporting more than one FIT specimen, we only included the results of the first determination.

Reference test

We included studies that reported an appropriate reference standard (colonoscopy or ≥ 2-year longitudinal follow-up of the controls).

Endpoints

Our main objective was to estimate the diagnostic accuracy of FIT for CRC detection. Secondary goals included assessing the usefulness of FIT to detect advanced neoplasia (AN) and significant colonic lesions (SCLs) in symptomatic patients. The definitions of AN and SCL differ from country to country, which should be considered when interpreting data. This issue will be subsequently outlined in detail for each study.

Data extraction and risk of bias

One reviewer (NP) extracted data and extractions were checked by a second reviewer (JC); any disagreements were resolved by means of discussion and consensus. In each study, potential risks of bias were calculated using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2)[8]. An inverted funnel or "Christmas tree" scatterplot was used to detect publication bias.

Data synthesis and statistical analysis

We classified studies on the basis of brand and threshold of faecal haemoglobin (f-Hb) concentration for a positive test result to limit heterogeneity. When four or more studies on a specific subgroup were available, bivariate analyses were applied to calculate pooled estimates of sensitivity, specificity and likelihood ratios using the statistical software package STATA (v14)[9,10]. A hierarchical summary receiver operating characteristic (HSROC) curve was generated to present the summary estimates of sensitivities and specificities along with their corresponding 95% confidence interval (CI) and prediction region. An area under the HSROC curve

(AUC) between 0.9 and 1.0 indicated that diagnostic accuracy was good[11].

When a bivariate random-effects approach was not possible due to limited number of studies, we applied a random effects model following DerSimonian's method using MetaDisc software[12]. In that case a summary receiver operating characteristics (sROC) curve was plotted using DerSimonian and Lair's model to present summary sensitivity and specificity estimates through the AUC or Q* index[13-15].

Subgroup analysis

To determine whether FIT´s accuracy to detect CRC out of screening setting was influenced by high-risk symptoms, studies were classified by percentage of reported symptoms and CRC prevalence. Cohorts formed solely by patients who consult for abdominal symptoms represent a population with a better chance of high-risk symptoms of CRC (*e.g.*, rectal bleeding). Prespecified CRC prevalence values (< 2.5% and ≥ 2.5%) were used to ensure an adequate number of data sets for each analysis. A bivariate model was fitted for each subgroup; direct comparison between them was performed using STATA (xtmelogit command)[16].

Threshold effect and other sources of heterogeneity

Threshold effect was examined by calculating Spearman's rank correlation ($P < 0.1$ was considered to be statistically significant), and ROC space plots were used to represent the sensitivity against 1-specificity of each study. In addition to the visual inspection of the forest plots of accuracy estimates, statistical tests, including Chi-square and Cochran's *Q* tests, were used to ascertain whether inter-study differences were greater than expected based on chance alone ($P < 0.1$ suggested heterogeneity); the inconsistency index (*I2*) was used as a measure to quantify the degree of heterogeneity. The statistical methods of this study were reviewed by Noel Pin Vieito from Complexo Hospitalario Universitario de Ourense.

RESULTS

Literature search and study characteristics

Our initial literature search yielded a total of 12657 references. After abstract review, we identified 342 complete papers retrieved for manual searching, yielding 5919 additional potential sources of information; of these, 81 articles were selected for full-text review and 14 studies were ultimately considered relevant for our purpose (Figure 1)[17-30]. Inter-rater reliability was moderate (kappa 0.58). Individual unpublished data from derivation[29] and validation[31] cohorts included in the COLONPREDICT study were also used as these patients fitted the inclusion criteria. In total, 15 cohorts (13073 patients) were selected for qualitative synthesis. Full details of these studies are shown in Tables 1 and 2, and Appendix 2.

Quality assessment

The QUADAS-2 instrument highlighted an important risk of bias in the patient selection domain (Figure 2). Some patients could have been enrolled in a non-consecutive manner[17], and another five studies also evaluated diseases or situations that could compete with CRC as a cause of a positive FIT as exclusion criteria[18,21,22,24,25]. The greatest applicability concern arose from the patient selection category, as none of the samples analysed was fully representative of patients with low risk gastrointestinal symptoms reported in NG12[3].

Diagnostic performance for colorectal cancer

Table 3 and Figure 3 present summary sensitivity and specificity estimates calculated with a random effects model following the approach of DerSimonian's method for each screening modality using OC-Sensor®. Figure 4 shows the sROC curves at different thresholds. The highest AUC was obtained at a 20 μg Hb/g faeces threshold (AUC = 0.93, 95%CI 0.90-0.96). Furthermore, studies using OC-Sensor® with various thresholds higher than 20 μg Hb/g faeces[17,18,23], and also studies using HM-JACK®[19,24], HM-JACKarc®[28] and FOB Gold®[30] have been published but their data could not be pooled due to the scarce number of studies in those thresholds. Individual data are shown in Table 4.

Heterogeneity assessment

We found substantial heterogeneity between studies when calculating the pooled sensitivity for almost every threshold analysed in the studies evaluating OC-Sensor® (Table 3). Spearman's rank correlation coefficient was higher than 0.1, suggesting an absence of threshold effect in all cases. The scarce number of studies limited our intent to determine the existence of publication bias using funnel plots. However, when

Table 1 Characteristics of the studies included in the meta-analysis

Test	Study, Year	Demographic characteristics				CRC	AN	SC-L	Exclusion criteria			Symptoms, %							
		N	Age (m/-md)	Sex (W%)	Area	%	%	%	IBD	OB	AD	AnS	WeL	AbPa	Hem	ChBo	Co	Di	An
Mixed cohorts																			
OC-S	Rozen, 2010[17]	1682	63.7	49.6	IL	1.2	8.9	0	yes	yes	yes	23	NA	NA	0	NA	NA	NA	NA
OC-S	Mc Donald, 2012[20]	280	63[1]	59.6	UK (S)	2.1	NA	21.4	NA	no	no	NA	NA	NA	NA	NA	NA	NA	NA
OC-S	Ou, 2013[21]	694	59.5[1]	55.9	CN	0.4	6.1	NA	yes	yes	no	NA	NA	NA	NA	NA	NA	NA	NA
OC-S	van Turenhout, 2014[18]	3022	59.7	55.0	NL	2.3	12.3	NA	yes	yes	no	44	2.9	11.7	0	18.1	3	4.2	0
OC-S	Symonds, 2016[23]	1381	64.1[1]	50.6	AU	4.8	17.2	NA	no	no	no	34.8	NA	NA	NA	NA	NA	NA	NA
HM-J	Woo, 2005[19]	85	56[1]	52.9	KR	7.1	NA	NA	NA	no	no	49.4	0	15.3	4.7	1.2	0	17.6	4.7
HM-Ja	Auge, 2016[22]	208	63[1]	55.8	ES	1.0	14.0	NA	yes	yes	yes	NA	NA	NA	0	NA	NA	NA	NA
FOB Gold®	Auge, 2018[30]	487	62	51.2	ES	2.5	14.6	NA	no	no	yes	54.2	NA	NA	NA	NA	NA	NA	NA
100% Symptomatic cohorts																			
OC-S	Mowat, 2016[26]	750	64[1]	54.7	UK (S)	3.7	NA	13.6	no	no	no	100	0.9	11	34.2	42.8	NA	16.8	8.9
OC-S	Rodriguez-Alonso, 2015[25]	1003	NA	46.8	ES	3.0	13.3	23.4	yes	no	no	100	19	36.4	34.2	NA	12.1	23.5	8.8
OC-S	Cubiella, 2014 (DC)[29]	1567	66.9	48.6	ES	13.7	26.7	29.5	no	no	no	100	24.5	43.8	59.9	57.2	14.5	22.2	34.8
OC-S	Cubiella, 2017 (VC)[31]	715	64.4	53.3	ES	9.4	21.1	25.3	no	no	no	100	NA	NA	54	47.9	NA	NA	NA
HM-J	Parente, 2012[24]	280	67	43.9	IT	16.8	47.2	0	yes	no	no	100	11.1	17.9	26.1	23.9	NA	NA	15
HM-Ja	Godber, 2016[27]	484	59[1]	60.1	UK (S)	2.3	NA	9.3	no	no	no	100	1.7	18.8	15.9	39.7	NA	NA	4.8
HM-Ja	Widlack, 2017[28]	430	67[1]	51.0	UK (E)	5.6	NA	NA	no	no	no	100	15.8	30	43	64.2	NA	NA	17.2

[1]Age is expressed as median; AbPa: Abdominal pain; AD: Antithrombotic discontinuity; An: Anaemia; AN: advanced neoplasia; AnS: Any symptom; AU: Australia; CN: China; Co: Constipation; CRC: Colorectal cancer; ChBo: Change in bowel habit; DC: Derivation cohort; Di: Diarrhoea; ES: Spain; HM-J: HM-JACK®; HM-Ja: HM-JACKarc®; Hem: Haematochezia; IBD: Inflammatory bowel disease; IL: Israel; IT: Italy; KR: South Korea; m: mean; md: median; NA: Non-available; NL: Netherlands; OC-S: OC-Sensor®; OB: Overt bleeding; SCL: Significant colonic lesion; UK (E): United Kingdom (England); UK (S): United Kingdom (Scotland); VC: Validation cohort; W%: Women%; WeL: Weight loss.

plotting each study's diagnostic odds ratio (dOR) in a logarithmic scale against its sample size, we did not identify any trends towards asymmetry around the axis traced by the pooled dOR value for any analysed threshold, which suggests the absence of this possibility (Figure 5).

Subgroup and bivariate analysis

Although the number of studies limited our ability to use bivariate and HSROC models for most subgroups, the number of available studies performed with the OC-Sensor® enabled us to perform a subgroup analysis based on CRC prevalence and percentage of symptoms at the 10 μg Hb/g faeces threshold (10400 patients). Pooled estimates of sensitivity for studies comprised solely by symptomatic patients (n = 4035) and mixed cohorts (n = 6365) were 94.1% (95%CI: 90.0% to 96.6%) and 85.5% (95%CI: 76.5% to 91.4%) respectively (P < 0.01), while there were no statistically significant differences between pooled sensitivity of studies with CRC prevalence < 2.5% (84.9%, 95%CI: 73.4% to 92.0%) and ≥ 2.5% (91.7%, 95%CI: 83.3% to 96.1%) (P = 0.25). FIT sensitivity was equal or higher than 90% for almost every situation analysed (Table 3 and Figure 6).

Conversely, pooled specificities were significantly different when comparing studies both by percentage of symptoms (solely symptomatic = 66.0%; 95%CI: 47.1% to 80.9% *vs* lesser percentage of reported symptoms = 89.3%; 95%CI: 84.1% to 93.0%, P = 0.01) as by CRC prevalence (CRC prevalence < 2.5% = 90.5%; 95%CI: 89.0% to 91.9% *vs* CRC prevalence ≥ 2.5% = 69.3%; 95%CI: 53.5% to 81.6%, P < 0.01).

A comparison between summary sensitivity and specificity estimates calculated with both methods is shown in Table 5 and generated HSROC curves in Figure 7. OC-Sensor® accuracy parameters (threshold 10 μgHb/g faeces) estimated by bivariate model from both '100% symptomatic' and ´mixed cohort´ subgroups, were used to calculate different post-test probabilities through Fagan nomograms on the basis of various CRC prevalence (Figures 8 and 9).

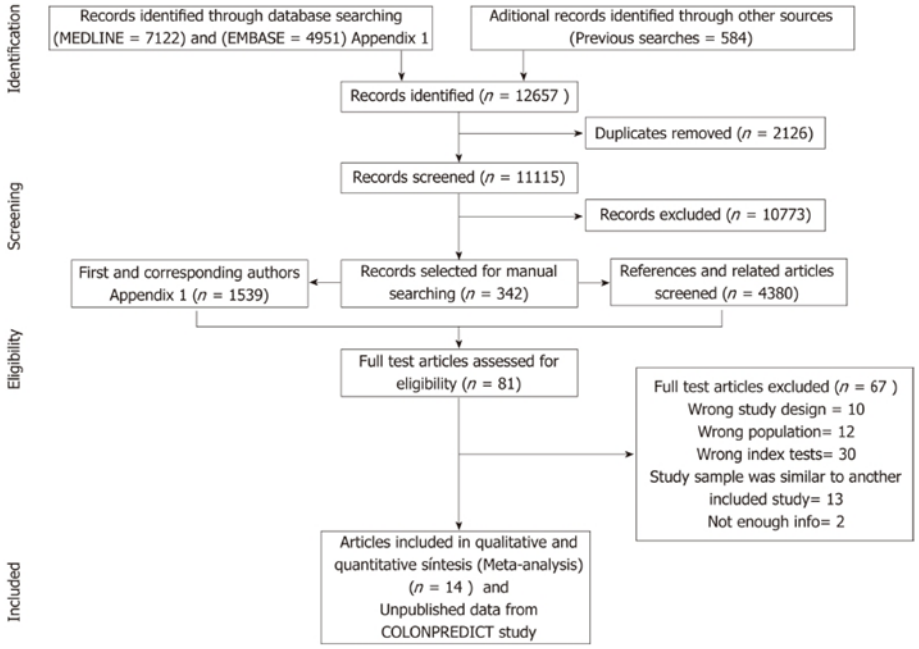

Figure 1 Summary of evidence search and selection.

Secondary endpoints: diagnostic performance for AN and SCL

Besides the COLONPREDICT study cohorts[29,31], nine[17,19-22,24-26,30] and four[20,26-28] studies provided information on the FIT's accuracy for AN and SCL detection, respectively, with heterogeneous definitions. Furthermore, Terhaar sive Droste *et al*[32] published data on FIT´s accuracy for AN detection in 2145 patients included in van Turenhout´s study[18]. AN was defined as CRC plus high-risk[19-21,26] *vs* advanced[17,22,24,25,30-32] adenoma. This variability was greater for the definition of SCL. Some studies defined SCL as cancer plus high-risk adenoma plus inflammatory bowel disease[20,26], whereas Godber *et al*[27] expanded that definition to include other types of colitis. A broader definition was used by Cubiella *et al*[29,31] including CRC, advanced adenoma, polyposis, colitis, polyps ≥ 10 mm, complicated diverticular disease, colonic ulcer and bleeding angiodysplasia. Auge *et al*[30] provided data about FOB Gold® accuracy for colonic lesion detection regardless of its importance. Finally, as long as Widlack *et al*[28] added a single case of high-grade dysplasia to 24 cases of CRC, we decided to include their study within the CRC group.

Summary sensitivity and specificity estimates for AN and SCL detection are shown in Table 6. Once again, studies evaluating OC-Sensor® with different thresholds[17,21,29,31,32], HM-JACK®[24], HM-JACKarc®[22,27] or FOB Gold®[30] have been published but their number was insufficient to enable pooling of data in homogeneous groups. Individual data are shown in Tables 7 and 8.

DISCUSSION

Statement of principal findings

This meta-analysis confirms that FIT is useful for triaging referrals in people with lower abdominal symptoms. Most studies have been performed using OC-Sensor® assay; using this brand, the high pooled estimates of sensitivity for CRC shown at f-Hb thresholds from limit of detection (LoD) to 20 μg Hb/g faeces, demonstrates this brand's ability to stratify which symptomatic patients are more likely to have CRC.

Furthermore, the optimal OC-Sensor® performance (maximising both sensitivity and specificity) appeared to occur with f-Hb thresholds between 10 and 20 μg Hb/g faeces as FIT specificity is too low at a LoD f-Hb threshold. Since fewer cases of CRC will be missed with the former, 10 μg Hb/g faeces may be the most suitable threshold for CRC assessment of patients with symptoms (sROC AUC 0.92). In fact, subgroup analysis at this threshold demonstrates that regardless of CRC prevalence, summary

Table 2 Possibility of data extraction on the accuracy of quantitative faecal immunochemical test for haemoglobin for detecting colorectal cancer, advanced neoplasia and significant colonic lesion

Study	CRC							AN							SCL						
	Threshold (U)					SxD	SD	Threshold (U)					SxD		Threshold (U)					SxD	
	0	10	15	20	Other			0	10	15	20	Other			0	10	15	20	Other		
Rozen, 2010[17]		x	x	x	25; 30; 40				x	x	x	25; 30; 40									
Van Turenhout, 2014[18]		x	x	x	40	x															
Mc Donald, 2012[20]		x							HRA							x					
Ou, 2013[21]					5							5; HRA									
Symonds, 2016[23]		x			60; 80		x														
Auge, 2016[22]								x	x		x	30; 40	x								
Woo, 2005[19]					33							3; HRA									
Auge, 2018[30]		x		x	30; 40; 50; 60		x		x		x	30; 40; 50; 60				x		x	30; 40; 50; 60		
Cubiella, 2014 (DC)[29]	x	x	x	x		x		x	x	x	x		x	x	x	x	x			x	
Cubiella, 2016 (VC)[31]	x	x	x	x		x		x	x	x	x		x	x	x	x	x			x	
Rodríguez-Alonso 2015[25]	x	x	x	x				x	x	x	x										
Mowat, 2016[26]	x	x						HRA	HRA					x	x						
Parente, 2012[24]				x							x										
Godber, 2016[27]															x	x	x	25; 30; 35; 40			
Widlack, 2017[28]																		7; HGD			

AN: Advanced neoplasia; CRC: Colorectal cancer; DC: Derivation cohort; HDG: High-grade dysplasia; HRA: High risk adenoma; SCL: Significant colonic lesion; SxD and SD: Differences between sex and stage respectively can be calculated VC: Validation cohort; (U): Threshold units: µgrams of haemoglobin per gram of faeces.

estimates of sensitivity are higher when calculated from studies where all patients are overtly symptomatic than from mixed cohorts. Moreover, if we aim to rule out not only CRC but also other SCL using the same threshold, OC-Sensor® accuracy decreases showing lower sensitivities without improving specificity.

Finally, although information related to FIT accuracy to detect different targets have been reported using other brands and thresholds (HM-JACK, HM-JACKarc and FOB Gold), we could not pool their data due to the scarce number of homogeneous studies. Consequently, we could not assume the same degree of evidence for them.

Strengths and weaknesses

The limited number of studies did not enable us to tackle the high expected heterogeneity for all the different thresholds and assays available. Several factors could account for the heterogeneity detected: CRC prevalence[33], demographic characteristics[34], tumour location and stage[35], sample contamination (*e.g.*, haemorrhoids)[36], or FITs[37]. As reported in Table 1, there were many inter-study differences, but the low number of studies included in our review did not enable us to perform a subgroup analysis for most of them. This also limited our ability to conduct statistical pooling using bivariate and HSROC models, which offer the strongest conclusions regarding diagnostic performance. In contrast, random effects methods incorporate a slight degree of heterogeneity among study results[38]. Where possible, we applied both models to calculate pooled estimates of accuracy showing very similar results. Despite this, the strategy to include both studies performed on different percentages of symptomatic patients and the individual data of the COLONPREDICT study[31], enabled us to determine the diagnostic accuracy of the FIT at different thresholds and check the test's diagnostic accuracy at different patient spectra with a different percentage of symptomatic patients and CRC prevalence.

An additional focal point of our review was to ascertain whether all FIT brands shared similar accuracy values. Only four studies with varying thresholds and settings reported the accuracy parameters of the HM-JACK®[19,24] HM-JACKarc®[28] and FOB Gold®[30] systems to detect CRC and no study to date has directly compared the

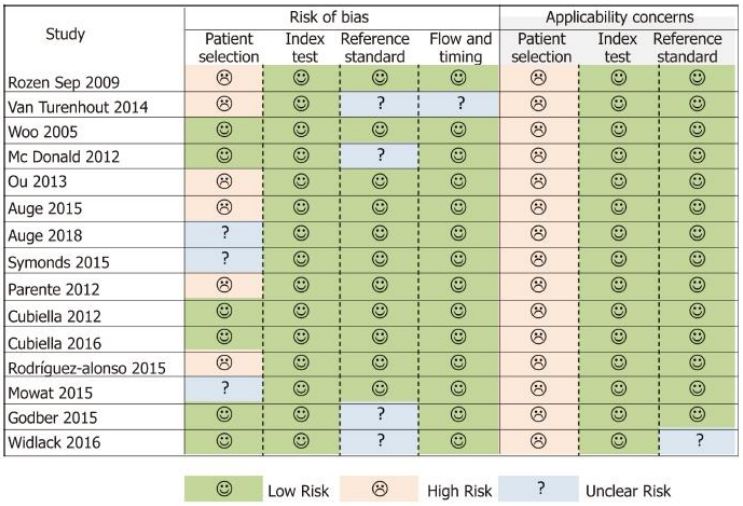

Figure 2 Quality Assessment of Diagnostic Accuracy Studies.

performance of different FITs. Finally, we evaluated the diagnostic performance of the FIT in detecting SCLs. However, we must highlight that the main limitations of our analysis were the varying definitions and diagnostic criteria for both advanced (or high-risk) adenoma and SCL among the studies.

Strengths and weaknesses in relation to other studies

A prior systematic review assessed the value of symptoms and additional diagnostic tests for CRC assessing, including FIT, in symptomatic primary care patients[39]. This review was completed in 2008 and included only three studies involving quantitative FITs. Another systematic review[3] was recently performed to provide information on the new NICE DG30 diagnostic guidelines[4]. We expanded previous inclusion criteria to assess the performance of FIT on samples with different percentage of symptoms and CRC prevalence, since the population included in that meta-analysis was not representative of the criteria reported in NG12[3]. In fact, the studies included had major variability in terms of CRC prevalence[6].

Moreover, to ascertain whether FIT´s accuracy to detect CRC changes in symptomatic patients may be challenging. There are few studies on heterogeneous populations outside a screening setting and categorising those studies according to the presence and type of symptoms is difficult due to unspecific abdominal symptoms commonly associated with bowel cancer (such as abdominal pain or changing bowel habit) are common and sometimes unreported among apparently healthy people[40]. This not only diminishes the value of symptoms as a diagnostic tool as previously reported[39,41,42], but means that even a significant proportion of individuals taking part in CRC screening programmes could suffer from unreported lower gastrointestinal symptoms. This could also explain why in some studies SCL prevalence has been revealed to be similar between patients suffering from nonspecific abdominal symptoms and supposedly 'asymptomatic' symptoms, unlike what is expected[43,44].

Our results suggest that although FIT may play a key role in the evaluation of symptomatic patients, it should not be used alone to rule out CRC. In fact, FIT should be interpreted considering the whole clinical spectrum including variables such as sex and age[34]. Moreover, high-risk symptoms like rectal bleeding or diarrhoea may affect the amount of f-Hb detected. FIT accuracy could be higher in this setting than in unspecific low-risk symptoms which are also more in line with the NG12 scenario reported[3].

This clinical concern may affect the expected number of missed CRC as previously discussed elsewhere[5]. Therefore, we checked the performance of FIT in different theoretical situations defined in Figure 8 by means of what we try to represent as the sources of uncertainty of actual decision-making. For example, if we 'erroneously' assumed that FIT sensitivity to rule out CRC is 94.1% for any symptomatic patient after being estimated by pooling '100% symptomatic' studies which have higher percentages of high-risk symptoms such as rectal bleeding, but the 'true value' were 85.5% (estimated by 'mixed cohorts') we would miss 1, 2 and 10 unexpected additional CRCs in populations with a CRC prevalence of 1%, 3% and 13%,

Table 3 Colorectal cancer detection: Diagnostic accuracy parameters based on quantitative faecal immunochemical test for haemoglobin threshold concentration and brand (DerSimonian´s method)"

Variable	Studies (*n*)	Sensitivity[1]	I^2[2]	Specificity[1]	I^2[2]	Positive LR[3]	I^2[2]	Negative LR[3]	I^2[2]	Diagnostic OR[3]	I^2[2]	*P*[3]
OC-Sensor, > LoD μg Hb/g faeces												
All studies	4	98.2 (96.2-99.3)	0.0	35.8 (34.2-37.3)	96.1	1.55 (1.37-1.75)	94.2	0.07 (0.03-0.14)	0.0	21.41 (10.07-45.5)	0.0	0.6
OC-Sensor, ≥ 10 μg Hb/g faeces												
All studies	8	90.8 (87.9-93.2)	69.7	79.9 (79.1-80.7)	99.4	4.79 (2.96-7.76)	99.1	0.15 (0.09-0.23)	52.7	31.44 (19.50-50.68)	44.7	0.09
100% Symptomatic	4	94.4 (91.4-96.6)	0.0	65.9 (64.4-67.4)	99.3	2.97 (1.78-4.95)	99.0	0.10 (0.06-0.15)	0.0	28.49 (17.77-45.67)	0.0	0.6
Mixed patients	4	83.2 (76.5-88.6)	44.5	88.2 (87.4-89.0)	96.7	7.78 (4.72-12.82)	95.1	0.21 (0.13-0.33)	30.7	35.36 (14.19-88.10)	71.0	0.6
CRC prevalence ≥ 2.5%	5	91.9 (88.7-94.3)	76.0	69.7 (68.5-71.0)	99.2	3.16 (1.99-5.0)	98.8	0.13 (0.07-0.25)	66.5	23.20 (14.76-36.47)	20.0	0.2
CRC prevalence < 2.5%	3	86.3 (77.7-92.5)	48.0	90.2 (89.4-91.1)	72.6	9.21 (7.23-11.74)	55.1	0.17 (0.09-0.33)	26.4	52.33 (27.23-100.58)	10.0	0.7
OC-Sensor, ≥ 15 μg Hb/g faeces												
All studies	5	91.0 (87.8-93.6)	73.3	81.8 (80.9-82.7)	99.7	4.77 (2.34-9.71)	99.4	0.15 (0.09-0.25)	57.3	36.64 (20.43-65.71)	49.7	0.04
100% Symptomatic[4]	3	93.6 (90.2-96.0)	32.6	65.8 (64.1-67.5)	99.5	2.91 (1.46-5.78)	99.3	0.11 (0.07-0.16)	0.0	29.10 (12.74-66.46)	35.5	0.67
OC-Sensor, ≥ 20 μg Hb/g faeces												
All studies	5	90.3 (86.9-93.0)	75.6(86.9-93.0)	83.4 (82.5-84.2)	99.7	5.30 (2.47-11.34)	99.4	0.15 (0.09-0.27)	67.2	39.02 (21.48-70.88)	56.1	0.04
100% Symptomatic[4]	3	92.9 (89.5-95.5)	26.1	68.0 (66.3-69.7)	99.5	3.14 (1.52-6.50)	99.3	0.11 (0.07-0.17)	0.0	29.81 (15.05-59.04)	29.2	0.67

[1]Values are expressed as percentages and its 95% confidence interval;
[2]Values are expressed as percentages;
[3]Values are expressed as absolute numbers and its 95% confidence interval;
[4]The studies that comprise the 100% symptomatic subgroup also have colorectal cancer prevalence ≥ 2.5%; *P*[a]: Significance of the threshold effect using the Spearman rank correlation ($P < 0.01$ is considered statistically significant). I^2: Inconsistency index; LoD: Limit of detection; LR: Likelihood ratio; OR: Odds ratio; CRC: Colorectal cancer.

respectively, for each 1000 symptomatic patients with CRC assessed.

Nevertheless, it is important to note that the aim of performing a FIT in a symptomatic patient is not only to rule out CRC as long as other conditions, such as IBD, may also present the same symptoms. Unfortunately, we could only estimate the pooled accuracy parameters of three studies performed with the OC-Sensor® at LoD and 10 μg Hb/g faeces thresholds respectively, with sensitivity estimates ranging from 91.7% to 80.4%. Despite the weakness previously discussed, these results are consistent with the results of Hogberg *et al*'s study[45], which demonstrated that a qualitative FIT with a LoD f-Hb threshold could identify 87.5% and 90% of cases of CRC and IBD in unselected primary care patients, respectively.

Unanswered questions and future research

Although our results support the use of FIT in optimising the number of urgent referrals and helping to define a patient cohort with a negligible risk of CRC that would not require any referral, caution is recommended when using it outside the screening setting for symptomatic patients. FIT´s accuracy for detecting SCL appears to be not equally reliable in every patient subgroup. Finally, whether to exclude the use of further diagnostic tests in symptomatic patients with high CRC prevalence is doubtful, especially if symptoms persist. Thus, existing FIT-based prediction models[25,31,46] and recently published results[47,48] should also be validated directly, comparing different FIT brands and stratifying by clinical spectrum, while future biomarkers[49,50] should also be evaluated and compared with the FIT to incorporate objective criteria that can safely rule out CRC diagnosis.

In conclusion, our meta-analysis reveals that sensitivity for CRC may change across populations with differences in clinical symptoms, irrespective of CRC prevalence. In addition, FIT is not sensitive enough to exclude other significant colonic diseases. Future studies solely concerned with patients consulting for low risk symptoms are needed to better assess the role of FIT in ruling out CRC in this subgroup. Meanwhile,

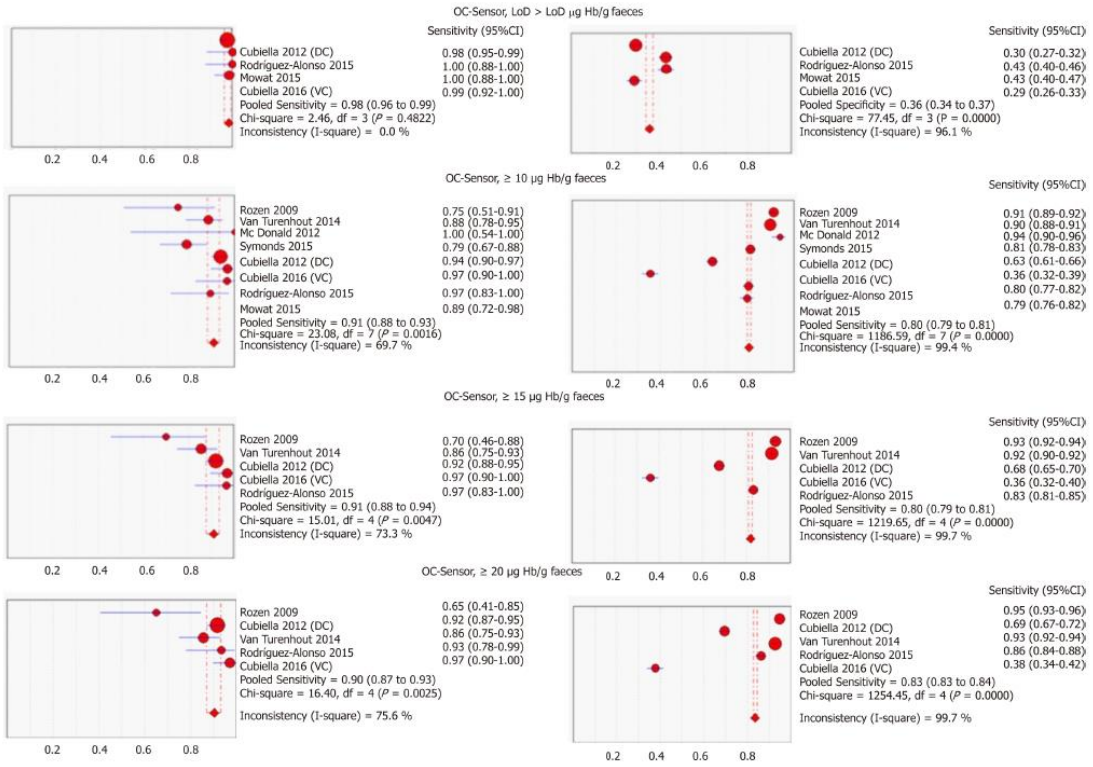

Figure 3 Pooled sensitivity and specificity of faecal immunochemical tests for colorectal cancer detection based on threshold and branch (DerSimonian´s method). CI: Confidence interval; DC: Derivation cohort; VC: Validation cohort.

a single f-Hb cut-off of 10 mg Hb/g faeces could be used in this population to identify which patients may benefit from a "watching and waiting" strategy without this involving to avoid further workup, irrespective of FIT result, if there is no response to treatment.

Table 4 Diagnostic accuracy parameters for colorectal cancer detection based on quantitative faecal immunochemical test for haemoglobin threshold concentration and brand

Brand	Threshold(μg/g faeces)	Author, year	Sensitivity[1]	Specificity[1]
Mixed cohorts				
OC-Sensor®	25	Rozen, 2010[17]	60.0 (36.1-80.9)	95.2 (94.0-96.2)
OC-Sensor®	30	Rozen, 2010[17]	55.0 (31.5-76.9)	95.8 (94.7-96.7)
OC-Sensor®	40	Rozen, 2010[17]	55.0 (31.5-76.9)	96.3 (95.3-97.2)
OC-Sensor®	40	van Turenhout, 2014[18]	75.4 (63.5-84.9)	94.8 (93.9-95.6)
OC-Sensor®	60	Symonds 2016[23]	63.6 (50.9-75.1)	91.9 (90.3-93.3)
OC-Sensor®	80	Symonds 2016[23]	59.1 (46.3-71.0)	93.4 (91.9-94.7)
HM-JACK®	33	Woo, 2005[19]	50.0 (11.8-88.2)	83.5 (73.5-90.9)
FOB Gold®	10	Auge, 2018[30]	91.7 (71.5-98.5)	82.2 (79.6-84.5)
FOB Gold®	20	Auge, 2018[30]	87.5 (66.5-96.7)	86.0 (83.6-88.1)
FOB Gold®	30	Auge, 2018[30]	83.3 (61.8-94.5)	89.2 (87.0-91.1)
FOB Gold®	40	Auge, 2018[30]	83.3 (61.8-94.5)	90.3 (88.2-92.1)
FOB Gold®	50	Auge, 2018[30]	83.3 (61.8-94.5)	91.4 (89.4-93.1)
FOB Gold®	60	Auge, 2018[30]	83.3 (61.8-94.5)	91.8 (89.9-93.5)
100% Symptomatic				
HM-JACK®	20	Parente, 2012[24]	61.7 (46.4-75.5)	88.8 (84.1-92.6)
HM-JACKarc®	7	Widlak, 2017[28]	84.0 (63.9-95.5)	93.1 (90.2-95.4)

[1]Values are expressed as percentages and its 95% confidence interval.

Table 5 OC-Sensor® diagnostic accuracy parameters for colorectal cancer detection (Threshold 10 μg Hb/g faeces) estimated with DerSimonian *vs* Bivariate methods

Variable	Studies (*n*)	Sensitivity[1]	Specificity[1]	Positive LR[2]	Negative LR[2]	Diagnostic OR[2]
All studies (DS)	8	90.8 (87.9-93.2)	79.9 (79.1-80.7)	4.79 (2.96-7.76)	0.15 (0.09-0.23)	31.44 (19.50-50.68)
All studies (Bv)	8	89.6 (82.7-94.0)	80.2 (67.2-88.9)	4.52 (2.73-7.50)	0.13 (0.08-0.20)	34.85 (20.74-58.57)
100% Symptomatic (DS)	4	94.4 (91.4-96.6)	65.9 (64.4-67.4)	2.97 (1.78-4.95)	0.10 (0.06-0.15)	28.49 (17.77-45.67)
100% Symptomatic (Bv)	4	94.1 (90.0-96.6)	66.0 (47.1-80.9)	2.77 (1.69-4.55)	0.09 (0.06-0.14)	30.93 (16.09-59.45)
Mixed patients (DS)	4	83.2 (76.5-88.6)	88.2 (87.4-89.0)	7.78 (4.72-12.82)	0.21 (0.13-0.33)	35.36 (14.19-88.10)
Mixed patients (Bv)	4	85.5 (76.5-91.4)	89.3 (84.1-93.0)	8.01 (5.07-12.65)	0.16 (0.10-0.28)	49.35 (19.88-122.5)
CRC prevalence ≥ 2.5% (DS)	5	91.9 (88.7-94.3)	69.7 (68.5-71.0)	3.16 (1.99-5.0)	0.13 (0.07-0.25)	23.20 (14.76-36.47)
CRC prevalence ≥ 2.5% (Bv)	5	91.7 (83.3-96.1)	69.3 (53.5-81.6)	2.99 (1.97-4.53)	0.12 (0.07-0.21)	24.95 (16.02-38.86)
CRC prevalence < 2.5% (DS)	3	86.3 (77.7-92.5)	90.2 (89.4-91.1)	9.21 (7.23-11.74)	0.17 (0.09-0.33)	52.33 (27.23-100.58)
CRC prevalence < 2.5% (Bv)	3	84.9 (73.4-92.0)	90.5 (89.0-91.9)	8.96 (7.63-10.53)	0.17 (0.09-0.30)	53.77 (26.99-107.11)

[1]Values are expressed as percentages and its 95% confidence interval;
[2]Values are expressed as absolute numbers and its 95% confidence interval. Bv: Bivariate; CRC: Colorectal cancer; D: DerSimonian; LR: Likelihood ratio; OR: Odds ratio.

Table 6 Advanced neoplasia and significant colonic lesion detection: Diagnostic accuracy parameters based on quantitative faecal immunochemical test threshold concentration and brand (DerSimonian´s method)

Variable	Studies,*n*	Sensitivity[1]	I^2[2]	Specificity[1]	I^2[2]	Positive LR[3]	I^2[2]	Negative LR[3]	I^2[2]	Diagnostic OR[3]	I^2[2]	*P*[3]
Advanced neoplasia												
OC-Sensor, > LoD μg Hb/g faeces												
All studies	3	91.0 (88.7-93.0)	87.9	36.9 (35.0-38.8)	95.2	1.40 (1.35-1.45)	0.0	0.26 (0.16-0.44)	76.6	5.44 (3.48-8.48)	58	< 0.001
OC-Sensor, ≥ 10 μg Hb/g faeces												
All studies	5	67.9 (65.1-70.5)	97.4	81.0 (80.0-82.0)	99.5	3.42 (1.97-5.94)	98.8	0.41 (0.30-0.57)	93.4	9.43 (8.10-10.98)	0.0	< 0.001

100% Symptomatic	3	79.7 (76.5-82.6)	94.6	67.3 (65.5-69.1)	99.4	2.43 (1.41-4.17)	98.5	0.32 (0.21-0.49)	86.5	8.67 (6.96-10.80)	5.8	< 0.001
Prevalence CRC ≥ 2.5%	4	71.7 (68.8-74.5)	97.1	76.7 (75.4-77.9)	99.5	2.96 (1.65-5.30)	98.9	0.36 (0.25-0.53)	91.8	9.29 (7.79-11.09)	9.3	< 0.001
OC-Sensor, ≥ 15 μg Hb/g faeces												
All studies	5	65.0 (62.2-67.8)	97.6	83.5 (82.5-84.4)	99.6	3.90 (2.04-7.47)	99.0	0.43 (0.31-0.60)	94.2	10.06 (8.14-12.44)	42.4	< 0.001
100% Symptomatic	3	76.8 (73.5-79.9)	95.6	70.3 (68.5-72.1)	99.4	2.63 (1.39-4.97)	98.8	0.34 (0.22-0.52)	88.4	8.88 (7.23-10.91)	0.0	< 0.001
Prevalence CRC ≥ 2.5%	4	69.3 (66.3-72.1)	97.1	79.4 (78.2-80.6)	99.6	3.33 (1.67-6.66)	99.1	0.38 (0.27-0.54)	91.1	9.72 (7.46-12.66)	55.4	< 0.001
OC-Sensor, ≥ 20 μg Hb/g faeces												
All studies	5	62.9 (60.1-65.7)	97.8	85.1 (84.2-86.0)	99.6	4.34 (2.16-8.73)	99.0	0.45 (0.32-0.62)	95.3	10.62 (8.24-13.67)	57.4	< 0.001
100% Symptomatic	3	75.1 (71.7-78.3)	96.1	72.4 (70.7-74.1)	99.5	2.85 (1.43-5.65)	98.8	0.35 (0.23-0.55)	90.4	9.19 (7.47-11.32)	1.8	< 0.001
Prevalence CRC ≥ 2.5%	4	67.5 (64.5-70.4)	97.3	81.2 (80.0-82.3)	99.6	3.66 (1.74-7.71)	99.1	0.40 (0.29-0.55)	91.7	10.19 (7.49-13.86)	66.5	< 0.001
Significant colonic lesion												
OC-Sensor, LoD μg Hb/g faeces												
All studies	3	91.7 (89.5-93.6)	0.0	36.9 (35.0-39.0)	94.2	1.45 (1.32-1.59)	80.4	0.24 (0.19-0.30)	0.0	6.01 (4.57-7.92)	0.0	< 0.001
OC-Sensor, ≥ 10 μg Hb/g faeces												
All studies	4	78.6 (75.6-81.4)	91.5	69.8 (67.9-71.6)	99.2	3.75 (2.08-6.76)	98.3	0.34 (0.27-0.42)	59.6	11.72 (6.41-21.45)	82.8	< 0.001
100% Symptomatic[4]	3	80.4 (77.4-83.2)	89.6	67.0 (65.0-68.9)	99.2	2.54 (1.45-4.46)	98.5	0.31 (0.26-0.37)	23.7	8.56 (6.18-11.86)	49.8	< 0.001

[1]Values are expressed as percentages and its 95% confidence interval;
[2]Values are expressed as percentages;
[3]Values are expressed as absolute numbers and its 95% confidence interval;
[4]The studies that comprise the 100% symptomatic subgroup also have CRC prevalence ≥ 2.5%; *P*[a]: Significance of the threshold effect using the Spearman rank correlation ($P < 0.01$ is considered statistically significant). *I2*: Inconsistency index; LoD: Limit of detection; LR: Likelihood ratio; OR: Odds ratio; CRC: Colorectal cancer.

Table 7 Diagnostic accuracy parameters for advanced neoplasia detection based on quantitative faecal immunochemical test for haemoglobin threshold concentration and brand

Brand	Threshold(μg/g faeces)	Author, year	Sensitivity[1]	Specificity[1]
		Mixed cohorts		
OC-Sensor®	5	Ou, 2013[21]	56.8 (39.5-72.9)	88.7 (85.7-91.2)
OC-Sensor®	25	Rozen, 2010[17]	27.5 (20.3-34.7)	96.7 (95.8-97.6)
OC-Sensor®	25	Terhaar sive Droste, 2010[32]	48.3 (42.6-53.9)	94.3 (93.2-95.3)
OC-Sensor®	30	Rozen, 2010[17]	26.8 (19.9-34.7)	97.3 (96.5-98.1)
OC-Sensor®	30	Terhaar sive Droste, 2010[32]	46.0 (40.4-51.7)	95.1 (94.1-96.1)
OC-Sensor®	40	Rozen, 2010[17]	26.2 (19.1-33.2)	97.8 (97.0-98.5)
OC-Sensor®	40	Terhaar sive Droste, 2010[32]	43.2 (37.6-48.9)	95.8 (94.8-96.7)
HM-JACKarc®	LoD	Auge, 2016[22]	96.6 (82.8-93.4)	10.6 (6.9-15.9)
HM-JACKarc®	10	Auge, 2016[22]	34.5 (19.9-52.7)	87.2 (81.6-91.3)
HM-JACKarc®	20	Auge, 2016[22]	31.0 (17.3-49.2)	92.8 (88.0-95.7)
HM-JACKarc®	30	Auge, 2016[22]	31.0 (17.3-49.2)	93.3 (88.7-96.1)
HM-JACKarc®	40	Auge, 2016[22]	27.6 (14.7-45.7)	93.9 (89.4-96.6)
FOB Gold®	10	Auge, 2018[30]	45.7 (33.7-58.1)	84.7 (80.8-88.0)
FOB Gold®	20	Auge, 2018[30]	37.1 (26.1-49.6)	87.9 (84.2-90.8)
FOB Gold®	30	Auge, 2018[30]	35.7 (24.6-48.1)	90.3 (87.0-93.1)
FOB Gold®	40	Auge, 2018[30]	32.9 (22.4-45.2)	91.1 (87.8-93.6)
FOB Gold®	50	Auge, 2018[30]	31.4 (20.9-43.6)	92.3 (89.3-94.7)
FOB Gold®	60	Auge, 2018[30]	30.0 (19.9-42.3)	92.3 (89.2-94.6)
		100% symptomatic		

HM-JACK®	20	Parente, 2012[24]	35.6 (27.9-44.1)	94.5 (89.7-97.2)

[1]Values are expressed as percentages and its 95% confidence interval.

Table 8 Diagnostic accuracy parameters for significant colonic lesion detection based on quantitative faecal immunochemical test for haemoglobin threshold concentration and brand

Brand	Threshold(μg/g faeces)	Author, year	Sensitivity[1]	Specificity[1]
Significant colonic lesion (100% symptomatic)				
OC-Sensor®	15	Cubiella (DC), 2014[29]	76.2 (72.0-80.0)	74.4 (71.7-76.9)
OC-Sensor®	15	Cubiella (VC), 2017[31]	89.5 (84.1-93.6)	40.6 (36.4-44.9)
OC-Sensor®	20	Cubiella (DC), 2014[29]	74.7 (70.5-78.6)	76.1 (73.5-78.6)
OC-Sensor®	20	Cubiella (VC), 2017[31]	87.8 (82.2-92.2)	42.1 (37.9-46.5)
HM-JACKarc®	10	Godber, 2016[27]	68.9 (53.2-81.4)	80.2 (76.1-83.7)
HM-JACKarc®	15	Godber, 2016[27]	66.7 (50.9-79.6)	83.1 (79.2-86.5)
HM-JACKarc®	20	Godber, 2016[27]	64.4 (48.7-77.7)	85.7 (81.9-88.7)
HM-JACKarc®	25	Godber, 2016[27]	64.4 (48.7-77.7)	87.5 (83.9-90.3)
HM-JACKarc®	30	Godber, 2016[27]	64.4 (48.7-77.7)	88.6 (85.2-91.4)
HM-JACKarc®	35	Godber, 2016[27]	64.4 (48.7-77.7)	89.2 (85.9-92.0)
HM-JACKarc®	40	Godber, 2016[27]	64.4 (48.7-77.7)	90.0 (86.7-92.5)

[1]Values are expressed as percentages and their 95% confidence interval. DC: Derivation cohort; VC: Validation cohort.

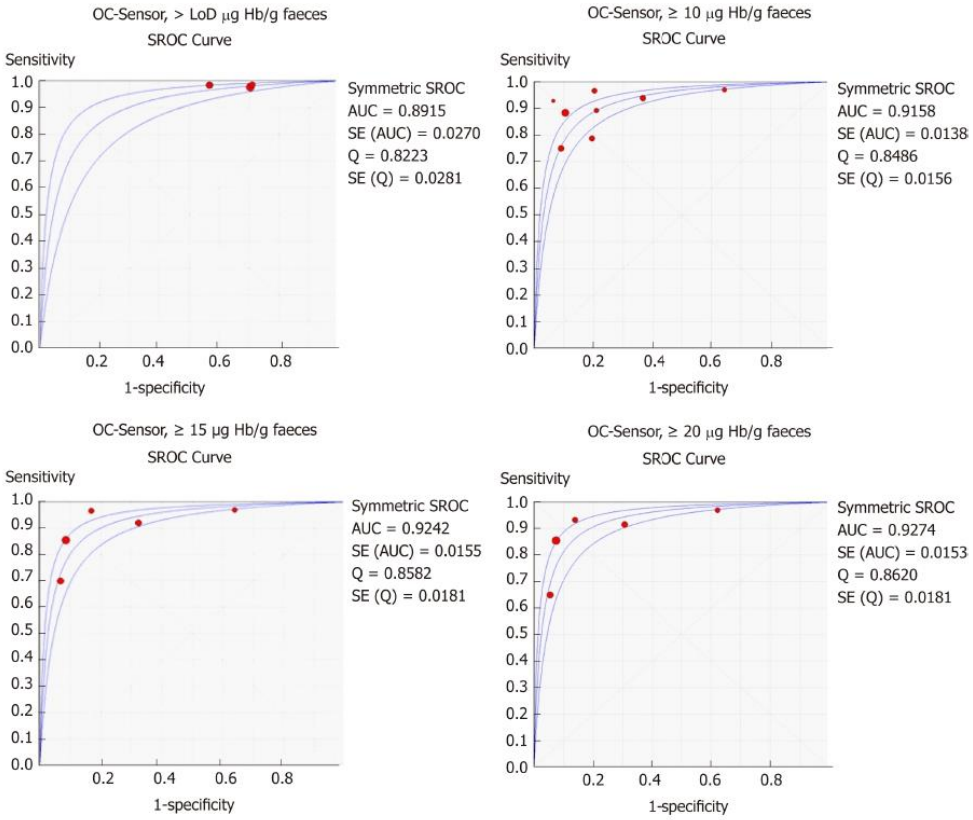

Figure 4 Summary receiver operating characteristic curve for colorectal cancer detection at different thresholds and branches (DerSimmonian and Lair´s model). LoD: Limit of detection; AUC: Area under the curve; SROC: Summary receiver operating characteristic.

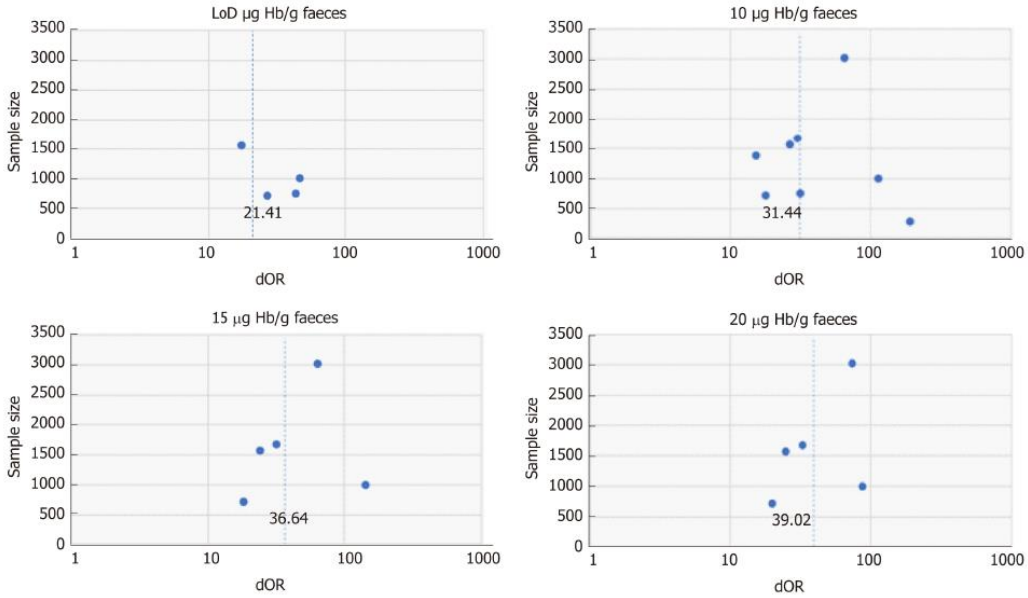

Figure 5 Funnel scatterplot to evaluate publication bias for studies using OC-Sensor® with different thresholds to detect colorectal cancer. Each point in the plot represents a study with its diagnostic odds ratio (dOR) and sample size. A symmetric image around an axis traced by the pooled dOR value suggests absence of publication bias. Asymmetry with study concentration on the right side (the side with higher diagnostic odds ratio values) suggests publication bias with less negative studies published. dOR: Diagnostic odds ratio.

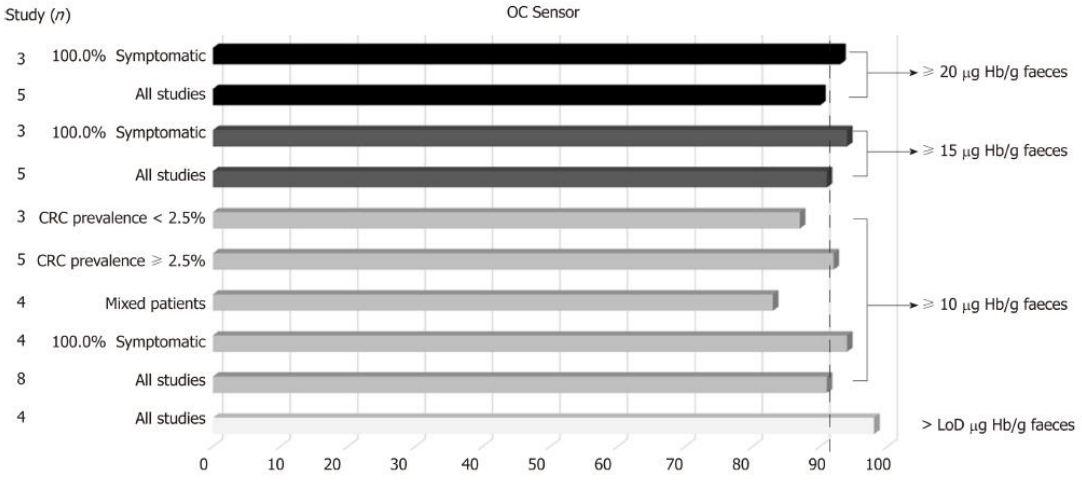

Figure 6 OC-Sensor® pooled sensitivity estimates for colorectal cancer detection (subgroup analysis using DerSimonian´s method). CRC: Colorectal cancer.

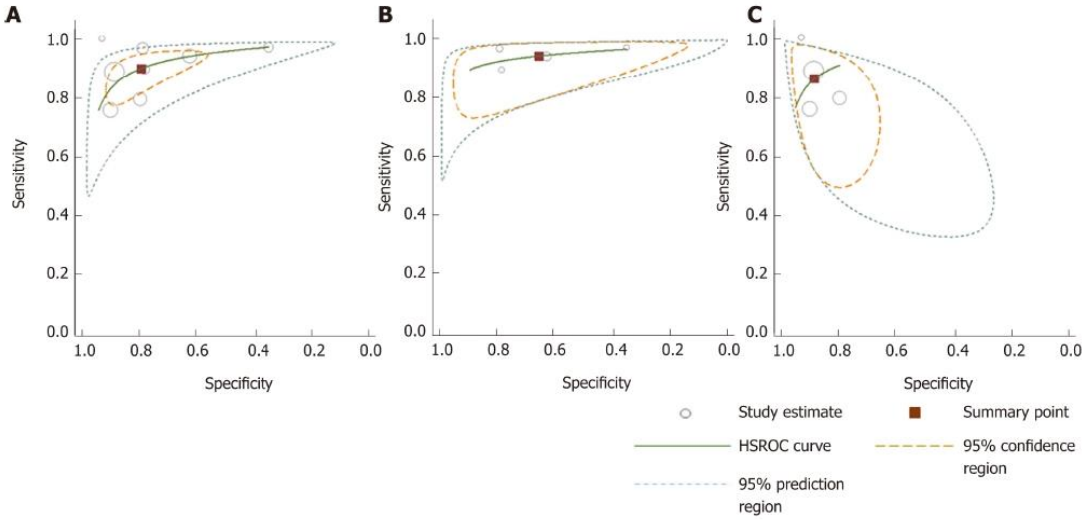

Figure 7 Hierarchical summary receiver-operating characteristic curves for colorectal cancer detection generated using different subgroups of studies. A: All studies; B: 100% symptomatic; C: Mixed cohorts. HSROC: Hierarchical summary receiver operating characteristic.

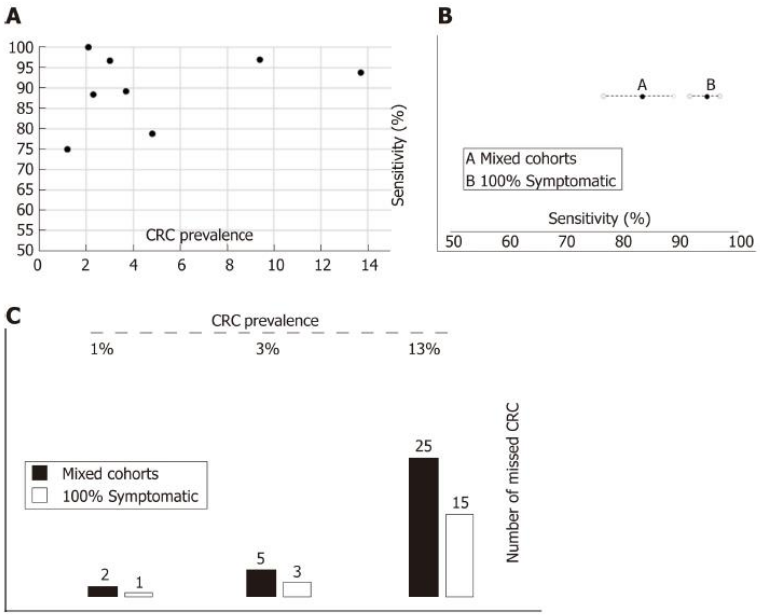

Figure 8 Relationship between colorectal cancer prevalence, clinical spectrum and accuracy of faecal immunochemical test for haemoglobin to rule out colorectal cancer. A: There is no correlation between colorectal cancer (CRC) prevalence and faecal immunochemical test for haemoglobin (FIT) sensitivity; B: Pooled FIT sensitivity to detect CRC cancer estimated from studies with 'Mixed cohorts' is significantly lower than estimated with '100% symptomatic' cohorts; C: Number of missed CRC per 1000 assessed symptomatic patients with colorectal cancer calculated through Fagan nomograms under various assumptions (FIT accuracy parameters estimated with mixed cohorts or 100% symptomatic cohorts) and CRC prevalence. CRC: Colorectal cancer; FIT: Faecal immunochemical test for haemoglobin.

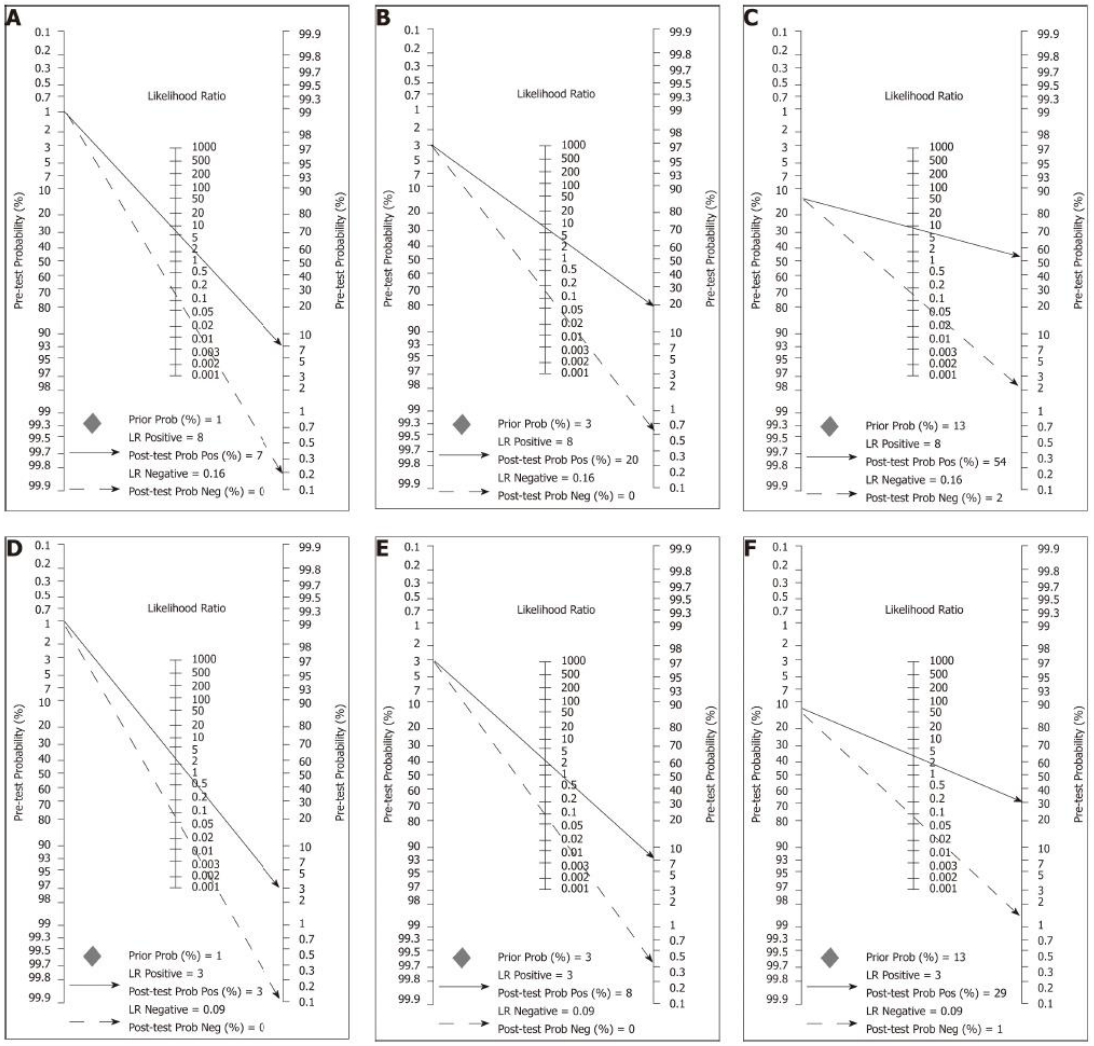

Figure 9 Fagan nomograms used to calculate post-test probabilities based on different scenarios defined by colorectal cancer prevalence and supposed accuracy of OC-Sensor (Threshold 10 μg Hb/g faeces). A-C; These scenarios are defined by colorectal cancer (CRC) prevalence of 1%, 3% and 13% respectively and faecal immunochemical test for haemoglobin (FIT) accuracy parameters used were the pooled estimates calculated with 'mixed cohorts' studies; D-F; These scenarios are defined by CRC prevalence of 1%, 3% and 13% respectively and FIT accuracy parameters used were the pooled estimates calculated with '100% symptomatic' studies. CRC: Colorectal cancer; FIT: Faecal immunochemical test for haemoglobin.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth leading cause of cancer-related death. The majority of cancers are still diagnosed after symptomatic presentation, and the quantitative faecal immunochemical test for haemoglobin (FIT) has been revealed to be more accurate for the detection of CRC than multiple clinical referral criteria in symptomatic patients referred for colonoscopy. Hence, The National Institute for Health and Care Excellence (NICE) has recently issued referral guidance for suspected CCR in which FIT is recommended for certain low risk symptomatic patients using a 10 μg Hb/g faeces threshold.

Research motivation

Although NICE recommendation applies only to patients with low risk symptoms in primary care, the studies done to date were mainly concerned with patients who had already been referred to secondary care and were not only concerned with patients with low risk symptoms. Thus, further work is required to find out if FIT´s ability to rule out CRC may change through the broad spectrum of symptomatic patients.

Research objectives
We aimed to systematically review the literature for published studies out of CRC screening programme setting, to compare FIT accuracy for CRC detection in different clinical spectrum through a meta-analysis. Secondary goal included assessing the usefulness of FIT to detect significant colonic lesions (SCLs) in symptomatic patients.

Research methods
We performed an electronic search in MEDLINE and EMBASE databases (from database inception to May 2018) using a sensitive search of "FIT for CRC" narrowing our search to prospective cohort studies performed on adult patients when at least a fraction of symptomatic patients was included. To identify further relevant studies, we checked the reference lists of all articles extracted. We classified studies on the basis of brand and threshold of faecal haemoglobin (f-Hb) concentration for a positive test result to limit heterogeneity. Finally, a bivariate model was fitted for subgroups defined by CRC prevalence and percentage of symptoms, for direct comparison between them.

Research results
We identified fourteen studies that matched the search criteria, and individual unpublished data from cohorts included in the COLONPREDICT study were also used enrolling 10400 patients using OC-Sensor® at the f-Hb cut-off of 10 mg Hb/g faeces. Pooled estimates of sensitivity for studies formed solely by symptomatic patients (94.1%) were significantly higher than for mixed cohorts (85.5%), while there were no statistically significant differences between pooled sensitivity of studies with different CRC prevalence (< 2.5% and ≥ 2.5%). At the same threshold, OC-Sensor® sensitivity to rule out any SCL was 78.6%.

Research conclusions
This meta-analysis suggests that FIT sensitivity to detect CRC is higher in studies solely including symptomatic patients irrespective of CRC prevalence, but may not be sensitive enough to rule out all SCLs. We hypothesize that differences between both groups could be justified due to cohorts solely including symptomatic patients could present a higher percentage of symptoms related to higher amounts of f-Hb as rectal bleeding or diarrhoea, but the study design is not suitable to prove this hypothesis.

Research perspectives
More data are warranted in order to compare FIT accuracy for CRC detection in patients with different clinical spectrum, to identify a subgroup of symptomatic patients where FIT can safely rule out CRC. Future prospective cohort studies solely concerned with patients consulting for low risk symptoms and stratifying by sex and age could help to get this aim.

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Appendix 1: Search strategy

We followed a Cochrane Collaboration recommended iterative process to design our search strategy.[1] As recommended, we avoided routine use of methodology search filters to identify diagnostic test accuracy studies.[2] First of all, we conducted a series of preliminary searches in PubMed to identify already known key articles or published search strategies in related reviews. We noted common text words and their variants as well as search terms or subject headings that database indexers have assigned to those articles. Additional relevant articles and subject headings were identified using the "Related Articles" and "MeSH Database" options, respectively. Thus, we identified the range of terminology (synonyms, abbreviations) likely to be used to denote:

- Index test being evaluated

1. ("Immunologic Tests/analysis"[Mesh] OR "Immunologic Tests/diagnosis"[Mesh] OR "Immunologic Tests/utilization"[Mesh]) (962)
2. ("Faeces/abnormalities"[Mesh] OR "Faeces/blood"[Mesh] OR "Faeces/diagnosis"[Mesh] OR "Faeces/immunology"[Mesh] OR "Faeces/prevention and control"[Mesh]) (855)
3. Fit test colon (138)
4. Fit test colon cancer (140)
5. Fecal occult blood test (2325)
6. Faecal occult blood test (1290)
7. Fecal occult blood tests (1431)
8. Faecal occult blood tests (833)
9. Fecal occult blood testing (1198)
10. Faecal occult blood testing (630)
11. Fecal immunochemical test (715)
12. Fecal immunochemical tests (500)
13. Fobt (1219)
14. Ifobt (113)
15. Ifobt sensitivity (71)
16. Hemosure (4)

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17. OC-Sensor (52)
18. OC-Hemodia (19)
19. "OC light" (6)
20. OC-micro (9)
21. "FOB Gold" (20)
22. Hem-SP (5)
23. "MagStream HT" (1)
24. Hemoccult (563)
25. Immudia (6)
26. Hemoquant (47)
27. Occultech (1)
28. Immocare (3)
29. Flexsure (30)
30. HM-JACK (2)
31. HM-JACKarc (7)
32. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 (6576)

- Patient population under study

33. abdominal pain [tiab] (49258)
34. abdominal discomfort [tiab] (2366)
35. chronic diarrhoea or diarrhea [tiab] (11092)
36. Constipation [tiab] (21321)
37. Digestive bleeding [tiab] (301)
38. painless rectal bleeding (154)
39. rectorrhagia (85)
40. abdominal distension [tiab] (3534)
41. constitutional syndrome [tiab] or constitutional symptoms [tiab] (2242)
42. weight loss [tiab] (74997)
43. #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 (154880)
44. ("Signs and Symptoms, Digestive/diagnosis"[Mesh]) AND #43 (5796)
45. "Signs and Symptoms, Digestive/prevention and control"[Mesh] AND #43 (1009)

46. #44 OR #45 (6722)

- Reference standard being used against which the accuracy of the index test is to be measured

47. Colonoscopy screening (24940)

48. "Colonoscopy"[Mesh] (27020)

49. #47 OR #48 (33552)

- Combining concepts

50. #46 AND #49 (249)

51. (fecal [tiab] or faecal [tiab] or fobt [tiab] or fit [tiab] or ifobt [tiab]) AND colonoscopy [tiab] AND (symptom* [tiab] OR pain [tiab] OR discomfort [tiab] OR constipat*[tiab] OR syndr*[tiab] OR bleed*[tiab] OR diarrhea [tiab] OR diarrhoea [tiab]) (662)

52. #32 OR #50 OR #51 (7122)

In order to repeat the previously reported search in EMBASE, we used MEDLINE subject headings (MeSH) in EMBASE format (EMTREE):

- Index test being evaluated

1. Occult blood test/ (3908)
2. Fit test.mp (1638)
3. Fecal occult blood test.mp (2100)
4. Faecal occult blood test.mp (841)
5. Fecal occult blood tests.mp (511)
6. Faecal occult blood tests.mp (245)
7. Fecal occult blood testing.mp (1090)
8. Faecal occult blood testing.mp (405)
9. Fecal occult blood test screening.mp (41)
10. Faecal occult blood test screening.mp (42)
11. Fecal occult blood test sensitivity.mp (2)
12. Fecal occult blood test false positive.mp (0)
13. Immunochemical faecal occult blood test.mp (101)
14. Fecal immunochemical tests.mp. or occult blood test/ (4040)
15. Fobt.mp (2267)
16. Ifobt.mp (205)

17. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 (8656)
18. Hemosure.mp (12)
19. OC-Sensor.mp (258)
20. OC-Hemodia.mp (24)
21. "OC light".mp (16)
22. OC-micro.mp (20)
23. "FOB Gold".mp (52)
24. Hem-SP.mp (10)
25. "MagStream HT".mp (2)
26. Hemoccult.mp (830)
27. Immudia.mp (9)
28. Hemoquant.mp (57)
29. Occultech.mp (1)
30. Immocare.mp (10)
31. Flexsure.mp (49)
32. HM JACK.mp (12)
33. HM JACKarc.mp (17)
34. #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 (1226)

- Target condition being detected

35. Colorectal tumor.mp. or colon cancer/or rectum carcinoma/or colorectal tumour/or rectum cancer/or *cancer diagnosis/or colon carcinoma/(155816)
36. Colon cancer.mp (88125)
37. Colorectal cancer.mp. or rectum tumor/or colorectal cancer/or colon tumour/(195171)
38. advanced colorectal cancer.mp (4384)
39. colon adenoma/ or advanced adenoma.mp. (6168)
40. #35 OR #36 OR #37 OR #38 OR #39 (329320)

- Patient population under study

41. diarrhoea/or Diarrhea.mp (249881)
42. (Nausea and vomiting).mp (202)
43. constipation/or Constipation.mp (86189)

44. abdominal pain.mp. or abdominal pain/(164227)

45. abdominal discomfort.mp. or abdominal discomfort/or weight reduction/(158911)

46. digestive system haemorrhage/or gastrointestinal hemorrhage/or Digestive bleeding.mp (60733)

47. painless rectal bleeding.mp (77)

48. rectorrhagia.mp. or rectum haemorrhage/(15015)

49. (constitutional syndrome or constitutional symptoms).mp (3966)

50. weight loss.mp (122192)

51. #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 (651849)

- Reference standard being used against which the accuracy of the index test is to be measured

52. colonoscopy/or Colonoscopy screening.mp (67259)

- Combining concepts

53. #40 AND #51 (22892)

54. #52 AND #53 (3641)

55. #17 AND #53 (268)

56. #17 AND #54 (393)

57. #34 OR #54 OR #55 OR #56 (4951)

Total selected: 7122 (MEDLINE) & 4951 (EMBASE)

Once we had reviewed the previous results, we also designed a filter to complete our search and simplify the future identification of FIT-related studies in PubMed by combining the first and corresponding authors of each potentially interesting article via the Boolean operator "OR"

("Atef SH" [au]) OR ("Bachir NM" [au]) OR ("Barber MD" [au]) OR ("Biondi A" [au]) OR ("Boereboom CL" [au]) OR ("Calogero A" [au]) OR ("Ferraris R" [au]) OR ("Hata K" [au]) OR ("Adelstein BA" [au]) OR ("Ahlquist DA" [au]) OR ("Ahmed S" [au]) OR ("Akbari A" [au]) OR ("Allameh Z" [au]) OR ("Allard J" [au]) OR ("Allison JE" [au]) OR ("Alvarez-Urturi C" [au]) OR ("Annibale B" [au]) OR ("Armitage N" [au]) OR ("Ashraf I" [au]) OR ("Astin M" [au]) OR ("Auge JM" [au]) OR ("Azlie S" [au]) OR ("Ballal MS" [au]) OR ("Ballantyne GH" [au]) OR ("Bampton PA" [au]) OR ("Barrett P" [au]) OR ("Barrison IG" [au]) OR ("Bassett ML" [au]) OR ("Bates T" [au]) OR ("Bernardini S" [au]) OR ("Bessa X" [au]) OR ("Bhargava A" [au]) OR ("Bini EJ" [au]) OR ("Bjerregaard NC" [au]) OR ("Bjornsson ES" [au]) OR ("Bosch LJ" [au]) OR ("Brault J" [au]) OR ("Brenner H" [au]) OR ("Brodersen J" [au]) OR ("Burch JA" [au]) OR ("Cade D" [au]) OR ("Cai QC" [au]) OR ("Capurso G" [au]) OR

("Carlsson L" [au]) OR ("Carroll M" [au]) OR ("Castells A" [au]) OR ("Castiglione G" [au]) OR ("Celestino A" [au]) OR ("Chang HJ" [au]) OR ("Chen HH" [au]) OR ("Chen LS" [au]) OR ("Chiang TH" [au]) OR ("Chiu HM" [au]) OR ("Church JM" [au]) OR ("Ciatto S" [au]) OR ("Cilona A" [au]) OR ("Clarke N" [au]) OR ("Collins JF" [au]) OR ("Corley DA" [au]) OR ("Corte C" [au]) OR ("Crotta S" [au]) OR ("Cubiella J" [au]) OR ("Dancourt V" [au]) OR ("Daveson AJ" [au]) OR ("de Vet HC" [au]) OR ("Dent OF" [au]) OR ("Diaz-Ondina M" [au]) OR ("Dilshad AT" [au]) OR ("Doi Y" [au]) OR ("Dominitz JA" [au]) OR ("Dutta AK" [au]) OR ("Eckardt VF" [au]) OR ("Elsafi SH" [au]) OR ("Eskeland SL" [au]) OR ("Ewald N" [au]) OR ("Faivre J" [au]) OR ("Falkson CB" [au]) OR ("Farkouh M" [au]) OR ("Farrands PA" [au]) OR ("Fauzi A" [au]) OR ("Favre H" [au]) OR ("Fenocchi E" [au]) OR ("Fisher DA" [au]) OR ("Flashman K" [au]) OR ("Fletcher RH" [au]) OR ("Fraser CG" [au]) OR ("Freedman A" [au]) OR ("Freitas BR" [au]) OR ("Friedman A" [au]) OR ("Fu R" [au]) OR ("Gandhi S" [au]) OR ("Garman KS" [au]) OR ("Gibson P" [au]) OR ("Gillberg A" [au]) OR ("Godber IM" [au]) OR (“Godos J” [au]) OR ("Gopalswamy N" [au]) OR ("Goulston KJ" [au]) OR ("Greenberg PD" [au]) OR (“Grosso G” [au]) OR ("Guardiola J" [au]) OR ("Guittet L" [au]) OR ("Haddy RI" [au]) OR ("Hamilton W" [au]) OR ("Han DS" [au]) OR ("Harmston C" [au]) OR ("Harrison AJ" [au]) OR ("Hatch QM" [au]) OR ("Haug U" [au]) OR ("Hazazi R" [au]) OR ("Heresbach D" [au]) OR ("Herrero J" [au]) OR ("Hewett DG" [au]) OR ("Hewitson P" [au]) OR ("Hill AG" [au]) OR ("Hippisley-cox J" [au]) OR ("Hirai HW" [au]) OR ("Hirayama Y" [au]) OR ("Hirobe K" [au]) OR ("Hoepffner N" [au]) OR ("Hogberg C" [au]) OR ("Hol L" [au]) OR ("Holden DJ" [au]) OR ("Holloway RH" [au]) OR ("Hope RL" [au]) OR ("Howden CW" [au]) OR ("Hreinsson JP" [au]) OR ("HU H-" [au]) OR ("Huang G" [au]) OR ("Hundt S" [au]) OR ("Hunt RH" [au]) OR ("Imperiale TF" [au]) OR ("Ioannidis JP" [au]) OR ("Ioannou GN" [au]) OR ("Ip S" [au]) OR ("Iwase N" [au]) OR ("Jamil S" [au]) OR ("Jeanson A" [au]) OR ("Jellema P" [au]) OR ("Jimbo M" [au]) OR ("Jin P" [au]) OR ("Kadakia SC" [au]) OR ("Kalimutho M" [au]) OR ("Kalra L" [au]) OR ("Kato J" [au]) OR ("Kaul A" [au]) OR ("Kemppainen M" [au]) OR ("Kepczyk MT" [au]) OR ("Khakimov N" [au]) OR ("Khasanova G" [au]) OR ("kim BC" [au]) OR ("Klewandrowski K" [au]) OR ("Ko CW" [au]) OR ("Koga Y" [au]) OR ("Kok L" [au]) OR ("Kolligs F" [au]) OR ("Konrad C" [au]) OR ("Koo JH" [au]) OR ("Kovarova JT" [au]) OR ("Kozlowski T" [au]) OR ("Krivec S" [au]) OR ("Kubisch H" [au]) OR ("Lanoy G" [au]) OR ("Lansdorp-Vogelaar I" [au]) OR ("Launois R" [au]) OR ("Lawson N" [au]) OR ("Lee FI" [au]) OR ("Lee JK" [au]) OR ("Lee TJ" [au]) OR ("Lee YC" [au]) OR ("Leicester RJ" [au]) OR ("Leis VM" [au]) OR ("Letsou G" [au]) OR ("Levi Z" [au]) OR ("Levy BT" [au]) OR ("Li R" [au]) OR ("Li ZC" [au]) OR ("Lieberman DA" [au]) OR ("Macrae FA" [au]) OR ("Mansouri D" [au]) OR ("Mansson J" [au]) OR ("Manus B" [au]) OR ("Marshall JK" [au]) OR ("Marshall TP" [au]) OR

("Matsumura Y" [au]) OR ("Maw A" [au]) OR ("McDonald CA" [au]) OR ("McDonald PJ" [au]) OR ("McDonald R" [au]) OR ("McDonald RL" [au]) OR ("Meijer GA" [au]) OR ("Mesquita MA" [au]) OR ("Miyoshi H" [au]) OR ("Moran A" [au]) OR ("Morikawa T" [au]) OR ("Morini S" [au]) OR ("Mowat C" [au]) OR ("Murakami R" [au]) OR ("Murphy J" [au]) OR ("Nagaoka S" [au]) OR ("Nakama H" [au]) OR ("Narula N" [au]) OR ("Niedermaier T" [au]) OR ("Niv Y" [au]) OR ("Olsson L" [au]) OR ("Oono Y" [au]) OR ("Oort FA" [au]) OR ("Ostrow JD" [au]) OR ("Ou C-" [au]) OR ("Parente FR" [au]) OR ("Park DD" [au]) OR ("Park JG" [au]) OR ("Park Y" [au]) OR ("Paz-Valiñas L" [au]) OR ("Peacock O" [au]) OR ("Petty MT" [au]) OR ("Pfeifer RM" [au]) OR ("Piperno A" [au]) OR ("Pochapin MB" [au]) OR ("Pongprasobchai S" [au]) OR ("Pye G" [au]) OR ("Quintero E" [au]) OR ("Rae AJ" [au]) OR ("Rai S" [au]) OR ("Rajasekhar PT" [au]) OR ("Ransohoff DF" [au]) OR ("Rao J" [au]) OR ("Rao SK" [au]) OR ("Rees CJ" [au]) OR ("Rentier B" [au]) OR ("Riboe DG" [au]) OR ("Rigas B" [au]) OR ("Ritchie MC" [au]) OR ("Robertson R" [au]) OR ("Robinson MH" [au]) OR ("Rockey DC" [au]) OR ("Rodriguez-Alonso L" [au]) OR ("Rodriguez-Moranta F" [au]) OR ("Rosman AS" [au]) OR ("Rozen P" [au]) OR ("Rubeca T" [au]) OR ("Saccomanno S" [au]) OR ("Saito H" [au]) OR ("Saldanha JD" [au]) OR ("Saquib N" [au]) OR ("Saratzis A" [au]) OR ("Scales CD" [au]) OR ("Schwartz S" [au]) OR ("Scriven AJ" [au]) OR ("Segal WN" [au]) OR ("Selinger RR" [au]) OR ("Selvachandran SN" [au]) OR ("Sequist TD" [au]) OR ("Shah R" [au]) OR ("Sharma VK" [au]) OR ("Shashideep S" [au]) OR ("Shastri YM" [au]) OR ("Shaw AG" [au]) OR ("Sheng J" [au]) OR ("Sieg A" [au]) OR ("Singh H" [au]) OR ("Singhal S" [au]) OR ("Skaife P" [au]) OR ("Smith A" [au]) OR ("Sohn DK" [au]) OR ("Songster CL" [au]) OR ("Sontag SJ" [au]) OR ("St John DJ" [au]) OR ("Stapley S" [au]) OR ("Steele RJ" [au]) OR ("Stegeman I" [au]) OR ("Stein J" [au]) OR ("Stelling HP" [au]) OR ("Stockbrugger RW" [au]) OR ("Stray N" [au]) OR ("Stubbs RS" [au]) OR ("Subramanian S" [au]) OR ("Sung JJ" [au]) OR ("Symonds EL" [au]) OR ("Tan V" [au]) OR ("Tannous B" [au]) OR ("Tao S" [au]) OR ("Tarpay Ad" [au]) OR ("Tate JJ" [au]) OR ("Thompson M" [au]) OR ("Tsoi KK" [au]) OR ("van Turenhout ST" [au]) OR ("Vega P" [au]) OR ("Weller D" [au]) OR ("Whitlock EP" [au]) OR ("Wu MS" [au]) OR ("Yansong J" [au]) OR ("Young GP" [au]) OR ("Zullo A" [au]) OR ("Terhaar sive Droste JS" [au]) OR ("Thomas WM" [au]) OR ("Thompson MR" [au]) OR ("Thomson AD" [au]) OR ("Tibble J" [au]) OR ("Tonus C" [au]) OR ("Trickett JP" [au]) OR ("Donaldson DR" [au]) OR ("Trojan J" [au]) OR ("Turunen MJ" [au]) OR ("Adlercreutz H" [au]) OR ("van Rijn AF" [au]) OR ("Vacante M" [au]) OR ("van Rossum LG" [au]) OR ("Vandvik P" [au]) OR ("van Roon AH" [au]) OR ("Vart G" [au]) OR ("Vasilyev S" [au]) OR ("Syrjanen K" [au]) OR ("Vaughan-Shaw PG" [au]) OR ("Wheeler JM" [au]) OR ("Vilkin A" [au]) OR ("Vironen J" [au]) OR ("Kellokumpu I" [au]) OR ("Wanebo HJ" [au]) OR ("de Wijkerslooth TR" [au]) OR ("Williams JA" [au]) OR ("Winawer SJ" [au])

OR ("Wong WM" [au]) OR ("Wong BC" [au]) OR ("Wong CK" [au]) OR ("Sadowski DC" [au]) OR ("Dube C" [au]) OR ("Wong MC" [au]) OR ("Woo HY" [au]) OR ("Park H" [au]) OR ("Wu D" [au]) OR ("Li JN" [au]) OR ("Guoxiang L" [au]) OR ("Jufang S" [au]) OR ("Yoshinaga M" [au]) OR ("Zhu MM" [au]) OR ("Widlak MM" [au]) OR ("Arasaradnam R" [au]) OR ("Ran ZH" [au]) OR ("Wen-xian Z" [au])

AND

((((((((((ifobt) OR fobt) OR Faecal occult blood) OR Fecal occult blood) OR Fit test colon cancer) OR Fit test colon) OR Fit test) OR "Occult Blood"[Mesh]) OR (("Immunological Tests/analysis"[Mesh] OR "Immunological Tests/diagnosis"[Mesh] OR "Immunological Tests/utilisation"[Mesh])))) (1539)

Appendix 2. Characteristics of the studies included in the systematic review

Author & Objective	Design & Setting	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Rozen P, 2010[17] Evaluate accuracy for CRC and advanced adenomatous polyps by the faecal threshold used to determine a positive test and the number of FITs prepared per test, to determine the least number of colonoscopies required to detect a CRC.	Cohort study; Sampling procedure: Mixed (consecutive plus patients included in previous study); Planning data collection: prospective. Setting: Primary care, Colonoscopy setting, Tel Aviv, Israel (Multicentre, Unknown recruitment period).	Patients with symptoms scheduled for colonoscopy plus high-risk patients (personal or family history of CRC) plus positive guaiac-based FOBT result (Hemoccult SENSA)	Hospitalization, visible rectal bleeding, known diagnosis of IBD, haematuria, menstruation, non-cooperation with preparing a faecal test or failure to reach the caecum	Enrolled: 2352; Included in 2x2 table: n=1682; Mean age: 63.7 years; Sex: 49.6% women. Prevalence CRC: 1.2% Prevalence AN: 8.9% Prevalence SCL: no info Symptomatic: 23% Asymptomatic: 77%	Index test: OC-Micro/Sensor. Three samples. They specify that patients observed no dietary or medication restrictions other than stopping aspirin and anticoagulant therapy before endoscopy. Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology.
Van Turenhout ST, 2014[18] Compare sensitivity and specificity of a FIT between males and females, and study potential explanatory variables.	Cohort study; Sampling procedure: 'all ambulatory patients scheduled'; Planning data collection: prospective. Setting: secondary care, Colonoscopy setting, Amsterdam, Netherlands (Multicentre-five hospitals, two rural areas & Two large teaching hospitals-, June 2006-October 2010).	Patients > 17 years old, scheduled for colonoscopy regardless of the indication for colonoscopy	Documented history of IBD, incomplete colonoscopy or inadequate bowel cleansing, failure in completing one of the tests or subjects in whom no written informed consent was obtained, visible rectal bleeding or anaemia	Enrolled: 4704; Included in 2x2 table: n=3022; Mean age: 59.7 years; Sex: 55% women. Prevalence CRC: 2.3% Prevalence AN: 12.3% Prevalence SCL: no info. Symptomatic: 44% (Weight loss 2.9%; Abdominal pain 11.7%; Altered bowel habit 18.1%; constipation 3.0%, diarrhoea 4.2%). Asymptomatic: 46.7% Unknown: 9.3%	Index test: OC-Micro/Sensor Reference standard: colonoscopy and histopathology. If a barium enema, virtual colonography or second colonoscopy was performed within six months after completing FIT and a first incomplete colonoscopy, evaluation of the colon was considered complete.
Woo HY, 2005[19] Evaluate the diagnostic validity of HM- Jack for detecting CRC in patients undergoing colonoscopy and compared its results with qualitative FITs Instant-View and	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting:	Patients scheduled for colonoscopy regardless of the indication for colonoscopy	Refusal to participate or no submission of faecal samples or poor bowel preparation	Enrolled: unreported; Included in 2x2 table: n=85; Median age: 56 years; Sex: 52.9% women. prevalence CRC: 7.1% AN/SCL: no info. Symptomatic 49.4%	Index test: HM-JACK Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology

OcculTech	Ambulatory patients, Colonoscopy setting, Seoul, South Korea, February 2004.			(Pain 15.3%; Altered bowel habit 1.2%; dyspepsia 10.6%; haematochezia 5.9%, melena 4.7%; anaemia 4.7%, diarrhoea 17.6%). Asymptomatic 40%	
McDonald PJ, 2012[20] Determine whether faecal haemoglobin concentration can assist in deciding which patient with lower abdominal symptoms will benefit from endoscopy.	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: Primary care Colonoscopy setting, NHS Tayside, UK, February 2010-March 2012.	Patients scheduled for colonoscopy regardless of the indication for colonoscopy	Patients under 16 years old, unable to understand instructions or to consent	Enrolled: 739; Included in 2x2 table: n=280; Median age: 63 years; Sex: 59.6% women. Prevalence CRC: 2.1% Prevalence AN: no info Prevalence significant neoplasia (CRC + High risk adenoma): 20.4 Prevalence SCL (CRC + HRA + IBD): 19.6% Unknown percentage of symptomatic patients	Index test: OC-Micro/Sensor Reference standard: colonoscopy and flexible sigmoidoscopy
Ou CH, 2013[21] Evaluate the performance of FIT for the screening of CRC.	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: Ambulatory patients, Colonoscopy setting, Taiwan, China, November 2009-June 2011.	Patients scheduled for colonoscopy regardless of the indication for colonoscopy	Patients who had overt gastrointestinal bleeding symptoms, IBD, repeated rectal bleeding or other causes of rectal bleeding such as angiodysplasia	Enrolled: 784; Included in 2x2 table: n=697; Median age: 60 years; Sex: 55.9% women. Prevalence CRC: 0.4% Prevalence AN: 6.0% Prevalence SCL: no info Unknown percentage of symptomatic patients	Index test: OC-Micro/Sensor Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology
Auge JM, 2016[22] Evaluate the diagnostic yield for advanced CRC in symptomatic patients using the first of two samples and the higher concentration of two samples.	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: 'Patients who attended Hospital Clinic',	Patients who required colonoscopy for the investigation of lower abdominal symptoms or colonic polyp surveillance	Patients undergoing CRC screening or with a history of gastrointestinal bleeding, active rectal bleeding, menstruation, haematuria or known ulcerative	Enrolled: no info; Included in 2x2 table: n=208; Median age: 63 years; Sex: 55.8% women. Prevalence CRC: 1.0% Prevalence AN: no info Prevalence SCL: no info Prevalence advanced	Index test: HM-JACKarc. Two samples. They specify that medications, such as aspirin and non-steroidal anti-inflammatory drugs (NSAID), were withdrawn 1 week before preparation for

	Barcelona, Spain, December 2013-March 2014.		colitis	colorectal neoplasia (CRC + HRA): 14% Unknown percentage of symptomatic patients	colonoscopy. Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology
Auge JM, 2018[30] Assess the analytical and diagnostic capabilities of SENTIFIT® 20 using SENTiFIT®-FOB Gold® latex reagent and SENTIFIT® pierce tube (Sentinel Diagnostics, Italy; Sysmex, Spain). As a secondary aim, to study the diagnostic yield for advanced CRC in symptomatic patients using the first of two samples vs. the mean and the higher concentration of two samples.	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: 'Patients who attended Hospital Clinic', Barcelona, Spain, June to October 2015.	Patients who required colonoscopy for the investigation of lower abdominal symptoms or colonic polyp surveillance	Not reported	Enrolled: no info; Included in 2x2 table: n=487; Average age: 62 years (range: 22-94 years); Sex: 51.2% women. Prevalence CRC: 2.5% Prevalence AN: 14.6% Prevalence any colonoscopy finding: 47.2% (AN 14.6%; hyperplastic or inflammatory polyps 5.7%; diverticular disease 23.4%; haemorrhoids 30.6% angiodysplasia 1.4%; IBD 1.6%; minor irrelevant lesions 1.2%) Symptomatic: 54.2% Asymptomatic: 45.8%	Index test: FOB Gold. Two samples. They specify that medications, such as aspirin and non-steroidal anti-inflammatory drugs (NSAID), were withdrawn 1 week before preparation for colonoscopy. Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology
Symonds EL, 2016[23] Compare performance of a new blood test for CRC (methylated BCAT1 and IKZF1 DNA) to OC Sensor in a study population with the full range of pathologies encountered in the colon and rectum.	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: Ambulatory patients. Multicentre, South Australia	Any adults (40-85 years) scheduled for colonoscopy for standard indications (Symptoms, positive FOBT, surveillance (personal or family history), screening, surveillance for IBD, diverticular disease and radiation proctitis).	Not reported	Enrolled: 4657; Included in 2x2 table: n=1381; Median age: 64.1 years; Sex: 50.6% women. Prevalence CRC: 4.8% Prevalence AN: 17.1% Prevalence SCL: no info Symptomatic: 34.8% Asymptomatic: 57.7% Unknown: 7.5%	Index test: OC-Micro/Sensor Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology
Parente F, 2012[24] Test a combination of faecal tests (HM-Jack® calprotectin and M2-PK) as	Cohort study; Sampling procedure: consecutive;	Any adults (50-80 years) scheduled for colonoscopy in suspicion of an	Patients who had undergone colonoscopy in the previous five years,	Enrolled: 299; Included in 2x2 table: n=280; Mean age: 67 years; Sex: 43.9%	Index test: HM-JACK Reference standard: colonoscopy up to the caecum or obstructing

markers for advanced neoplasia in a selected series of patients requiring colonoscopy for the suspicion of CRC.	Planning data collection: prospective. Setting: Secondary care, Multicentre (Rome, Lecco, Bologna), Italy.	organic bowel disease due to symptoms for at least three weeks.	IBD, coexisting serious illness or were on medication known to be associated with intestinal inflammation or intestinal infection, incomplete colonoscopy or inadequate cleansing	women. Prevalence CRC: 16.8% Prevalence AN: 47.1% Prevalence SCL: no info 100% Symptomatic (Weight loss 11.0%; Pain 17.9%; Altered bowel habit 23.1%; haematochezia 26.1%, anaemia 15%).	carcinoma plus histopathology
Rodríguez-Alonso L, 2015[25] Evaluate whether quantitative FIT performs better than NICE and SIGN referral criteria	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: Primary and secondary care, Barcelona, Spain, September 2011-October 2012.	Patients scheduled for colonoscopy due to gastrointestinal symptoms	Patients referred for adenoma surveillance and postoperative surveillance of CRC, Hospitalized, Previous colectomy, IBD and polyp syndromes, incomplete colonoscopies.	Enrolled: 1054; Included in 2x2 table: n=1003; Age: < 40 years 7.1%;41-50 yea 13%; 51-60 years 22.4%; 61-70 years 29.1%; > 70 years 28.4%; Sex: 46.8% women. Prevalence CRC: 3.0%; Prevalence AN: 13.3%; Prevalence SCL: no info. 100% Symptomatic (Weight loss 19.0%; Pain 36.4%; haematochezia 34.2%, anaemia 8.9%; constipation 12.1%; diarrhoea 23.5%).	Index test: OC-Micro/Sensor Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology
Mowat C, 2016[26] Study the diagnostic accuracies of faecal haemoglobin and faecal calprotectin in a cohort of symptomatic patients	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: Primary care, NHS Tayside, UK, October 2013-March 2014.	All adult patients referred for investigation of bowel symptoms (if patients had more than one symptom, they were attributed only one in order of decreasing importance: rectal bleeding, anaemia, diarrhoea, altered bowel habit, abdominal pain and weight loss)	Not reported	Enrolled:2189; Included in 2x2 table: n=750; Median Age 64; Sex: 54.7% women. Prevalence CRC: 3.7% Prevalence SCL (CRC + HRA + IBD) 10.0%.100% Symptomatic (Weight loss 0.9%; Pain 11.0%; haematochezia 34.2%, anaemia 8.9%; change in bowel habit 42.8%; diarrhoea 16.8%).	Index test: OC-Micro/Sensor Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology
Godber IM, 2016[27]	Cohort study;	Patients referred for	Patients under 16	Enrolled: 909;	Index test: HM-JACKarc

Determine whether patients with lower abdominal symptoms can be investigated quickly using results of FIT, and whether this test could form part of a diagnostic pathway for significant colorectal disease	Sampling procedure: consecutive; Planning data collection: prospective. Setting: Primary care, NHS Lanarkshire, UK, June 2013-December 2013.	colonoscopy examination	years old, unable to understand instructions or to consent	Included in 2x2 table: n=484; Median Age 59; Sex: 60.1% women. Prevalence CRC: 2.3% Prevalence AN: no info Prevalence SCL (CRC + HRA + IBD + colitis) 9.3% 100% Symptomatic (Weight loss 1.7%; Pain 18.8%; haematochezia 15.9%, anaemia 4.8%; change in bowel habits 39.7%).	Reference standard: colonoscopy
Widlak MM 2017[28] Assess using FIT or faecal calprotectin to detect CRC and adenoma in symptomatic patients referred from primary care	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective. Setting: Secondary care, Multicentre, UK, January 2015-March 2016.	Referral as per national two week wait guidance – bowel symptoms suggestive of colorectal cancer	Patients who declined to participate, were deemed physically unfit for further investigation or unable to provide valid consent due to language barrier, visual impairment or illness (i.e. dementia)	Enrolled: 2822; Included in 2x2 table: n=430; Median Age 67; Sex: 51% women. Prevalence CRC: no info (CRC + High grade dysplasia) 5.7% Prevalence AN: no info Prevalence SCL: no info 100% Symptomatic (Weight loss 15.8%; Pain 30%; haematochezia 43.0%, anaemia 17.2%; change in bowel habit 64.2%)	Index test: HM-JACKarc Reference standard: colonoscopy and histopathology / CT colonography or CT abdomen/pelvis with contrast plus flexible sigmoidoscopy (CT = computed tomography)
Cubiella, 2014[29] Primary and secondary care, Multicentre (2 Hospitals), Spain, Derivation cohort: Ourense March 2012-September 2013	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective	Patients scheduled for colonoscopy due to gastrointestinal symptoms	Age under 18, pregnancy, asymptomatic individuals who were undergoing surveillance colonoscopy, hospitalised, patients whose symptoms had ceased within 3 months before evaluation or who declined participation	Derivation cohort: Enrolled: 2381; Included in 2x2 table: n=1567; Mean age: 66.9 years; Sex: 48.6% women. Prevalence CRC: 13.7% Prevalence AN: 26.7% Prevalence SCL (CRC, AN, polyposis (>10 polyps of any histology, including serrated lesions), histologically confirmed colitis, polyps ≥10 mm,	Index test: OC-Micro/Sensor They were specifically instructed to sample a stool where no blood was visible. Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology

				complicated diverticular disease, colonic ulcer, bleeding angiodysplasia): 29.5	
Cubiella, 2017[31] Primary and secondary care, Multicentre (11 Hospitals), Spain, Validation cohort: Multicentre, March 2014-March 2015	Cohort study; Sampling procedure: consecutive; Planning data collection: prospective	Patients scheduled for colonoscopy due to gastrointestinal symptoms	Age under 18, pregnancy, asymptomatic individuals who were undergoing surveillance colonoscopy, hospitalised, patients whose symptoms had ceased within 3 months before evaluation or who declined participation	Validation cohort: 1481; Included in 2x2 table: n=715; Mean age: 64.4 years; Sex: 53.3% women. Prevalence CRC: 9.4% Prevalence AN: 21.1% Prevalence SCL: 25.3%	Index test: OC-Micro/Sensor They were specifically instructed to sample a stool where no blood was visible. Reference standard: colonoscopy up to the caecum or obstructing carcinoma plus histopathology

Metodología y resultados - Artículo 2

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RESEARCH ARTICLE

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Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study

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Factor de impacto: 3.549

Segundo cuartil del Journal Citations Report

Objetivo

Describir la precisión diagnóstica para la detección de CCR en la práctica clínica en atención primaria de nuestro entorno y comprobar si se corresponde con la literatura existente.

Métodos

Estudio observacional retrospectivo con seguimiento. Se incluyeron los sujetos del área metropolitana de San Sebastián (SS) y de la provincia de Ourense (Ou) con un test de SOH-i (OC-Sensor®) solicitado entre enero de 2012 y diciembre de 2016 en el centro de salud, y seguimiento de al menos dos años tras la realización del test. Este periodo identifica los cánceres prevalentes en el caso de que existan síntomas [165], y corresponde al intervalo de realización de un test de SOH-i si la indicación es cribado oportunista de CCR [166]. Se excluyeron aquellos sujetos con un CCR diagnosticado en los dos años previos a la realización del test.

Se realizó una exportación de información desde la base de datos del laboratorio de análisis clínicos, recogiendo el motivo de solicitud de SOH-i, edad categorizada (< 50, 50-69 y > 69 años), y sexo del paciente, centro solicitante, tipo de test utilizado y fecha de realización.

Por otra parte, se define como objetivo la incidencia de CCR en los dos años siguientes a la realización de SOH-i. Se considera que un paciente presenta un CCR incidente, si posee al menos un registro de alta hospitalaria en la base de datos de documentación clínica de su centro de referencia (CMBD) asociado al diagnóstico de CCR [167,168]. Para ello se tuvieron en cuenta los siguientes códigos de la clasificación CIE-9: Categorías 153 (153.0-153.9), 209.1 (209.10-209.17), 154.0, 154.1 y 154.8 [169].

Análisis estadístico: Descripción de variables categóricas como porcentajes y cuantitativas a través de la mediana y su desviación estándar. Las diferencias entre ambas cohortes se evaluaron por medio del test de Ji cuadrado y U Mann-Whitney en el caso de las variables cualitativas y cuantitativas respectivamente.

Se realizó el cálculo de la precisión diagnóstica para detectar CCR de forma global mediante la determinación de la sensibilidad y especificidad, valor predictivo positivo y negativo, razones de verosimilitud y odds ratio de diagnóstico (DOR) para los puntos de corte de 10 µg Hb/g de heces y 20 µg Hb/g de heces respectivamente.

Adicionalmente, se realizaron análisis por subgrupos para ambos umbrales utilizando en su comparación el test de Chi-cuadrado: centro hospitalario (área), grupo etario, sexo y en la cohorte de SS en función de la indicación del test (cribado CCR /evaluación síntomas) y la localización del CCR (derecho -proximal al ángulo esplénico- o izquierdo).

Finalmente se estudió la eficacia de utilizar SOH-i en los diferentes puntos de corte (10 µg Hb/g de heces y 20 µg Hb/g de heces) para cada subgrupo demográfico (sexo y edad) y motivo de solicitud del test por medio del cálculo de a) número de CCR perdidos por cada 1000 pacientes evaluados y b) número necesario a tratar (NNT) definido como el número de sujetos con un resultado de Hb-f por encima del umbral escogido a los que sería necesario realizar colonoscopia para realizar un diagnóstico de CCR.

Resultados

En el periodo analizado, se solicitó la realización de un test de SOH-i a 38,675 sujetos (54,0% mujeres), 12,674 pacientes en SS y 26,001 en Ou con diferencias estadísticamente significativas respecto a la edad (SS=61.2±25.9, Ou=66.8±23.8;

p<0,001) y la prevalencia de CCR (SS=1.1%, Ou=2.0%; p<0.001). En SS el 44.4% de los test SOH-i se indicaron por la presencia de síntomas.

La Sensibilidad y Especificidad global del test de SOH-i en los umbrales de 10 y 20 µg Hb/g de heces fue de 90.5% (IC 95% 88.0-92.5) vs 87.7% (IC 95% 84.9-90.0) y 81.4% (IC 95% 81.0-81.8) vs 86.7% (IC 95% 86.3-87.0) respectivamente.

En cuanto al análisis por subgrupos, existieron diferencias en la sensibilidad en función del centro solicitante para el umbral de 10 µg Hb/g de heces (SS 83.0, IC 95% 75.7-88.4, Ou 92.4%, IC 95% 89.8-94.4; p < 0.01), y en la localización (CCR derecho 69.4% IC95% 55.5-80.5, CCR izquierdo 91.0% IC95% 82.6-95.6; p < 0.01), mientras que no hubo diferencias en relación al sexo (hombres 91.6%, IC 95% 88.6-93.9, mujeres 88.4% IC 95% 83.7-91.9; p=0.18), el grupo etario (<50a 93.1% , IC 95% 78.0-98.1, 50-69a 91.5%, IC 95% 86.8-94.6, >69a 89.8%, IC 95% 86.5-92.3; p=0.70) o la indicación, explorada exclusivamente en los pacientes de San Sebastián (síntomas 81.3%, IC 95% 71.3-88.3, cribado oportunista 84.9%, IC 95% 72.9-92.1, seguimiento 100.0%, IC 95% 34.2-100.0; p=0.70).

La Especificidad fue diferente entre subgrupos excepto para la localización del CCR (SS 85.0%, IC95% 84.4-85.6, Ou 79.6%, IC95% 79.1-80.1; p<0.001); (hombres 79.9%, IC95% 79.3-80.5, mujeres 82.6%, IC95% 82.1-83.2; p<0.001); (‘menos de 50’ 88.5%, IC95% 87.9-89.2, ‘entre 50 y 69’ 83.6, IC95% 83.0-84.2, ‘más de 69’ 75.0%, IC95% 74.3-75.7; p<0.001); (síntomas 84.1%, IC95% 83.1-85.1, cribado oportunista 86.0%, IC95% 85.1-86.8, seguimiento 82.5%, IC95% 79.2-85.4; p<0.05); (CCR derecho 85.0% IC95% 84.4-85.6, CCR izquierdo 85.0% IC95% 84.4-85.6; p 0.4).

El porcentaje de pacientes con un resultado por encima del umbral fue de 20.7% y 14.6% para los puntos de corte de 10 µg Hb/g de heces y 20 µg Hb/g de heces respectivamente. A pesar de que la sensibilidad disminuyó un 3.1% al usar el umbral de

20 µg Hb/g de heces con respecto al umbral menor, el valor predictivo negativo fue al menos de 99.2% en cualquier subgrupo evaluado. Utilizando el umbral de 20 µg Hb/g de heces, menos de un paciente con CCR dejaría de ser identificado por cada 1000 pacientes evaluados mientras que sería preciso realizar aproximadamente 1.3 veces más colonoscopias para identificar un paciente con CCR en comparación con el uso del umbral menor para cualquier subgrupo evaluado.

Conclusión

Este análisis confirma la elevada precisión diagnóstica de SOH-i para la detección de CCR en atención primaria independientemente del centro, edad, sexo o indicación. La elección del umbral de SOH-i debería estar en relación con los recursos disponibles y la prevalencia del CCR en cada población.

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RESEARCH ARTICLE

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Optimal diagnostic accuracy of quantitative faecal immunochemical test positivity thresholds for colorectal cancer detection in primary health care: A community-based cohort study

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Abstract

Background: Optimizing colonoscopy resources is challenging, and information regarding performing diagnostic quantitative faecal immunochemical test (FIT) in daily clinical practice in primary health care is still limited. This study aimed to assess the sensitivity, specificity, positive predictive value and negative predictive value of varying FIT positivity thresholds on colorectal cancer (CRC) detection in primary health care.

Methods: A retrospective cohort study of 38,675 asymptomatic and symptomatic patients with a FIT (OC-Sensor™) performed between 2012 and 2016 in a primary health-care setting, using a clinical laboratory database of two Spanish areas linked with the National Health System's Hospital Discharge Records Database. The primary outcome was 2-year CRC incidence.

Results: The mean age of the participants was 63.2 years; 17,792 (46.0%) were male. CRC prevalence was 1.7% (650/38,675). The percentage of patients with a FIT result above the threshold was 20.7% and 14.6% for 10 μg Hb/g faeces and 20 μg Hb/g faeces thresholds, respectively. Sensitivity was 90.5% (95% confidence interval 88.0%–92.5%) at a 10 μg Hb/g faeces threshold, and this decreased by 3.1% when a 20 μg Hb/g faeces threshold was used. The negative predictive value for CRC was at least 99.2% in any subgroup analysed. At a 20 μg Hb/g faeces threshold, less than one additional CRC would be missed per 1000 patients investigated, while approximately 1.3 times more colonoscopy examinations were needed to identify an incidence of CRC using the lowest threshold for any situation analysed.

Conclusions: In primary health care, a quantitative FIT threshold should be tailored to colonoscopy capacity and CRC prevalence in specific populations.

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KEYWORDS
colorectal cancer, diagnostic performance, faecal biomarkers, faecal haemoglobin, faecal immunochemical test, primary health care

INTRODUCTION

Although colorectal cancer (CRC) screening programmes have been extended widely in Western Europe, most cases of CRC are still diagnosed in symptomatic patients.[1] Unfortunately, the majority of lower gastrointestinal symptoms have a low positive predictive value (PPV) for CRC (3%–4%),[2] and several studies included in previous meta-analyses have revealed that a quantitative faecal immunochemical test for haemoglobin detection (FIT) can be used to identify those symptomatic patients with a higher CRC risk. Therefore, this assists primary health care in determining who should be referred for colonoscopy.[3,4]

The threshold to determine which patients would benefit from further investigation plays a crucial role in any diagnostic strategy for CRC detection, as it may be locally selected on the basis of regional variables such as CRC incidence, colonoscopy capacity and population demographics (sex, age) which could affect FIT diagnostic performance among others.[5,6]

Furthermore, the National Institute for Health and Care Excellence (NICE) recommends (NICE DG30) FIT to guide referral in primary care for suspected CRC. This would be in people without rectal bleeding who have unexplained symptoms but who do not meet the criteria for a suspected cancer pathway referral using a 10 μg Hb/g faeces threshold regardless of sex or age.[7] However, the main concern for implementation of this strategy is that information regarding FIT diagnostic performance in primary health care is still limited, and large studies are required to validate its use.[8]

Since then, some studies have been conducted in this scenario using different FIT platforms.[9–12] A recent study revealed that faecal haemoglobin (f-Hb) <10 μg Hb/g faeces, in the absence of iron-deficient anaemia, rectal bleeding, a palpable mass or persistent diarrhoea, identifies patients with an extremely low risk of developing CRC.[9] However, use of f-Hb, regardless of variables which define the clinical spectrum of an individual patient, could lead to missing CRC in some subgroups of patients while at the same time overusing colonoscopy resources in others.

We designed a retrospective study that aimed to assess the diagnostic accuracy of FIT in daily clinical practice in primary health care for CRC diagnosis in two areas of northern Spain between 2012 and 2016.

METHODS

We followed the Standards for Reporting of Diagnostic Accuracy Group initiative checklist for diagnostic tests and the Strengthening the Reporting of Observational studies in Epidemiology statement to conduct and report our study.[13,14]

Participants and setting

This population-based retrospective cohort study included asymptomatic and symptomatic patients aged ≥18 years from two northern Spanish health areas (Ourense and San Sebastian) who consulted their general practitioners between 1 January 2012 and 31 December 2016, who requested a FIT as part of their medical treatment.

Data on their consultations and laboratory results were linked to the Spanish Health System's Hospital Discharge Records Database (CMBD). This database receives information about hospital discharges from approximately 98% of public hospitals in Spain and, since 2005, has gradually covered private hospitals. This information includes diagnoses made during hospital admission, which are mainly coded based on the Spanish version of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9- CM) and 10th revision. Patients with a history of CRC in the 2 years prior to FIT determination were excluded.

Index test

The FIT used in both health areas is OC-Sensor™ (Eiken Chemical Co.). Use of this FIT in our community has been reported before.[15] In short, patients were told to collect a faecal sample from one bowel movement without specific diet or medication restrictions, and each sample was processed as previously reported at each regional reference hospital's laboratory.[16] Estimates of f-Hb were quantitated as μg Hb/g of faeces so that results could be compared across analytical systems.[17]

FIT performance was assessed using the thresholds of 10 and 20 μg Hb/g faeces. When a patient had more than one FIT determination in the database, only the former was used. Reasons for FIT request were classified into three groups: (a) opportunistic screening (outside the scope of regional CRC screening programmes), (b) study of symptoms and (c) follow-up of gastrointestinal pathology. An overview of FIT data collection is shown in Figure S1.

Outcome variables

The main outcome was 2-year CRC incidence. Patients were included as having CRC if a diagnosis was recorded in the CMBD, and latency was defined as the time elapsed between FIT determination and the earliest record of CRC assigned in the CMBD.

CRC was recorded as 'right-sided' when located proximal to the splenic flexure.

Data analysis

Differences between both cohorts were evaluated using chi-square and Mann-Whitney U-tests for qualitative and quantitative variables, respectively. Discriminatory ability for detecting CRC was assessed using the receiver operating characteristics curve and its area under the curve (AUC). Sensitivity, specificity, PPV, negative predictive value (NPV), positive and negative likelihood ratio, diagnostic odds ratio and their 95% confidence interval (CI) were calculated using 10 and 20 μg Hb/g faeces as thresholds. Subgroup analysis was conducted to assess differences between centre, age category (<50, 50–69 and >69 years), sex, presence of symptoms and CRC location due to their potential association with FIT accuracy. The number of colonoscopy examinations needed to detect a subject with CRC (number necessary to scope) and the number of missed CRC per 1000 patients evaluated were calculated for each subgroup. A *p*-value of <0.05 was deemed statistically significant. Statistical analysis was performed using SPSS v15.0 (SPSS, Inc.).

RESULTS

Participants

In the study period, 54,327 FIT samples were submitted from primary health care to San Sebastián's and Ourense's referral laboratories. Reasons for exclusion are detailed in the study population flow chart (Figure 1). We analysed data from 38,675 participants. Their median age was 65.2 years (interquartile range 25.1), and 54.0% (20,883/38,675) were female. Patient cohort characteristics are provided in Table 1.

Colorectal cancer

CRC was detected in 650 (1.7%) patients, with differences in prevalence regarding health area (San Sebastian = 1.1%, Ourense = 2.0%; $p < 0.001$), age group (<50 years old = 0.3%, 50–69 years old = 1.4%, >69 years old = 2.8%; $p < 0.001$) and sex (female = 1.1%, male = 2.3%; $p < 0.001$). Information regarding FIT indication and CRC location was only available for San Sebastian. The prevalence of CRC according to FIT indication was 1.4% in patients with gastrointestinal symptoms, 0.8% in opportunistic CRC screening and 0.4% in patients with gastrointestinal tract disorders different from CRC ($p = 0.02$). The rate of right-sided CRC was more common in females (females 49.1%, males 31.1%; $p = 0.04$). The delay between FIT determination date and the first recorded date in CMBD was significantly higher in FIT negative patients (<10 μg Hb/g faeces = 10.6 months, ≥10 μg Hb/g faeces = 5.9 months; $p < 0.001$) and inversely correlated with the amount of f-Hb detected ($r = -0.2$; $p < 0.001$).

Percentage of FIT above threshold

For the whole cohort, the percentage of patients with FIT result above the threshold was 20.7% and 14.6% at 10 and 20 μg Hb/g faeces thresholds, respectively, with statistically significant differences ($p < 0.01$) according to area, sex and CRC location (Tables 2 and 3).

Diagnostic accuracy for CRC detection

The AUC of FIT for CRC detection was 0.89 (95% CI 0.88–0.91), as shown in Figure S2. At the 10 μg Hb/g faeces threshold, the sensitivity and specificity for detecting CRC were 90.5% (95% CI 88.0%–92.5%) and 81.4% (95% CI 81.0%–81.8%), respectively (Table 2). In contrast, at the 20 μg Hb/g faeces threshold, sensitivity decreased by 3.1% and specificity increased by 6.5%. The PPV for CRC increased from 7.7% to 10.1% without changes in the NPV.

Effect of demographic variables on FIT performance characteristics

FIT sensitivity was not significantly different between sex or age category ($p > 0.1$). However, there were differences in specificity

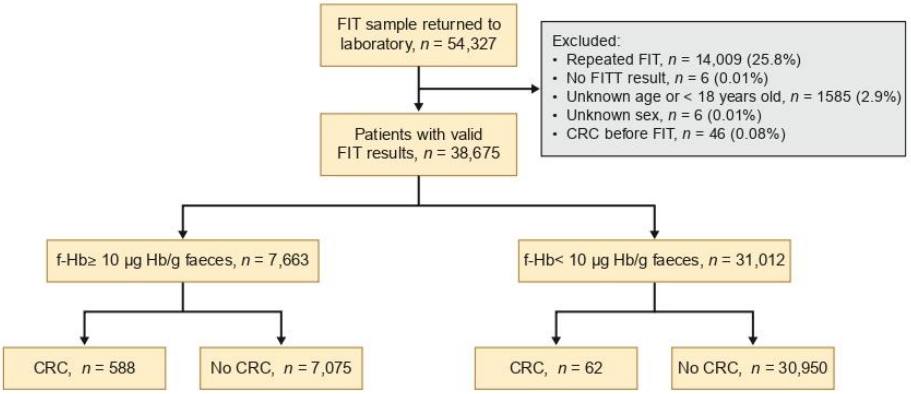

FIGURE 1 Study population flow chart. CRC, colorectal cancer; f-Hb, faecal haemoglobin concentration; FIT, faecal immunochemical test (threshold 10 μg Hb/g faeces)

TABLE 1 Characteristics of the individuals included in the analysis

	San Sebastián	Ourense	Total	*p*
CRC RSP starting year	2009	2015		
n (%)	12,674 (32.8)	26,001 (67.2)	38,675 (100)	
Median age (IQR)	61.2 (25.9)	66.8 (23.8)	65.2 (25.1)	0.000
<50 years (%)	3735 (29.5)	5131 (19.7)	8866 (22.9)	
50–69 years (%)	4664 (36.8)	9841 (37.8)	14,505 (37.5)	
≥70 years (%)	4275 (33.7)	11,029 (42.4)	15,304 (39.6)	
Female sex (%)	13,927 (53.6)	6956 (54.9)	20,883 (54.0)	0.01
CRC (%)	135 (1.1)	515 (2.0)	650 (1.7)	0.000
Right-sided[a]	49 (36.3)	ND		
Left-sided	78 (57.8)	ND		
Unknown side	8 (5.9)	ND		
Median latency (IQR)[b]	4.9 (6.1)	4.9 (5.8)	4.9 (5.8)	0.9
Median f-Hb (IQR)[c]	3.0 (22.0)	48.0 (136.0)	16.0 (81.0)	0.000
FIT ≥10 μg Hb/g faeces (%)	1993 (18.1)	5670 (21.8)	7663 (20.7)	0.000
FIT ≥20 μg Hb/g faeces (%)	1502 (11.9)	4143 (15.9)	5645 (14.6)	0.000
FIT indication (%)[d]				
Opportunistic screening	6383 (50.4)	ND		
Symptom study	5623 (44.4)	ND		
L-GI	4543 (80.8)	ND		
U-GI	526 (9.4)	ND		
Unspecific	554 (9.8)	ND		
Follow-up[e]	568 (4.5)	ND		

Abbreviations: CRC, colorectal cancer; FIT, faecal immunochemical test; f-Hb, faecal haemoglobin; IQR, interquartile range; L-GI, lower gastrointestinal symptom; ND, no data; RSP, regional screening programme; U-GI, upper gastrointestinal symptom.

[a]Right-sided CRC were located proximal to the splenic flexure.

[b]Latency was defined as the time elapsed between FIT determination and the date of hospital discharge in the Spanish Health System's Hospital Discharge Records Database (months).

[c]Median f-Hb was evaluated using continuous data from Ourense (n = 9300) and San Sebastián (n = 10,982).

[d]Indication was unknown in 100 (0.7%) patients.

[e]Indication was follow-up of known gastrointestinal pathology other than CRC or polyps: oesophagitis, gastritis, peptic ulcer, duodenitis, colonic diverticula, inflammatory bowel disease, haemorrhoids, ischaemic or infectious colitis and benign anorectal pathology.

between health area, sex and age category ($p < 0.001$). The PPV for CRC detection in the different subgroups ranged from 2.6% to 9.9%. However, the NPV for CRC was at least 99.6% for all subgroups analysed (Table 2).

Influence of symptoms and CRC location

Table 3 shows FIT characteristics based on CRC location and reason for FIT request in the San Sebastian cohort. These are detailed in Table 4. Sensitivity did not change significantly between symptomatic and asymptomatic patients (p = 0.7) despite differences in FIT positivity in those groups. However, specificity was significantly higher in opportunistic screening setting at both 10 and 20 μg Hb/g faeces thresholds ($p < 0.05$). Conversely, FIT specificity was similar regardless of CRC location (p = 0.4), while sensitivity decreased significantly in right-sided CRC at 10 and 20 μg Hb/g faeces thresholds ($p < 0.05$).

Effect of threshold on diagnostic yield for CRC

The difference in missed CRC using both thresholds was less than one in 1000 patients evaluated for any subgroup analysed.

TABLE 2 Diagnostic accuracy of a FIT for colorectal cancer by category and threshold

Threshold	Variable		*n*	P	% AT	Sensitivity[a]		Specificity[b]		PPV[a]	NPV[a,b]	LR+	LR−	DOR
≥10 μg Hb/g faeces	Area	Ourense	26,001	2.0	21.8	92.4 (89.8–94.4)	$p < 0.01$	79.6 (79.1–80.1)	$p < 0.001$	8.4 (7.7–9.1)	99.8 (99.7–99.9)	4.54	0.10	45.40
		San Sebastián	12,674	1.1	15.7	83.0 (75.7–88.4)		85.0 (84.4–85.6)		5.6 (4.7–6.7)	99.8 (99.7–99.9)	5.53	0.20	27.65
	Sex	Male	17,792	2.3	21.8	91.6 (88.6–93.9)	$p < 0.18$	79.9 (79.3–80.5)	$p < 0.001$	9.9 (9.0–10.8)	99.7 (99.7–99.8)	4.56	0.11	41.45
		Female	20,883	1.1	18.1	88.4 (83.7–91.9)		82.6 (82.1–83.2)		5.4 (4.8–6.2)	99.8 (99.8–99.9)	5.09	0.14	36.36
	Age	<50 years	8866	0.3	11.7	93.1 (78.0–98.1)	$p < 0.70$	88.5 (87.9–89.2)	$p < 0.001$	2.6 (1.8–3.8)	99.97 (99.91–99.99)	8.12	0.08	101.50
		50–69 years	14,505	1.4	17.4	91.5 (86.8–94.6)		83.6 (83.0–84.2)		7.3 (6.3–8.3)	99.9 (99.8–99.9)	5.59	0.10	55.90
		>69 years	15,304	2.8	26.8	89.8 (86.5–92.3)		75.0 (74.3–75.7)		9.2 (8.4–10.1)	99.6 (99.5–99.7)	3.59	0.14	25.64
	All patients		38,675	1.7	19.8	90.5 (88.0–92.5)		81.4 (81.0–81.8)		7.7 (7.1–8.3)	99.8 (99.7–99.8)	4.86	0.11	44.18
≥20 μg Hb/g faeces	Area	Ourense	26,001	2.0	15.9	89.9 (87.0–92.2)	$p < 0.01$	85.6 (85.1–86.0)	$p < 0.001$	11.2 (10.3–12.2)	99.8 (99.7–99.8)	6.22	0.11	56.54
		San Sebastián	12,674	1.1	11.9	79.3 (71.7–85.2)		88.9 (88.3–89.4)		7.1 (5.9–8.5)	99.7 (99.6–99.8)	7.12	0.23	30.96
	Sex	Male	17,792	2.3	16.6	89.4 (86.1–92.0)	$p < 0.07$	85.1 (84.6–85.6)	$p < 0.001$	12.6 (11.5–13.9)	99.7 (99.6–99.8)	6.02	0.12	50.17
		Female	20,883	1.1	12.9	84.5 (79.4–88.6)		87.9 (87.5–88.4)		7.3 (6.4–8.4)	99.8 (99.7–99.9)	7.01	0.18	38.94
	Age	<50 years	8866	0.3	8.5	89.7 (73.6–96.4)	$p < 0.85$	91.8 (91.2–92.3)	$p < 0.001$	3.4 (2.4–5.0)	99.96 (99.89–99.99)	10.87	0.11	98.82
		50–69 years	14,505	1.4	12.4	88.5 (83.3–92.2)		88.7 (88.1–89.2)		9.8 (8.6–11.3)	99.8 (99.7–99.9)	7.81	0.13	60.08
		>69 years	15,304	2.8	26.8	87.2 (83.6–90.0)		81.7 (81.1–82.3)		11.9 (10.8–13.1)	99.6 (99.4–99.7)	4.76	0.16	29.75
	All patients		38,675	1.7	14.6	87.7 (84.9–90.0)		86.7 (86.3–87.0)		10.1 (9.3–10.9)	99.8 (99.7–99.8)	6.57	0.14	46.93

Abbreviations: % AT, percentage of FIT above threshold; DOR, diagnostic odds ratio; FIT, faecal immunochemical test; LR, likelihood ratio; NPV, negative predictive value; P, colorectal cancer prevalence; PPV, positive predictive value.

[a]Values are expressed as percentages and their 95% confidence interval.

[b]Some NPV results are rounded to two decimals, as they could be incorrectly interpreted if they were rounded to one decimal (100.0).

TABLE 3 Diagnostic accuracy of a FIT for colorectal cancer by indication, location and threshold in San Sebastián

Threshold	Variable		*n*	P	% AT	Sensitivity[a]		Specificity[a]		PPV[a]	NPV[a]	LR+	LR−	DOR
≥10 µg Hb/g faeces	Indication	Opportunistic screening	6383	0.8	14.6	84.9 (72.9–92.1)	$p < 0.7$	86.0 (85.1–86.8)	$p < 0.05$	4.8 (3.6–6.4)	99.9 (99.7–99.9)	6.05	0.18	33.61
		Symptom study	5623	1.4	16.8	81.3 (71.3–88.3)		84.1 (83.1–85.1)		6.9 (5.4–8.7)	99.7 (99.5–99.8)	5.12	0.22	23.27
		Follow-up	568	0.4	21.6	100.0 (34.2–100.0)		82.5 (79.2–85.4)		2.0 (0.5–6.9)	100.0 (99.2–100.0)	5.72	0.00	NA
	Location	Right sided	12,588	0.4	15.2	69.4 (55.5–80.5)	$p < 0.01$	85.0 (84.4–85.6)	$p < 0.4$	1.8 (1.3–2.5)	99.9 (99.8–99.9)	4.63	0.36	12.86
		Left sided	12,617	0.6	15.5	91.0 (82.6–95.6)		85.0 (84.4–85.6)		3.6 (2.9–4.6)	99.9 (99.87–99.97)	6.07	0.11	55.18
≥20 µg Hb/g faeces	Indication	Opportunistic screening	6383	0.8	11.0	79.2 (66.5–88.0)	$p < 0.7$	89.6 (88.8–90.3)	$p < 0.05$	6.0 (4.5–8.0)	99.8 (99.7–99.9)	7.64	0.23	33.22
		Symptom study	5623	1.4	12.8	78.8 (68.6–86.3)		88.2 (87.3–89.0)		8.8 (6.9–11.1)	99.7 (99.4–99.8)	6.66	0.24	27.75
		Follow-up	568	0.4	13.6	100.0 (34.2–100.0)		86.7 (83.7–89.3)		2.6 (0.7–9.0)	100.0 (99.2–100.0)	7.55	0.00	NA
	Location	Right sided	12,588	0.4	11.3	65.3 (51.3–77.1)	$p < 0.01$	88.9 (88.3–89.4)	$p < 0.4$	2.2 (1.6–3.1)	99.8 (99.8–99.9)	5.87	0.39	15.05
		Left sided	12,617	0.6	11.6	87.2 (78.0–92.9)		88.9 (88.3–89.4)		4.6 (3.7–5.9)	99.9 (99.84–99.95)	7.84	0.14	56.00

Abbreviations: % AT, percentage of FIT above threshold; DOR, diagnostic odds ratio; FIT, faecal immunochemical test; LR, likelihood ratio; NPV, negative predictive value; P, colorectal cancer prevalence; PPV, positive predictive value.

[a]Values are expressed as percentages and their 95% confidence interval.

However, FIT positivity was higher using the lowest threshold (Tables 5 and 6).

DISCUSSION

Statement of principal findings

In this study, we evaluated performing FIT (OC-Sensor^{TM}) at different thresholds in daily clinical practice in primary health care, outside the scope of regional CRC screening programmes. We confirm FIT has high sensitivity to detect CRC in this setting using both 10 and 20 µg Hb/g faeces thresholds. Furthermore, unlike specificity, FIT sensitivity was not significantly influenced by characteristics related to the patient clinical spectrum such as demographics (sex and age group) or symptoms. Conversely, sensitivity was significantly impaired in right-sided lesions. Most importantly, NPV was >99.2% in any situation evaluated, covering a wide range of CRC prevalence. Thus, at the 20 µg Hb/g faeces threshold, fewer than one additional CRC would be missed per 1000 patients evaluated, while approximately 1.3 more colonoscopy examinations were needed to identify a CRC using the lowest threshold for any situation analysed.

Strengths and weaknesses

The main strength of this study is the large sample size. In addition, our data were collected from a daily clinical practice setting where initial suspicion of CRC arises and comprised any requested FIT in the aforementioned scenario. The main limitation of this study was the absence of colonoscopy as a reference standard.

Previous studies reported overestimation of sensitivity in registry-based studies evaluating diagnostic performance of FIT, but that bias mainly affected studies with 1 year of follow-up.[18] Furthermore, one meta-analysis detected similar sensitivity and specificity between studies using colonoscopy to follow-up all participants and those using 2-year registry follow-up.[19] Moreover, our study included cases of CRC requiring hospitalization, which is not equivalent to the true CRC incidence in the population, as in situ CRC would not be detected by the CBMD. The effect of this information bias could be to overinflate sensitivity, as a significant number of supposed 'true negatives' might actually be fully endoscopically resectable CRC which therefore would not require hospital admission. However, the effect of this bias could also be the opposite. Our study could underestimate FIT sensitivity, as detectable f-Hb has been revealed to correlate with the severity of an underlying lesion, and many false positives could be related not only to advanced adenomas or other significant colonic lesions but also to in situ colorectal carcinomas.[20] Another weakness of the study is the lack of detailed information on the clinical spectrum of patients. Non-specific gastrointestinal symptoms commonly associated with CRC are common and sometimes unreported among apparently

TABLE 4 Diagnostic accuracy of a FIT for colorectal cancer by indication and threshold in San Sebastián

Threshold	Indication[a]		*n*	P	% AT	Sensitivity[b]	Specificity[b]	PPV[b]	NPV[b]	LR+	LR−	DOR
≥10 μg Hb/g faeces	Opportunistic screening	Scheduled analysis	2332	0.7	12.4	82.4 (59.0–93.8)	88.1 (86.7–89.4)	4.8 (2.9–8.0)	99.9 (99.6–99.95)	6.93	0.20	34.65
		Non-digestive issue	2047	1.0	15.3	90.5 (71.1–97.3)	85.4 (83.8–86.9)	6.1 (3.9–9.3)	99.9 (99.6–99.97)	6.21	0.11	56.45
		Personal background	290	1.0	15.2	100.0 (43.9–100.0)	85.7 (81.2–89.3)	6.8 (2.3–18.2)	100.0 (98.5–100.0)	7.00	0.00	NA
		Other[c]	1182	1.0	20.9	75.0 (46.8–91.1)	79.7 (77.3–81.9)	3.6 (1.9–6.8)	99.7 (99.1–99.9)	3.69	0.31	11.90
	Symptom study	L-GI symptom	4543	1.6	17.6	80.6 (70.0–88.4)	83.4 (82.3–84.5)	7.3 (5.7–9.3)	99.6 (99.4–99.8)	4.87	0.23	21.17
		• Abdominal pain	1008	0.9	13.5	88.9 (56.5–98.0)	87.2 (85.0–89.1)	5.9 (3.0–11.2)	99.9 (99.4–99.98)	6.94	0.13	53.38
		• Diarrhoea	825	1.3	18.2	90.9 (62.3–98.4)	82.8 (80.1–85.2)	6.7 (3.7–11.8)	99.9 (99.2–99.97)	5.29	0.11	52.9
		• Constipation	319	1.2	20.4	100.0 (51.0–100.0)	80.6 (75.9–84.6)	6.2 (2.4–14.8)	100.0 (98.5–100.0)	5.16	0.00	NA
		• High-risk patients[d]	1800	2.7	24.3	77.6 (64.1–87.0)	77.2 (64.1–87.0)	8.7 (6.4–11.7)	99.2 (98.6–99.5)	3.40	0.30	11.33
		• Other[e]	1129	0.5	10.6	83.3 (43.7–97.0)	89.8 (87.8–91.4)	4.2 (1.8–9.4)	99.9 (99.4–99.98)	8.14	0.19	42.84
		U-GI symptom	526	1.0	11.4	80.0 (37.6–96.4)	89.3 (86.3–91.6)	6.7 (2.6–15.9)	99.8 (98.9–99.96)	7.44	0.22	33.82
		Unspecific symptom[f]	554	0.5	15.7	100.0 (43.9–100.0)	84.8 (81.5–87.5)	3.4 (1.2–9.7)	100.0 (99.2–100.0)	6.56	0.00	NA
	Follow-up	Benign anorectal	259	0.4	16.2	100.0 (20.7–100.0)	84.1 (79.2–88.1)	2.4 (0.4–12.3)	100.0 (98.3–100.0)	6.29	0.00	NA
		U-GI pathology	121	0.8	13.2	100.0 (20.7–100.0)	87.5 (80.4–92.3)	6.3 (1.1–28.3)	100.0 (96.5–100.0)	8.00	0.00	NA
≥20 μg Hb/g faeces	Opportunistic screening	Scheduled analysis	2332	0.7	8.9	70.6 (46.9–86.7)	91.6 (90.4–92.6)	5.8 (3.3–9.9)	99.8 (99.4–99.9)	8.38	0.32	26.19
		Non-digestive issue	2047	1.0	11.2	85.7 (65.4–95.0)	89.5 (88.1–90.8)	7.8 (5.0–12.0)	99.8 (99.5–99.9)	8.19	0.16	51.19
		Personal background	290	1.0	11.4	100.0 (43.9–100.0)	89.5 (85.5–92.6)	9.1 (3.1–23.6)	100.0 (98.5–100.0)	9.60	0.00	NA
		Other[c]	1182	1.0	17.0	75.0 (46.8–91.1)	83.6 (81.4–85.6)	4.5 (2.4–8.3)	99.7 (99.1–99.9)	4.57	0.30	15.23
	Symptom study	L-GI symptom	4543	1.6	13.4	77.8 (66.9–85.8)	87.6 (86.6–88.6)	9.2 (7.1–11.7)	99.6 (99.3–99.7)	6.29	0.25	25.16
		• Abdominal pain	1008	0.9	9.8	88.9 (56.5–98.0)	90.9 (88.9–92.5)	8.1 (4.2–15.1)	99.9 (99.4–99.98)	9.76	0.12	81.33
		• Diarrhoea	825	1.3	14.2	81.8 (52.3–94.9)	86.7 (84.2–88.9)	7.7 (4.1–14.0)	99.7 (99.0–99.9)	6.18	0.21	29.43
		• Constipation	319	1.2	16.0	100.0 (51.0–100.0)	85.1 (80.7–88.6)	7.8 (3.1–18.5)	100.0 (98.6–100.0)	6.70	0.00	NA
		• High-risk patients[d]	1800	2.7	19.1	73.5 (59.7–83.8)	82.5 (80.6–84.2)	10.5 (7.7–14.2)	99.1 (80.4–83.9)	4.19	0.32	13.09
		• Other[e]	1129	0.5	8.1	83.3 (43.7–97.0)	92.3 (90.6–93.8)	5.5 (2.4–12.2)	99.9 (99.5–99.98)	10.88	0.18	60.44
		U-GI symptom	526	1.0	8.7	80.0 (37.6–96.4)	91.9 (89.3–94.0)	8.7 (3.4–20.3)	99.8 (99.8–99.96)	9.92	0.22	45.09
		Unspecific symptom[f]	554	0.5	11.4	100.0 (43.9–100.0)	89.1 (86.2–91.4)	4.8 (1.6–13.1)	100.0 (99.2–100.0)	9.18	0.00	NA
	Follow-up	Benign anorectal	259	0.4	12.7	100.0 (20.7–100.0)	87.6 (83.0–91.1)	3.0 (0.5–15.3)	100.0 (98.3–100.0)	8.06	0.00	NA
		U-GI pathology	121	0.8	7.4	100.0 (20.7–100.0)	93.3 (87.4–96.6)	11.1 (2.0–43.5)	100.0 (96.7–100.0)	15.00	0.00	NA

Abbreviations: % AT, percentage of FIT above threshold; CRC, colorectal cancer; DOR, diagnostic odds ratio; FIT, faecal immunochemical test; L-GI, lower gastrointestinal symptom; LR, likelihood ratio; NPV, negative predictive value; P, colorectal cancer prevalence; PPV, positive predictive value; U-GI, upper gastrointestinal symptom.

[a]FIT accuracy could not be assessed, as there was no CRC in the following categories: 'opportunistic screening due to family background (colorectal cancer or polyp)' (387 patients; 17 with a FIT above threshold), 'opportunistic screening due to unexplained blood test abnormality (except anaemia)' (145 patients; 24 with a FIT above threshold) and 'follow-up of lower gastrointestinal pathology' (188 patients; 43 with a FIT above threshold). Indication was not specified in 100 patients.

[b]Values are expressed as percentages and their 95% confidence interval.

[c]Other situations where a primary care physician decided to perform a FIT in an asymptomatic patient outside the scope of the regional colorectal screening programme.

[d]High-risk patients: patients aged ≥50 years with unexplained rectal bleeding ($n = 143$) and patients aged ≥60 years with anaemia ($n = 1208$) or diarrhoea ($n = 445$) and patients with abdominal mass ($i = 4$).

[e]Other: patients aged <50 years with unexplained rectal bleeding ($n = 93$) and patients aged <60 with anaemia ($n = 656$) or diarrhoea ($n = 380$).

[f]Unspecific symptoms: dizziness, syncope, weight or appetite loss, fatigue, general malaise or asthenia.

healthy people,[21] and categorizing a patient as 'asymptomatic' based on a recorded reason for FIT request has a high risk of bias.

Strengths and weaknesses in relation to other studies

Our findings are consistent with previous meta-analyses summarizing studies performed in different settings.[3,4]

Information on sex differences in population-based FIT screening has been conflicting, and sex-tailored thresholds were proposed by some authors to increase the optimal use of colonoscopy resources.[22] A recent meta-analysis did not detect any statistically significant differences in FIT accuracy by sex or age,[19] and our results were in line with this meta-analysis conclusion.

An interesting finding in the subgroup analysis is the different FIT sensitivity between areas. Despite cohorts from San Sebastian and Ourense being statistically different in terms of demographic characteristics, stratified subgroup analysis by sex and age groups in both cohorts, as well as the previously mentioned studies discussing the effect of age and sex on FIT sensitivity, suggest that those differences do not account for the different performance of FIT to rule out CRC between them.

For proper interpretation of results, it is important note that the regional CRC screening programme began in San Sebastian and Ourense in 2009 and 2015, respectively. The impact of those preventive programmes on pathology detected in subsequent colonoscopy explorations has been reported before.[23,24]

Our study revealed both lower CRC prevalence and FIT positivity for any demographic subgroup evaluated in San Sebastian, which is in line with those studies and could explain the decrease in FIT sensitivity in that population with regard to the population of Ourense.

Moreover, FIT-based screening programmes have an impact both on proximal and distal CRC surgery rates.[25] Since right-sided lesions are known to be more difficult to detect by FIT,[26] subsequent screening rounds could select not only CRC with lower rates of bleeding (i.e. early-stage CRC) but also right-sided CRC.

It was also noteworthy that our data revealed a downward trend in FIT sensitivity for the group of females older than 69 years from San Sebastian compared to data for males of the same age. Although data are only available for the area of San Sebastian, females older than 69 years have been shown to present a right-sided CRC prevalence, which is significantly higher than males in the same age group,[27] thus providing a possible explanation for this finding. However, we would need to know the percentage of right-sided CRC in Ourense to confirm this assumption. Another hypothesis suggested to account for differences in FIT screening between females and males (i.e. different amount of globin or colonic transit time between the sexes) could not account for the differences in FIT sensitivity between females of the same age group from both areas.[19,28]

TABLE 5 Performance of FIT when threshold is increased from 10 μg Hb/g faeces to 20 μg Hb/g faeces by sex and age

		Threshold 10 μg Hb/g faeces			Threshold 20 μg Hb/g faeces		
Patient	P	FP (%)	Missed CRC[a] (95% CI)	NNS (95% CI)	FP (%)	Missed CRC[a] (95% CI)	NNS (95% CI)
<50 years							
Male	0.4	12.5	0.3 (0.0–1.7)	31.8 (19.8–51.3)	9.2	0.6 (0.2–2.0)	25.1 (15.5–41.2)
Female	0.2	10.5	0.2 (0.0–1.3)	48.4 (27.3–86.4)	7.4	0.2 (0.0–1.2)	34.4 (19.5–61.2)
All	0.3	11.4	0.3 (0.1–0.9)	38.5 (26.7–55.9)	8.2	0.4 (0.1–1.1)	29.0 (20.0–42.4)
50–69 years							
Male	2.0	18.1	1.9 (1.1–3.4)	11.0 (9.3–13.0)	13.2	2.1 (1.3–3.7)	8.4 (7.2–9.9)
Female	0.8	14.3	1.0 (0.4–2.1)	20.5 (15.8–26.6)	9.2	1.5 (0.8–2.8)	14.6 (11.2–19.1)
All	1.4	16.1	1.4 (0.9–2.3)	13.8 (12.0–15.9)	11.2	1.8 (1.2–2.7)	10.2 (8.8–11.7)
>69 years							
Male	3.9	25.4	4.8 (3.2–7.2)	8.2 (7.3–9.3)	19.0	5.6 (3.9–8.0)	6.5 (5.8–7.4)
Female	1.9	23.5	3.1 (2.0–4.8)	15.3 (13.0–17.9)	16.8	3.6 (2.4–5.3)	11.6 (9.9–13.6)
All	2.8	24.3	3.8 (2.8–5.2)	10.8 (9.9–11.9)	17.8	4.4 (3.4–5.8)	8.4 (7.7–9.3)
Total							
Male	2.3	19.6	2.5 (1.8–3.5)	10.1 (9.2–11.2)	14.5	3.0 (2.2–4.0)	7.9 (7.2–8.7)
Female	1.1	17.2	1.6 (1.1–2.3)	18.4 (16.1–21.0)	11.9	2.0 (1.4–2.7)	13.6 (11.9–15.6)
All	1.7	18.3	2.0 (1.6–2.6)	13.0 (12.1–14.1)	13.1	2.4 (1.9–3.0)	9.9 (9.2–10.7)

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; FP, percentage of patients without CRC and a FIT value above the threshold; NNS, number necessary to scope; P, colorectal cancer prevalence.

[a]Missed CRC per 1000 patients evaluated with FIT.

Implications for clinical practice and research

Our data confirm that FIT can be used as an aid to daily clinical practice in primary health care, as reported in recent studies,[9–12] but also suggest that an increase in the NICE recommended threshold does not lead to a rise in the number of missed CRC in any demographic subgroup and avoids unnecessary colonoscopy examinations. This may be of particular relevance to special situations such as the current coronavirus disease 2019 pandemic in which colonoscopy availability is severely curtailed, and also in the many European countries that have limited colonoscopy capacity.

Despite this, it can be argued that some of these examinations could lead to an advanced adenoma diagnosis, thus contributing to CRC prevention. However, CRC develops from a premalignant lesion (adenomatous polyp) in >70% of cases throughout a process that can last approximately 10 years.[29] Therefore, it is likely that this kind of lesion could be subsequently diagnosed when it is still in an endoscopically fully resectable stage. A recent study in a screening setting used three categories of FIT below 20 μg Hb/g faeces—0 to 3.8 μg Hb/g faeces, 3.9–9.9 μg Hb/g faeces and 10.0–19.9 μg Hb/g faeces—and demonstrated that the probability of testing positive and being diagnosed in subsequent screening rounds of advanced neoplasia or CRC interval rose with increasing values of FIT.[30] Thus, repeating FIT determination in a scheduled interval could also be an alternative strategy in the assessment of patients in primary health care to 'rescue' those early-stage lesions without increasing colonoscopy resource demand. Another recent proposal is to refer for colonoscopy those patients with cumulative f-Hb concentration ≥20 μg Hb/g faeces over two 'negative' tests.[31] We believe that these data provide the basis to justify a clinical trial in which the risks and benefits of both thresholds could be prospectively compared.

Meanwhile, prioritizing individuals for colonoscopy examinations by f-Hb concentration could diminish latency time to diagnosis.[5] Ideally, this should be in a dynamic waitlist manner. The Model for End-Stage Liver Disease is also used to prioritize a liver transplant waitlist. Furthermore, close monitoring of FIT characteristics locally could enable rapid adjustment of FIT thresholds to optimize each area's resources.[32]

Moreover, managing colonoscopy resources efficiently goes beyond the costs.[33] A recent study reported that latency higher than 12 months after the initial positive FIT was associated with more advanced disease and higher mortality due to CRC.[34] In our study, the mean time from FIT determination to initial hospital discharge with a CRC diagnosis exceeded 10 months for FIT negative patients, and was almost twice with respect to patients with a positive FIT result. Another study revealed that a direct referral to colonoscopy from primary health care reduces the risk of mortality.[35] It is therefore important that FIT can be introduced into daily clinical practice at this care level at an optimal threshold.

TABLE 6 Performance of FIT when threshold is increased from 10 μg Hb/g faeces to 20 μg Hb/g faeces by indication and location (San Sebastián)

			Threshold 10 μg Hb/g faeces			Threshold 20 μg Hb/g faeces		
			Missed CRC[a]			Missed CRC[a]		
Variable		P	FP (%)	(95% CI)	NNS (95% CI)	FP (%)	(95% CI)	NNS (95% CI)
Opportunistic screening	Scheduled analysis	0.7	11.8	1.5 (0.5-4.3)	20.6 (12.6-34.4)	8.4	2.3 (1.0-5.5)	17.3 (10.1-29.9)
	Non-digestive issue	1.0	14.4	1.1 (0.3-4.2)	16.5 (10.8-25.6)	10.4	1.7 (0.6-4.8)	12.8 (8.3-20.0)
	Personal background	1.0	14.1	0.0 (0.0-15.4)	14.7 (5.5-42.6)	10.3	0.0 (0.0-14.7)	11.0 (4.2-31.8)
	Other[b]	1.0	20.1	3.2 (1.1-9.4)	27.4 (14.8-51.8)	16.2	3.1 (1.0-8.9)	22.3 (12.1-42.1)
Symptom study	L-GI symptom	1.6	16.3	3.7 (2.2-6.3)	13.8 (10.8-17.7)	12.2	4.1 (2.5-6.6)	10.9 (8.5-14.0)
	• Abdominal pain	0.9	12.7	1.1 (0.2-6.5)	17.0 (8.9-33.2)	9.0	1.1 (0.2-6.2)	12.4 (6.6-24.1)
	• Diarrhoea	1.3	17.0	1.5 (0.3-8.3)	15.0 (8.4-27.3)	13.1	2.8 (0.8-10.2)	13.0 (7.2-24.4)
	• Constipation	1.3	19.1	0.0 (0.0-14.9)	16.2 (6.8-41.3)	14.7	0.0 (0.0-14.1)	12.8 (5.4-32.3)
	• High-risk patient[c]	2.7	22.2	8.1 (4.5-14.4)	11.5 (8.8-15.7)	17.1	8.9 (5.2-15.2)	9.5 (7.0-13.0)
	• Other[d]	0.5	10.2	1.0 (0.2-5.6)	24.0 (10.7-55.8)	7.6	1.0 (0.2-5.4)	18.2 (8.2-42.2)
	U-GI symptom	1.0	10.6	2.2 (0.4-12.1)	15.0 (6.3-38.1)	8.0	2.1 (0.4-11.7)	11.5 (4.9-29.1)
	Non-specific symptom[e]	0.5	15.2	0.0 (0.0-8.2)	29.0 (10.4-84.7)	10.8	0.0 (0.0-7.8)	21.0 (7.6-61.2)
Follow up	Benign anorectal	0.4	15.8	0.0 (0.0-17.4)	42.0 (8.1-237.0)	12.4	0.0 (0.0-16.7)	33.0 (6.5-186.2)
	U-GI	0.8	12.4	0.0 (0.0-55.3)	16.0 (3.5-89.9)	6.6	0.0 (0.0-33.2)	9.0 (2.3-50.3)
Location	Left sided	0.6	14.9	0.7 (0.3-1.4)	27.5 (21.9-34.6)	11.1	0.9 (0.5-1.7)	21.5 (17.1-27.2)
	Right sided	0.4	14.9	1.4 (0.8-2.3)	56.3 (40.5-78.6)	11.1	1.5 (0.9-2.4)	44.6 (31.8-62.8)

Abbreviations: CI, confidence interval; CRC, colorectal cancer; FIT, faecal immunochemical test; FP, percentage of patients without CRC and a FIT value above the threshold; L-GI, lower gastrointestinal symptom; NNS, number necessary to scope; P, colorectal cancer prevalence; U-GI, upper gastrointestinal symptom.

[a]Missed CRC per 1000 patients evaluated with FIT.

[b]Other situations where a primary care physician decided to perform a FIT in an asymptomatic patient outside the scope of the regional colorectal screening programme.

[c]High-risk patients: patients aged ≥50 years with unexplained rectal bleeding (n = 143) and patients aged ≥60 years with anaemia (n = 1208) or diarrhoea (n = 445) and patients with abdominal mass (n = 4).

[d]Other: patients aged <50 years with unexplained rectal bleeding (n = 93) and patients aged <60 years with anaemia (n = 656) or diarrhoea (n = 380).

[e]Unspecific symptoms: dizziness, syncope, weight or appetite loss, fatigue, general malaise or asthenia.

CONCLUSIONS

Our study confirms that FIT is highly sensitive for CRC detection in daily primary health care using a threshold of either 10 or 20 μg Hb/g faeces. The use of a threshold higher than that recommended by NICE (20 μg Hb/g instead of 10 μg Hb/g faeces) could reduce the number of colonoscopy examinations and therefore the latency time of FIT positive patients to be evaluated without missing more than one CRC per 1000 patients evaluated belonging to the low-risk group defined by the NICE recommendation. Right-sided CRC are more likely to be missed by FIT and may justify a relevant percentage of false-negative results in elderly, particularly female, patients. Any strategy using FIT to aid clinical assessment of this particular demographic subgroup must be especially monitored.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

The study protocol is compliant with the ethics guidelines of the 1975 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Galicia (Code 2017/277) under the resolution dated 20 June 2017. This committee confirmed that no formal written consent for ethics approval was required in this study. Data were anonymised after linkage between databases.

INFORMED CONSENT

No formal written consent was required in this study.

ORCID

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SUPPORTING INFORMATION

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

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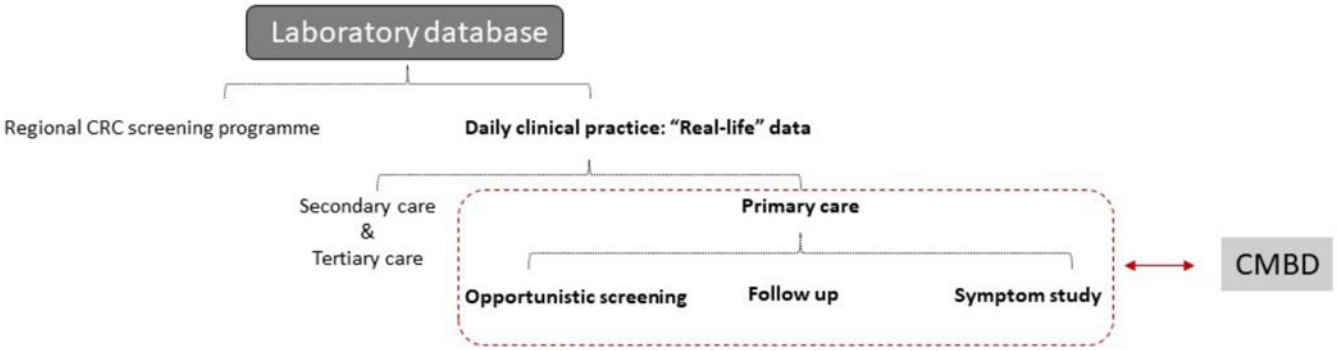
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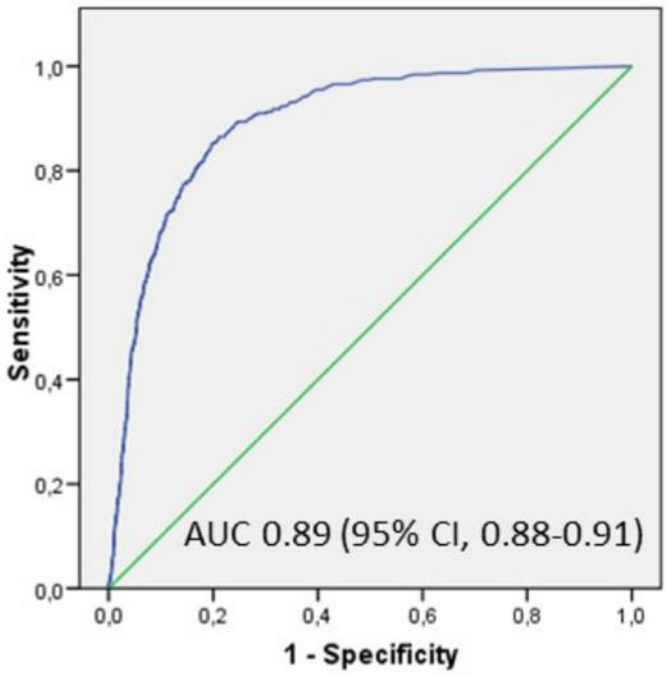
Daily clinical practice: "Real-life" data
Secondary care
&
Tertiary care
Primary care
Opportunistic screening
Follow up
Symptom study
CMBD


Sensitivity
1 - Specificity
AUC 0.89 (95% CI, 0.88-0.91)
0,0
0,2
0,4
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0,8
1,0

Metodología y resultados - Artículo 3

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk of gastrointestinal cancer in a symptomatic cohort after a complete colonoscopy: Role of faecal immunochemical test

Noel Pin-Vieito, María J Iglesias, David Remedios, Lorena Rodríguez-Alonso, Francisco Rodriguez-Moranta, Victoria Álvarez-Sánchez, Fernando Fernández-Bañares, Jaume Boadas, Eva Martínez-Bauer, Rafael Campo, Luis Bujanda, Ángel Ferrandez, Virginia Piñol, Daniel Rodríguez-Alcalde, Jordi Guardiola, Joaquín Cubiella, on behalf of the COLONPREDICT study investigators

Factor de impacto: 5.742

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Objetivo

Calcular el riesgo de detección de tumores del tracto gastrointestinal (TTGI) y muerte en pacientes sintomáticos con una determinación de SOH-i positiva sin CCR en una colonoscopia completa con buena preparación intestinal.

Métodos

Análisis retrospectivo post hoc dentro del estudio COLONPREDICT [134], destinado a evaluar la precisión de SOH-i para detectar CCR en una cohorte ambulatoria de pacientes con síntomas digestivos a los que se solicita una determinación de Hb-f previa a la realización de colonoscopia como parte de su evaluación. Se incluyeron aquellos pacientes con colonoscopia completa sin CCR y seguimiento de al menos dos años, definiendo dos cohortes: SOH-i $\geq$ 20 µg Hb/g de heces y < 20 µg Hb/g de heces.

Se revisó la historia clínica recogiendo las variables sexo, edad, fecha de diagnóstico de cáncer (tipo y localización) o muerte durante el seguimiento y presencia previa de lesión colónica significativa (LCS) (adenoma avanzado, colitis, angioectasia sangrante, diverticulosis o úlcera rectal complicada).

Se realizó un análisis descriptivo de los TTGI detectados durante el seguimiento y la mortalidad. Se estimaron las diferencias de riesgo de detección de TTGI y mortalidad entre las dos cohortes mediante regresión logística y de riesgos proporcionales ajustando por edad, sexo y presencia de lesiones colónicas significativas (LCS) en la colonoscopia.

Resultados

Se incluyeron 2,709 pacientes con colonoscopia completa sin CCR en el momento de inclusión, 730 (26.9%) con un resultado de SOH-i por encima del umbral escogido.

Las dos cohortes presentaron diferencias significativas respecto a edad (SOH-i positiva 65.5 ± 13.0 años vs 62.9 ± 13.5 años; $p < 0.001$) y sexo (SOH-i positiva 47.7% vs 54.8% mujeres; $p = 0.001$).

Durante un seguimiento medio de 45.5 ± 20.0 meses se detectaron 57 (2.1%) TTGI, de ellos 35 (1.3%) estaban localizados en el tracto gastrointestinal alto (6 lesiones esofágicas, 25 lesiones gástricas, 1 adenocarcinoma duodenal, 2 ampulomas y un tumor del estroma duodenal) y 14 (0.5%) en el colon (CCR). Además, se diagnosticaron 8 (0.3%) lesiones localizadas en áreas donde la realización de una gastroscopia o una colonoscopia no permite el diagnóstico (3 colangiocarcinomas, 2 adenocarcinomas de intestino delgado, 1 linfoma de intestino delgado, 1 carcinoma del seno piriforme y 1 carcinoma lingual). Por otra parte, fallecieron 36 (1.3%) pacientes en relación con TTGI: 22 (0.8%) en relación con una lesión en el tracto gastrointestinal alto y 9 (0.3%) debido a CCR.

Los pacientes con un resultado de SOH-i ≥ 20 μg Hb/g de heces mostraron un incremento significativo de riesgo de detección de CCR (HR 3.8, IC 95% 1.2-11.9) tras ajustar por edad, sexo y LCS. No se encontraron diferencias significativas en el riesgo de cáncer en el tracto gastrointestinal alto (HR 1.0, IC 95% 0.5-2.2). De la misma manera, los pacientes con un resultado de SOH-i ≥ 20 μg Hb/g de heces mostraron un incremento significativo de riesgo de fallecer por TTGI (HR 2.2, IC 95% 1.1-4.3) en relación con un mayor riesgo de muerte por CCR (HR 10.8, IC 95% 2.1-57.1) sin que existiesen diferencias en el riesgo de muerte por lesiones en tracto gastrointestinal alto (HR 1.4 IC 95% 0.6-3.3).

A lo largo del primer año tras la realización de una colonoscopia se detectaron lesiones en el tracto gastrointestinal alto en 22 (0.8%) pacientes. Se identificaron dos

variables asociadas de forma independiente: la presencia de anemia (OR 5.6, IC 95% 2.2-13.9) y la edad ≥ 70 años (OR 2.7, IC 95% 1.1-7.0)

Conclusión

Los pacientes con síntomas abdominales y una colonoscopia normal tienen un incremento moderado del riesgo de presentar una neoplasia en el tracto gastrointestinal alto independientemente del resultado de SOH-i. Los pacientes con con un resultado de SOH-i ≥ 20 μg Hb/g de heces tienen mayor riesgo de ser diagnosticados de CCR a pesar de tener una colonoscopia normal.

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the data and accuracy of the data analysis; Cubiella J and Pin-Vieito N acted as full guarantors of the research.

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Institutional review board statement: This is a post hoc cohort analysis performed within two prospective diagnostic test studies. The protocols of both studies conform to the ethical guidelines of the 1975 Declaration of Helsinki. COLONPREDICT study was approved by the Clinical Research Ethics Committee of Galicia (Code 2011/038) under resolution dated 11 April, 2012. The study of Rodríguez-Alonso *et al*. was approved by Bellvitge Hospital Clinical Research Ethics Committee (Code 21/11) on 1 December, 2011.

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Abstract

BACKGROUND

Faecal immunochemical test (FIT) has been recommended to assess symptomatic patients for colorectal cancer (CRC) detection. Nevertheless, some conditions could theoretically favour blood originating in proximal areas of the gastrointestinal tract passing through the colon unmetabolized. A positive FIT result could be related to other gastrointestinal cancers (GIC).

AIM

To assess the risk of GIC detection and related death in FIT-positive symptomatic patients (threshold 10 μg Hb/g faeces) without CRC.

METHODS

Post hoc cohort analysis performed within two prospective diagnostic test studies evaluating the diagnostic accuracy of different FIT analytical systems for CRC and significant colonic lesion detection. Ambulatory patients with gastrointestinal symptoms referred consecutively for colonoscopy from primary and secondary healthcare, underwent a quantitative FIT before undergoing a complete colonoscopy. Patients without CRC were divided into two groups (positive and negative FIT) using the threshold of 10 μg Hb/g of faeces and data from follow-up were retrieved from electronic medical records of the public hospitals involved in the research. We determined the cumulative risk of GIC, CRC and upper GIC. Hazard rate (HR) was calculated adjusted by age, sex and presence of significant colonic lesion.

RESULTS

We included 2709 patients without CRC and a complete baseline colonoscopy, 730 (26.9%) with FIT ≥ 10 μgr Hb/gr. During a mean time of 45.5 ± 20.0 mo, a GIC was detected in 57 (2.1%) patients: An upper GIC in 35 (1.3%) and a CRC in 14 (0.5%). Thirty-six patients (1.3%) died due to GIC: 22 (0.8%) due to an upper GIC and 9 (0.3%) due to CRC. FIT-positive subjects showed a higher CRC risk (HR 3.8, 95%CI: 1.2-11.9) with no differences in GIC (HR 1.5, 95%CI: 0.8-2.7) or upper GIC risk (HR 1.0, 95%CI: 0.5-2.2). Patients with a positive FIT had only an increased risk of CRC-related death (HR 10.8, 95%CI: 2.1-57.1) and GIC-related death (HR 2.2, 95%CI: 1.1-4.3), with no differences in upper GIC-related death (HR 1.4, 95%CI: 0.6-3.3). An upper GIC was detected in 22 (0.8%) patients during the first year. Two variables were independently associated: anaemia (OR 5.6, 95%CI: 2.2-13.9) and age ≥ 70 years (OR 2.7, 95%CI: 1.1-7.0).

CONCLUSION

Symptomatic patients without CRC have a moderate risk increase in upper GIC, regardless of the FIT result. Patients with a positive FIT have an increased risk of post-colonoscopy CRC.

Key words: Colonoscopy; Colorectal cancer; Faecal immunochemical test; Gastric cancer; Gastroesophageal cancer; Gastrointestinal cancer; Symptoms

Core tip: Our study, evaluates for the first time whether symptomatic patients with a positive faecal immunochemical test (FIT) result, no colorectal cancer (CRC) and a complete exploration of the colon have increased risk of related gastrointestinal cancer (GIC) detection or death. We found that this cohort of patients only have an increased risk of related CRC and death when compared with the cohort with a negative FIT result. Although the risk of upper GIC is higher than expected, the probability of detecting an upper GIC is unrelated to the FIT result and only associated with anaemia and advanced age.

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INTRODUCTION

The use of quantitative faecal immunochemical test (FIT) is increasing outside the screening setting. FIT has proved its ability to identify which symptomatic patients are more likely to have an underlying colorectal cancer (CRC) or even other significant colonic lesions (SCL). Therefore, it is useful to improve the suitability of referrals for investigation of abdominal symptoms[1].

In this sense, the National Institute for Health and Care Excellence (NICE) has recently recommended adoption of FIT in primary care to guide referral for suspected CRC in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral, and results should be reported using a threshold of 10 μg Hb/g faeces[2,3].

This has been possible due to the progressive replacement of the guaiac-based faecal occult blood test by the immunochemical-based test. FIT reacts with human globin, a protein digested by enzymes in the upper gastrointestinal tract (GIT), so it should have greater specificity to detect lower GIT lesions than guaiac-based tests and is not modified by diet[4,5]. Nevertheless, some conditions (*e.g.*, altered bowel habit, prior gastrectomy) could theoretically favour blood originating in proximal areas of the GIT passing through the colon unmetabolized. A previous systematic review led to the conclusion that there is insufficient evidence to recommend for or against routine esophagogastroduodenoscopy (EGD) in patients with a positive faecal occult blood test followed by negative colonoscopy[6].

However, all the studies included were mainly based on faecal occult blood test that used the guaiac method or had been performed in a screening setting. Thus, conclusions drawn from these data cannot be extrapolated to the application of FIT in symptomatic patients. These patients may require additional diagnostic workup as long as complaints could be related to bleeding lesions located in the GIT proximal to the colon[7]. Thus, we aim to assess the risk of gastrointestinal cancers (GIC) detection and related death in symptomatic patients with a positive determination of FIT (≥ 10 μg Hb/g faeces) without CRC at baseline quality colonoscopy and to evaluate whether it might be worthwhile to perform additional evaluations to detect an upper GIC.

MATERIALS AND METHODS

Study design

This is a post hoc cohort analysis performed within two prospective diagnostic test studies evaluating the diagnostic accuracy of different FIT analytical systems for CRC and SCL detection[8,9].

We followed the Strengthening the Reporting of Observational studies in Epidemiology statement to conduct and report our study[10]. The main characteristics of the different cohorts have been detailed elsewhere[8,9].

Inclusion and exclusion criteria

The study population consisted of ambulatory patients with gastrointestinal symptoms referred consecutively for colonoscopy from primary and secondary healthcare in ten out of the thirteen hospitals that took part in the primary studies. Patients included in the analysis underwent a quantitative FIT before undergoing a complete colonoscopy. Patients were excluded from this analysis if a CRC was detected on baseline exploration or the colonoscopy was incomplete. A colonoscopy was considered complete if more than 90% of the mucosa could be evaluated according to the Aronchick scale and caecal intubation was achieved[11]. In addition, patients were excluded from this analysis if follow-up after colonoscopy was insufficient (< 2 years) or a GIC was diagnosed before basal colonoscopy.

Definition of cohorts

Patients were divided into two groups (positive and negative FIT) using the threshold of 10 μg Hb/g of faeces. All individuals collected a stool sample from one bowel movement without specific diet or medication restrictions before colonoscopy. Characteristics of the different FIT system used are shown in Table 1. Estimates of faecal haemoglobin (f-Hb) were quantitated as μg Hb/g of faeces so that results could be compared across analytical systems[12].

Colonoscopy and pathology

The colonoscopist was blinded to the FIT results. The bowel was cleansed and sedated as previously reported and all colonoscopies were performed by experienced endoscopists who reported any colorectal lesion and obtained biopsies if appropriate[13]. All polyps were removed either upon baseline exploration or afterwards.

SCL was defined as advanced adenoma (any adenoma ≥ 10 mm, with high-grade dysplasia or villous histology), histologically confirmed colitis (any aetiology), polyps ≥ 10 mm, polyposis (> 10 polyps of any histology), complicated diverticular disease (bleeding, diverticulitis), bleeding angiodysplasia and colonic ulcer. Any other colonic lesion was considered non-significant.

Follow up and main outcome

The main outcomes of this analysis are GIC detection and GIC-related death. Data from follow-up were retrieved from electronic medical records of the public hospitals involved in the research. For all patients, cancer diagnoses of any aetiology were recorded. We classified all cancers that could justify the presence of blood in the GIT as a GIC: Oral, throat, oesophageal, gastric, intestinal and CRC. We defined an upper GIC as a cancer that can be detected in an EGD exploration: Oesophageal, gastric, duodenal or ampullary cancer. The cause and date of death were recorded. We pooled the different causes of death into five categories: related to (1) GIC, (2) Upper GIC, (3) CRC, (4) Global cancer or (5) Global death.

Data analysis

We first performed a descriptive analysis of the cohorts included in the analysis. We determined whether there were differences using the Chi-square and student *t* test in the qualitative and quantitative variables, respectively. We calculated cumulative risk and number of cases per 1000 patient-years and its 95% confidence interval (CI). Differences in cumulative risk were analysed with the Chi-square test and Cochran–Mantel–Haenszel statistics and expressed as the risk ratio (RR) and its 95%CI. In order to control confounding variables, age, sex and SCL, we performed a Cox regression analysis to determine the hazard ratio (HR) of detecting a new cancer and cancer-related death respectively.

In order to determine whether there was an association between the baseline faecal haemoglobin concentration and length of time to GIC detection, we performed a descriptive analysis and a correlation analysis. We determined the Spearman correlation coefficient (r).

Finally, we evaluated which variables were associated with detection of any upper GIC during the first year after baseline colonoscopy. In this respect, we determined which variables had a statistically significant association with detection of an upper GIC using the Chi-square and the Cochran–Mantel–Haenszel statistics and expressed the differences as RR and its 95%CI. We included variables with a statistically significant association ($P < 0.05$) in a multivariate logistic regression analysis and expressed the association as the odds ratio (OR) and 95%CI. Statistical analysis was performed using SPSS statistical software, version 15.0 (SPSS Inc., Chicago, IL, USA)

The statistical methods of this study were reviewed by Noel Pin Vieito from Complexo Hospitalario Universitario de Ourense.

RESULTS

Participants and descriptive data

We excluded 1347 patients out of the 4056 symptomatic patients initially included in both studies, yielding a final sample of 2709 (Figure 1).

Of these participants, 1979 (73.1%) and 730 (26.9%) had a negative and positive FIT, respectively. The cohorts included were different in terms of age, sex, healthcare referring to colonoscopy, colonoscopy indication, findings in baseline exploration and length of follow-up as shown in Table 2.

Table 1 Characteristics of the different faecal immunochemical tests evaluated

Ref.	Country	Analytical system for estimation of faecal haemoglobin concentration
Cubiella *et al*[9], 2016 (DC)	Spain	OC-Sensor: 100%
Rodríguez-Alonso *et al*[8], 2015	Spain	OC-Sensor: 100%
Cubiella *et al*[9], 2016 (VC)	Spain	OC-Sensor: 49.7%; OC-Auto 3 Latex 13.8%; FOB Gold 2.4%; Linear i-FOB 34.1%
Overall	Spain	OC-Sensor: 81.8%; OC-Auto 3 Latex 5.0%; FOB Gold 0.9%; Linear i-FOB 12.3%

DC: Derivation cohort; VC: Validation cohort.

Cancer incidence and death

During a mean time of 45.5 ± 20.0 mo, a GIC was detected in 57 (2.1%) patients: An upper GIC (six oesophageal carcinomas, 25 gastric carcinomas, one duodenal adenocarcinoma, two ampullary carcinomas and one duodenal GIST) in 35 (1.3%), a CRC in 14 (0.5%) and other GIC (three cholangiocarcinomas, two small bowel adenocarcinomas, one small bowel lymphoma, one lingual carcinoma and one piriform sinus carcinoma) in 8 (0.3%). The distribution of the GIC according to the FIT result is shown in Figure 1. Thirty-six patients (1.3%) died due to GIC: 22 (0.8%) due to an upper GIC and 9 (0.3%) due to CRC. Finally, 205 (7.6%) patients developed a cancer and 197 (7.3%) died, 98 (3.5%) due to cancer. Cumulative risk and number of cancers and death per 1000 patient-years is shown in Table 3.

Patients with positive FIT showed greater GIC risk (≥ 10 μg/g of faeces = 3.2%, < 10 μg/g of faeces = 1.7%; RR 1.9, 95%CI: 1.1-3.2) and GIC-related mortality (≥ 10 μg/g of faeces = 2.3%, < 10 μg/g of faeces = 1.0%; OR 2.5, 95%CI: 1.3-4.6). In the subgroup analysis, patients in the positive FIT cohort had an increased risk of CRC (≥ 10 μg/g of faeces = 1.1%, < 10 μg/g of faeces = 0.3%; RR 3.6, 95%CI: 1.3-10.5) and CRC-related mortality (≥ 10 μg/g of faeces = 1.0%, < 10 μg/g of faeces = 0.1%; RR 9.5, 95%CI: 2.0-46.2) but no differences in upper GIC or upper GIC-related mortality as shown in Table 3. However, in the Cox's proportional multivariate regression analysis, patients with a positive FIT had only an increased risk of CRC (HR 3.8, 95% CI 1.2-11.9), CRC-related death (HR 10.8, 95%CI: 2.1-57.1) and GIC-related death (HR 2.2, 95%CI: 1.1-4.3), after adjusting for confounding variables. The cumulative risk of cancer and related death calculated in the Cox's multivariate regression analysis is shown in Figure 2.

Faecal haemoglobin concentration and time of cancer diagnosis

Figure 3 links time elapsed until diagnosis of each GIC throughout follow-up with the FIT result. We did not detect a correlation between time to GIC diagnosis (r = -0.1; P = 0.4) or related death (r = -0.2; P = 0.3) and FIT result as shown in Figure 4.

Detection of upper GIC during the first year of follow-up

During the first year after baseline colonoscopy, 22 (0.8%) upper GIC were detected: 17 cases of gastric carcinomas, 4 oesophageal carcinomas and one ampullary carcinoma. Only two variables were independently associated with detection of an upper GIC during the first year: anaemia (OR 5.6, 95%CI: 2.2-13.9), defined as < 11 g/100 mL in men and < 10 g/100 mL in non-menstruating women, and age ≥ 70 years (OR 2.7, 95%CI: 1.1-7.0), as shown in Table 4.

Diagnosis of gastrointestinal cancer during follow up based on SCL detection at baseline colonoscopy

The distribution of GIC according to FIT result and presence of SCL at baseline colonoscopy is shown in Figure 5. For each subgroup, the minimum diagnostic yield of an upper endoscopy performed at the time of FIT determination, has been calculated assuming a theoretical 100% sensitivity for any esophageal or gastric bleeding tumor developed over the first year since performing baseline colonoscopy.

There were no significant differences in gastroesophageal cancer (GEC) diagnoses irrespective of FIT result, both in the subgroup of patients with SCL as well as in the subgroup with normal baseline colonoscopy.

Those results were similar when the analysis was limited to people aged 50 and older (Figure 6).

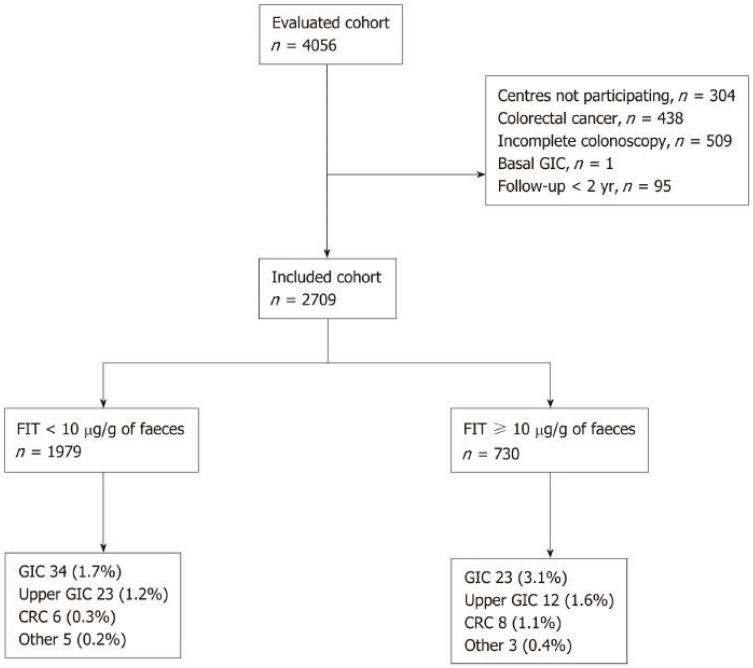

Figure 1 Study population flowchart. CRC: Colorectal cancer; FIT: Faecal immunochemical test; GIC: Gastrointestinal cancer.

DISCUSSION

Statement of principal findings

Our study, for the first time, evaluates whether symptomatic patients with a positive FIT result, no CRC and a complete exploration of the colon have increased risk of related GIC detection or death. We found that this cohort of patients only have an increased risk of related CRC and death when compared with the cohort with a negative FIT result. There are no differences in the risk of upper GIC between both cohorts. In addition, we have identified two variables independently associated with detection of an upper GIC during the first year: Anaemia and advanced age.

Strengths and weaknesses of our study

Our analysis has several strengths. The main one is that we have included a wide number of symptomatic patients who underwent FIT and colonoscopy in several public hospitals in Spain. In this sense, we have limited our analysis to subjects with complete baseline colonoscopy and resection of pre-neoplastic lesions. On the other hand, we performed follow-up analysis by means of search in the electronic medical records of our centres linked to the National Health System's Hospital Discharge Records Database (CMBD in Spanish), which receives notifications from around 98% of Spanish public hospitals that have seen to more than 99% of the Spanish population[14]. Since 2005, the CMBD also has partial coverage from private hospitals[15].

However, the main weakness of our analysis arises from differences between the cohorts in terms of demographics, basal symptoms, endoscopic findings or follow-up. Moreover, the risk of GIC during follow-up, as expected, is low. To solve this limitation, we performed a Cox multivariate regression analysis controlling by confounding variables and final results are consistent.

Strengths and weaknesses in relation to other studies with discussion of important differences in results

Our study detected a higher than expected risk of GIC in the patients evaluated, mainly related to upper GIC and CRC. Estimated 30-year risk of developing an upper GIC in the United States is 0.98%[16], which is lower than the risk detected in our symptomatic cohort. Moreover, the incidence of GEC is also notable even in patients

Table 2 Characteristics of the individuals included in the analysis, *n* (%)

Characteristics	Overall (*n* = 2709)	FIT < 10 μg/g (*n* = 1979)	FIT ≥ 10 μg/g (*n* = 730)	*P* value[8]
Demographic				
Age (yr)	62.9 ± 13.5	62.0 ± 13.5	65.5 ± 13.0	< 0.001
Female sex	1432 (52.9)	1084 (54.8)	348 (47.7)	0.001
Primary healthcare referral[1]	617 (24.2)	397 (21.2)	220 (32.2)	< 0.001
Previous colonoscopy[2]	444 (25.9)	287 (25.8)	157 (26.0)	0.9
Daily using ASA[2]	330 (19.2)	193 (17.3)	137 (22.7)	0.01
Indications				
Rectal bleeding[1]	1234 (48.3)	843 (45.1)	391 (57.2)	< 0.001
Change of bowel habit[1]	1271 (49.8)	913 (48.8)	358 (52.4)	0.1
Anaemia[3,4]	368 (16.2)	236 (13.9)	132 (23.1)	< 0.001
Abdominal pain[5]	766 (41.3)	587 (41.8)	179 (40.0)	0.4
Weight loss[5]	391 (21.1)	301 (21.4)	90 (20.1)	0.6
Basal colonoscopy findings				
Benign anorectal lesion[2]	756 (44.0)	495 (44.4)	261 (43.3)	0.6
Significant colonic lesions[6]	480 (17.7)	204 (10.3)	276 (37.8)	< 0.001
Advanced adenoma[1,7]	337 (13.2)	139 (7.4)	198 (29.0)	< 0.001
Follow-up (mo)	45.5 ± 20.0	47.9 ± 21.2	39.2 ± 14.1	< 0.001

Missing data in
[1]156,
[2]992,
[3]441 and
[4]Defined as < 11 g/100 mL in men and < 10 g/100 mL in non-menstruating women.
[5]856 patients.
[6]Advanced adenoma (≥ 10 mm, villous histology, high-grade dysplasia), polyposis (> 10 polyps of any histology), colitis (any aetiology), polyps ≥ 10 mm, complicated diverticular disease, colonic ulcer and/or bleeding angiodysplasia.
[7]Adenoma ≥ 10 mm, villous histology or high-grade dysplasia.
[8]Differences between both groups in the Chi-square test in the qualitative variables and in the student *t* test in the quantitative variables. Differences with *P* < 0.05 are considered statistically significant. Qualitative variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as mean and standard deviation. ASA: Acetyl salicylic acid; FIT: Faecal immunochemical test.

with a positive FIT result who were diagnosed with a SCL in the baseline colonoscopy, which could theoretically justify the presence of haemoglobin in faeces. This is related to the lack of specificity of symptoms related to diagnosis of cancer. In this sense, we believe that most GIC detected are prevalent. As an example, anaemia, although mainly related to CRC, is related to any GIC with positive predictive values ranging between 1% and 5% of the population seen in primary healthcare[21].

FIT has been recommended for adoption in primary care to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral. Furthermore, NICE has recommended 10 μg Hb/g of faeces as the threshold for further evaluation referral[3]. This recommendation is based on the high accuracy of the test for CRC detection in symptomatic patients[1,17]. However, one practical doubt when using FIT in symptomatic patients is what to do with "false positive" results. Most evidence available comes from asymptomatic patients and suggests that a positive FIT is not predictive of prevalent GIC[7,18,19]. A recently published study revealed that only 0.14% of all persons with a positive FIT result were diagnosed with gastric or oesophageal cancer within 3 years and the risk was similar to the group with negative FIT[20]. Our study evaluates, for the first time, the risk of GIC after a false positive FIT result. In this sense, the probability of detecting an upper GIC is not modified by the FIT result.

It is noteworthy that our study did not exclude patients with high risk symptoms as rectal bleeding which are outside of NICE recommendation. However, most of the studies included in the meta-analysis that supports NICE recommendation[1], were not only concerned with patients with low risk symptoms (*i.e.*, rectal bleeding is described in several patients in those studies). That clinical concern was highlighted by Fraser[21] and led to the development of an additional review and meta-analysis to obtain more information about the accuracy of FIT through the broad spectrum of symptomatic patients[17]. In our cohort, the risk of GIC cancer tends to be lower in patients with rectal bleeding. Probably, this is due to this symptom's being less subjective than others like abdominal pain and more specific to the colon. Thus, unlike other

Table 3 Risk of cancer and death according to faecal immunochemical test result

Event	Risk	Overall (*n* = 2709)	FIT < 10 μg/g (*n* = 1979)	FIT ≥10 μg/g (*n* = 730)	RR[1] (95%CI)	HR[2] (95%CI)
GIC	Cumulative[3]	2.1% (1.6-2.6)	1.7% (1.1-2.3)	3.2% (1.9-4.4)	1.9 (1.1-3.2)	1.5 (0.8-2.7)
GIC	Density[4]	5.6 (4.1-7.0)	4.3 (2.9-5.8)	9.7 (5.8-13.7)		
GIC	Cumulative death[3]	1.3% (0.9-1.8)	1.0% (0.5-1.4)	2.3% (1.2-3.4)	2.5 (1.3-4.7)	2.2 (1.1-4.3)
GIC	Death density[4]	3.5 (2.4-4.6)	2.4 (1.3-3.5)	7.1 (3.7-10.5)		
Up GIC[5]	Cumulative[3]	1.3% (0.9-1.7)	1.2% (0.7-1.6)	1.6% (0.7-2.6)	1.4 (0.7-2.8)	1.0 (0.5-2.2)
Up GIC[5]	Density[4]	3.4 (2.3-4.6)	2.9 (1.7-4.1)	5.1 (2.2-8.0)		
Up GIC[5]	Cumulative death[3]	0.8% (0.5-1.2)	0.7% (0.3-1.0)	1.2% (0.4-2.0)	1.6 (0.7-3.7)	1.4 (0.6-3.3)
Up GIC[5]	Death density[4]	2.1 (1.2-3.0)	1.6 (0.8-2.5)	3.8 (1.3-6.2)		
CRC	Cumulative[3]	0.5% (0.2-0.8)	0.3% (0.1-0.5)	1.1% (0.3-1.9)	3.6 (1.3-10.5)	3.8 (1.2-11.9)
CRC	Density[4]	1.4 (0.7-2.1)	0.8 (0.2-1.4)	3.4 (1.0-5.7)		
CRC	Cumulative death[3]	0.3% (0.1-0.5)	0.1% (0.0-0.2)	1.0% (0.3-1.7)	9.5 (2.0-46.2)	10.8 (2.1-57.1)
CRC	Death density[4]	0.9 (0.3-1.4)	0.3 (-0.1-0.6)	2.9 (0.8-5.1)		
Cancer	Cumulative[3]	7.6% (6.6-8.6)	7.3% (6.2-8.5)	8.2% (6.2-10.2)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Cancer	Density[4]	20.5 (17.7-23.3)	18.8 (15.8-21.9)	25.9 (19.4-32.5)		
Cancer	Cumulative death[3]	3.6% (2.9-4.3)	3.2% (2.4-4.0)	4.8% (3.2-6.3)	1.5 (1.0-2.3)	1.4 (0.9-2.2)
Cancer	Death density[4]	9.5 (7.6-11.4)	8.0 (6.0-9.9)	14.7 (9.8-19.6)		
Death	Cumulative[3]	7.3% (6.3-8.2)	7.0% (5.9-8.1)	7.9% (6.0-9.9)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
Death	Density[4]	19.2 (16.5-21.8)	17.6 (14.7-20.5)	24.3 (18.1-30.6)		

[1]Differences in cumulative incidence were analysed with the Chi-square and the Cochran–Mantel–Haenszel statistics and expressed as the RR and its 95%CI in the qualitative variables.
[2]Differences in the risk of cancer and death adjusted by age, sex and presence of significant colonic lesion were analysed with a Cox multivariate regression and expressed as HR and its 95%CI.
[3]Cumulative risk is expressed as percentage and its 95%CI.
[4]Risk density rate is expressed per 1000 patient-years and its 95%CI.
[5]Defined as a cancer located in the oesophagus, stomach, duodenum or ampulla. CI: Confidence interval; CRC: Colorectal cancer; FIT: Faecal immunochemical test; GIC: Gastrointestinal cancer RR: Risk ratio; Up GIC: Upper gastrointestinal cancer.

indications, patients with overt bleeding who underwent a quality colonoscopy that ruled out CRC were less likely to be diagnosed with an upper GIC.

Although the risk is low, CRC risk is increased in symptomatic subjects with positive FIT even after a high-quality colonoscopy when compared to patients with a negative test. This finding is worthy of several comments. CRC detected fall into the definition of a post-colonoscopy colorectal cancer (PCCRC)[22]. In fact, the rate of PCCRC detected, approximately 3%, is located in the expected segment between 2.5% and 7.7%. However, we must highlight that the risk of PCCRC is higher after a positive FIT, probably due to the higher prevalence in this group of patients. This finding should be taken into account by physicians if symptoms persist after a normal colonoscopy. Finally, the risk of PCCRC calculated per 1000 colonoscopies is higher than the risk previously documented ranging between 0.8 and 2.4[23]. Our population consists of symptomatic patients with a CRC prevalence in the original studies ranging between 3.0% and 13.7%. We therefore suggest that the risk of PCCRC should be evaluated on the basis of the colonoscopy indication. However, the sample size of our analysis and the low number of PCCRC detected did not enable us to analyse additional factors that could predict the risk of PCCRC, such as age, comorbidity and diverticular disease, or the relationship with baseline symptoms[24].

A recent study conducted in patients taking part in CRC screening has associated the presence of detectable f-Hb with increased risk of death from a wide range of causes unrelated to CRC or even GIC[25]. In that study, Libby *et al*[26] consider the possibility of detectable f-Hb originating from subclinical colonic inflammation due to a generalised inflammatory state. We did not find such an association. However, the threshold used in our study (10 μg Hb/g faeces) is much lower than the concentration of approximately 80 μg Hb/g faeces required to attain a positive result by means of the qualitative method used by Libby *et al*[26].

Meaning of the study: Possible explanations and implications for clinicians and policymakers

Early diagnosis of GIC is challenging as long as abdominal symptoms are common, mostly related to benign diseases and non-specific to a particular cancer. In fact, abdominal symptoms are very common among patients with cancer (23%), mainly

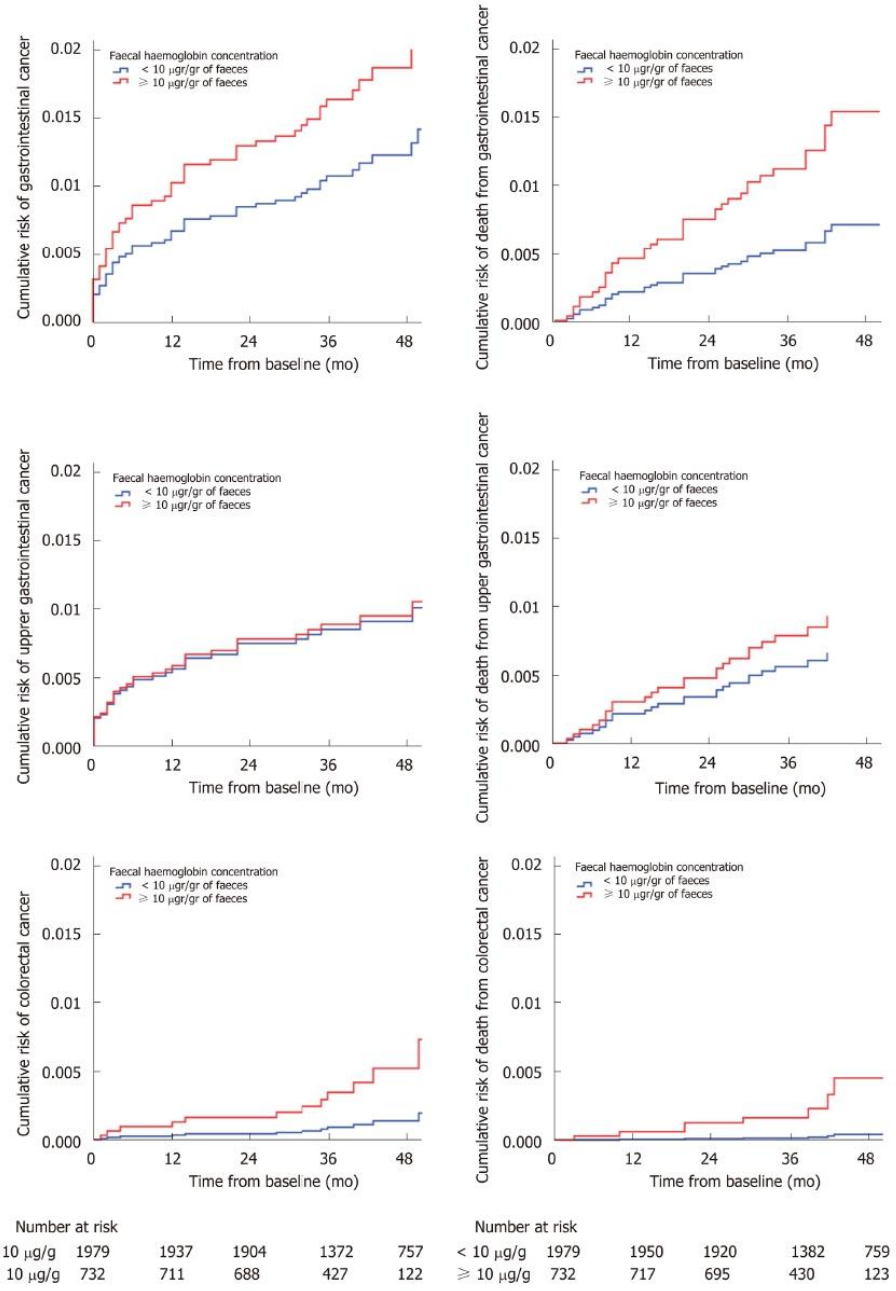

Figure 2 Cumulative risk of gastrointestinal cancer and related death. Cumulative risk of gastrointestinal cancer and related death during the first four years after baseline evaluation according to faecal haemoglobin concentration and adjusted by sex, age and presence of significant colonic lesion. The figure is calculated with a Cox's multivariate regression.

related to GIC and CRC in particular[27]. In contrast with breast cancer or melanoma, GIC have a broad symptom signature with varying predictive value[28]. In order to reduce delays in patients with lower abdominal symptoms with a low positive predictive value for CRC, FITs are recommended for adoption in primary care to guide referral for suspected CRC[3]. Our analysis aims to resolve a frequent issue that will take place when patients with lower abdominal symptoms are evaluated with a FIT. Hypothetically, 179-229 out of 1000 symptomatic patients will have a positive FIT

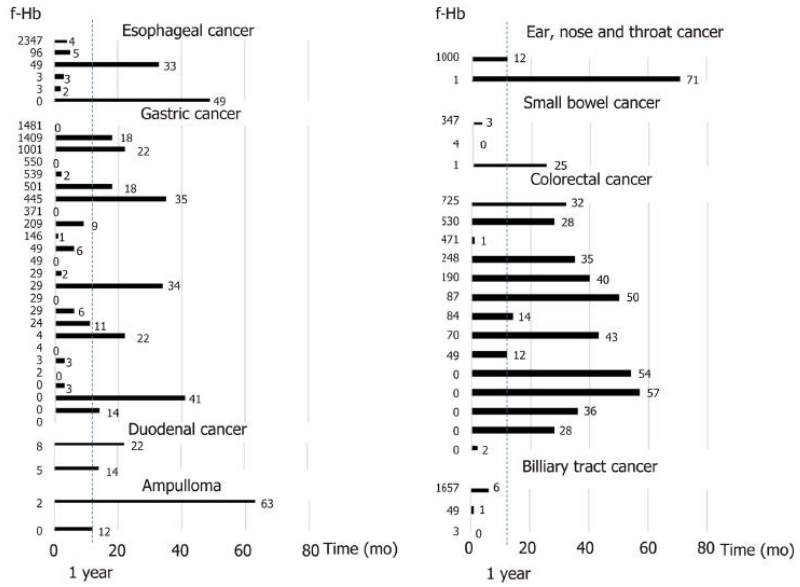

Figure 3 Time (mo) until gastrointestinal cancer diagnosis according to location, diagnostic test and faecal immunochemical test result. f-Hb: Faecal haemoglobin (μg Hb/g of faeces).

and colonoscopy without CRC[3]. As our results show, this patient cohort has a similar risk of GIC as the cohort with a negative FIT. In this situation, an EGD should be recommended in patients with anaemia especially if they are elderly. However, special caution should be taken with the risk of PCCRC after positive FIT and normal colonoscopy if abdominal symptoms persist or reappear.

Unanswered questions and future research

Our results are the basis to design a large prospective follow-up study including patients treated in primary healthcare with abdominal symptoms. In these patients, diagnostic evaluation should not be restricted to GIC. Other abdominal cancers in addition to benign gastrointestinal diseases should be evaluated to determine the positive predictive value and the best diagnostic strategy for each group of symptoms.

Additionally, a recent study concluded that endoscopic gastric cancer screening could be cost-effective if combined with a screening colonoscopy in countries with a gastric cancer risk ≥ 10 per 100000[39]. Given the gastroesophageal cancer incidences shown during the first year since FIT determination in our cohort irrespective of SCL finding in the basal colonoscopy, the cost-utility of combining upper and lower endoscopies should be investigated also in this setting.

To summarise, the risk of GIC is higher than expected in patients with low gastrointestinal symptoms and no CRC detected in a complete colonoscopy. The probability of detecting an upper GIC is unrelated to the FIT result and only associated with the presence of anaemia and advanced age. Finally, the risk of PCCRC in our study is within the ranges expected and clearly associated with the FIT result.

Table 4 Factors associated with upper gastrointestinal cancer detection the first year after baseline colonoscopy, *n* (%)

	Upper gastrointestinal cancer	Odds ratio (95 %CI)[1]	Odds ratio (95 %CI)[2]
Sex			
Female (*n* = 1432)	10 (0.7)	1	
Male (*n* = 1277)	12 (0.9)	1.3 (0.6-3.1)	
Age			
< 70 yr (*n* = 1757)	8 (0.5)	1	1
≥ 70 yr (*n* = 952)	14 (1.5)	3.3 (1.4-7.8)	2.7 (1.1-7.0)
Primary healthcare referral			
No (*n* = 1936)	19 (1.0)	1	
Yes (*n* = 617)	3 (0.5)	0.5 (0.1-1.7)	
Rectal bleeding			
No (*n* = 1319)	16 (1.2)	1	
Yes (*n* = 1234)	6 (0.5)	0.4 (0.1-1.0)	
Change of bowel habit			
No (*n* = 1282)	12 (0.9)	1	
Adequate (*n* = 1271)	10 (0.8)	0.8 (0.4-1.9)	
Anaemia[3]			
No (*n* = 2077)	13 (0.6)	1	1
Yes (*n* = 191)	8 (4.2)	6.9 (2.8-17.0)	5.6 (2.2-13.9)
Abdominal pain			
No (*n* = 1319)	12 (1.1)	1	
Yes (*n* = 1234)	5 (0.7)	0.6 (0.2-1.7)	
Weight loss			
No (*n* = 1462)	12 (0.8)	1	
Yes (*n* = 391)	5 (1.3)	1.5 (0.5-4.4)	
Faecal immunochemical test			
< 10 μg/g (*n* = 1979)	14 (0.7)	1	
≥ 10 μg/g (n = 730)	8 (1.1%)	1.5 (0.6-3.7)	
Benign anorectal lesion			
No (*n* = 961)	7 (0.7)	1	
Yes (*n* = 756)	6 (0.8)	1.1 (0.4-3.2)	
Significant colonic lesion[4]			
No (*n* = 2216)	16 (0.7)	1	
Yes (*n* = 480)	6 (1.3)	(0.7-4.5)	
Advanced adenoma[5]			
No (*n* = 2968)	16 (0.7)	1	
Yes (*n* = 337)	6 (1.8)	2.5 (1.0-6.4)	

[1]Differences were analysed with the Chi-square and Cochran–Mantel–Haenszel statistics and expressed as the odds ratio and its 95%CI.
[2]Variables with statistically significant differences were introduced in a multivariate logistic regression analysis. The association is expressed as odds ratio and its 95 %CI.
[3]Defined as < 11 g/100 mL in men and < 10 g/100 mL in non-menstruating women.
[4]Advanced adenoma (≥ 10 mm, villous histology, high-grade dysplasia), polyposis (> 10 polyps of any histology), colitis (any aetiology), polyps ≥ 10 mm, complicated diverticular disease, colonic ulcer and/or bleeding angiodysplasia.
[5]Adenoma ≥ 10 mm with villous histology or high-grade dysplasia.

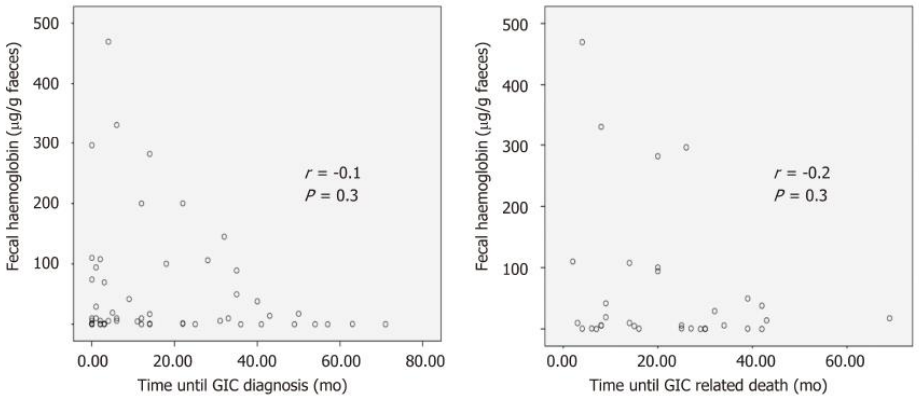

Figure 4 Correlation between faecal haemoglobin concentration and time to gastrointestinal cancer detection and gastrointestinal cancer-related death. GIC: Gastrointestinal cancer; *r*: Spearman correlation coefficient.

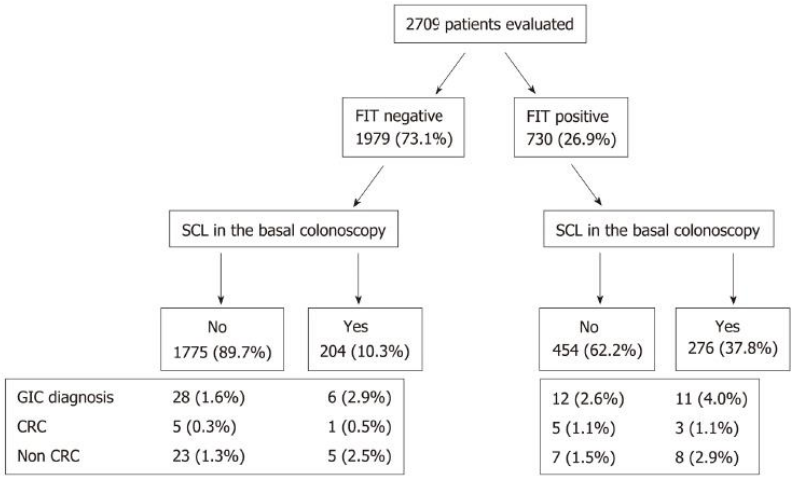

Figure 5 Gastrointestinal cancer diagnosis during follow up based on faecal immunochemical test result and significant colonic lesion in the basal colonoscopy. CRC: Colorectal cancer; FIT: Faecal immunochemical test; GITN: Gastrointestinal tract neoplasm; SCL: Significant colonic lesion.

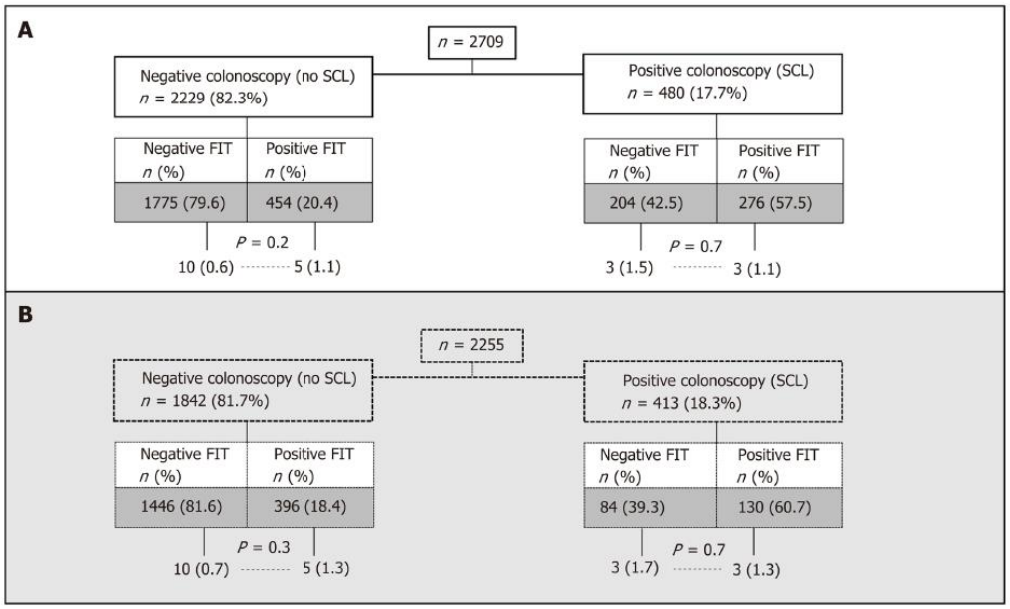

Figure 6 Minimum diagnostic yield of an upper endoscopy performed at the time of faecal immunochemical test for haemoglobin determination. A: All subjects; B: subjects aged 50 years old and older. FIT: Faecal immunochemical test for haemoglobin; SCL: Significant colonic lesion; *P*: Differences were analysed with the Chi-square statistics.

ARTICLE HIGHLIGHTS

Research background

Faecal immunochemical test for haemoglobin (FIT) is more specific and appears to be equal to or more sensitive than guaiac-based tests when used for colorectal cancer (CRC) screening. FIT reacts with human globin, so it should have greater specificity to detect lower gastrointestinal tract (GIT) lesions than guaiac-based tests. However, a previous systematic review led to the conclusion that there is insufficient evidence to recommend for or against routine esophagogastroduodenoscopy in asymptomatic patients with a positive faecal occult blood test followed by negative colonoscopy.

Research motivation

Out of a screening setting, several approaches have been developed to improve the suitability of referrals for investigation of symptoms suggestive of CRC and reduce delays in diagnosis and some include using FIT. Therefore, it will be increasingly common for clinicians to face the uncertainty of a patient with non-specific digestive symptoms, a positive FIT result and normal colonoscopy.

Research objectives

We aim to assess the risk of gastrointestinal cancer (GIC) detection and related death in symptomatic patients with a positive determination of FIT (threshold 10 μg Hb/g faeces) without CRC at baseline quality colonoscopy.

Research methods

We performed a post hoc cohort analysis within two prospective diagnostic test studies evaluating the diagnostic accuracy of FIT for CRC detection. Outpatients with gastrointestinal symptoms referred consecutively for colonoscopy from primary and secondary healthcare were divided into two groups (positive and negative FIT) using the threshold of 10 μg Hb/g of faeces and data from follow-up were retrieved from their electronic medical records. We determined the cumulative risk of GIC, CRC and upper GIC. Hazard rate was calculated adjusted by age, sex and presence of significant colonic lesion on basal colonoscopy.

Research results

This study revealed high neoplasia and death rates in our cohort (n = 2709) of people consulting with a physician for non-acute symptoms suggestive of lower gastrointestinal tract disorders. FIT-positive patients have higher incidence of GIC during follow-up. However, this did not result in a statistically significant increase in the risk of upper GIC development after multivariate adjustment. Moreover, we found that this cohort of patients only has an increased

risk of related CRC and death when compared to the cohort with a negative FIT result.

Research conclusions

This study suggests that FIT positivity using the threshold of 10 μg Hb/g of faeces is not enough to differentiate which patients would benefit from continuing workup to rule out a GIC out of screening setting. Nevertheless, small amounts of f-Hb may originate in the upper GI tract or the small bowel and this possibility must be considered along with other false-positive risk factors when interpreting FIT requested to rule out CRC or another significant colonic lesion.

Research perspectives

We hypothesize that benign lesions (*i.e.* due to non-steroid anti-inflammatory drugs) are much more prevalent than GIC in the upper tract regardless of symptoms. Thus, it is much more likely that a small amount of detectable (unmetabolized) haemoglobin, originally from any kind of lesion located in the upper tract or the small bowel will be unrelated to a GIC. However, the study design is not suitable to prove this hypothesis. A large prospective follow-up study which takes competitive FIT positive causes and other risk factors into consideration would provide a predictive model to guide decision-making.

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The contents of this manuscript have not been published previously in any journal nor deposited on a pre-print server. Furthermore, this paper has not been presented at any scientific meeting in abstract form.

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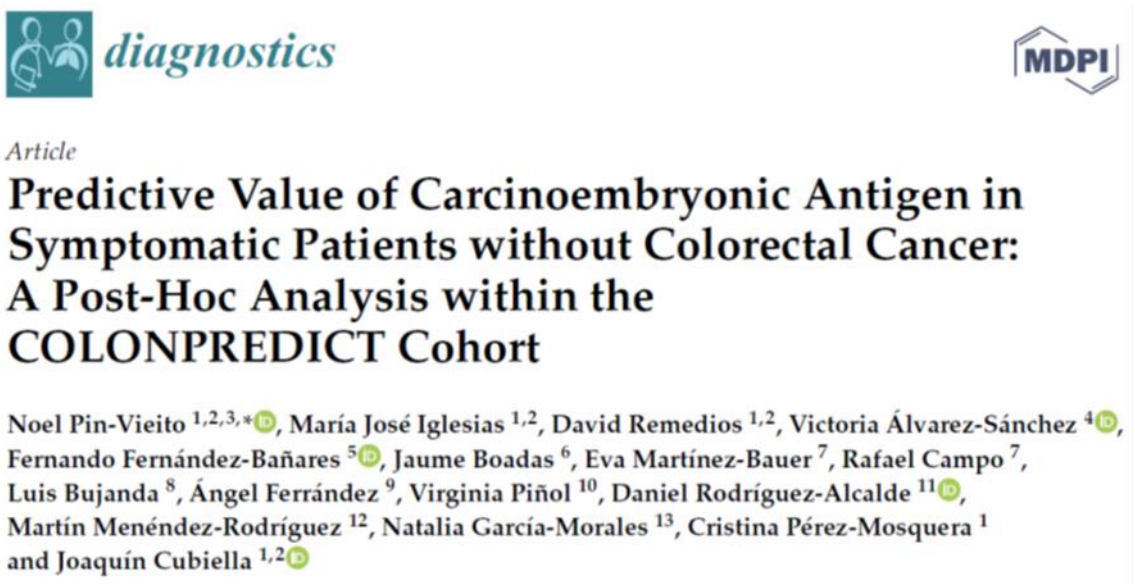
Metodología y resultados – Artículo 4



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Predictive Value of Carcinoembryonic Antigen in Symptomatic Patients without Colorectal Cancer: A Post-Hoc Analysis within the COLONPREDICT Cohort

Noel Pin-Vieito [1,2,3,*], María José Iglesias [1,2], David Remedios [1,2], Victoria Álvarez-Sánchez [4], Fernando Fernández-Bañares [5], Jaume Boadas [6], Eva Martínez-Bauer [7], Rafael Campo [7], Luis Bujanda [8], Ángel Ferrández [9], Virginia Piñol [10], Daniel Rodríguez-Alcalde [11], Martín Menéndez-Rodríguez [12], Natalia García-Morales [13], Cristina Pérez-Mosquera [1] and Joaquín Cubiella [1,2]

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Objetivo

Evaluar la incidencia y la mortalidad por cáncer de cualquier origen asociada a la presencia de niveles séricos elevados de CEA, en pacientes sintomáticos con una colonoscopia basal completa sin CCR.

Métodos

Análisis retrospectivo post hoc dentro del estudio COLONPREDICT [134], destinado a evaluar la precisión de SOH-i para detectar CCR en una cohorte ambulatoria de pacientes con síntomas digestivos a los que se solicita una determinación de Hb-f previa a la realización de colonoscopia como parte de su evaluación.

Se incluyeron aquellos pacientes con colonoscopia completa sin CCR y seguimiento de al menos dos años. Se definieron dos cohortes: CEA ≤ 3 ng / dL y > 3 ng/ dL y los datos del seguimiento se recuperaron de la historia clínica electrónica. Para todos los pacientes, se registraron los diagnósticos de cáncer de cualquier etiología y la causa de muerte. Se calcularon las tasas de riesgo (HR) ajustando por edad, sexo y presencia de adenoma avanzado. Finalmente, se valoró qué variables estaban asociadas de forma independiente con la detección de cualquier tipo de cáncer durante el primer año.

Resultados

Se analizaron 1,431 pacientes, de los que 238 (16.6 %) mostraron niveles séricos de CEA > 3 ng/dL. Los pacientes con niveles de CEA > 3 ng/dl tenían una mediana de edad significativamente mayor que aquéllos con niveles de CEA más bajos (64.7 vs 67.4 años; $p < 0.01$). Sin embargo, no se apreciaron diferencias ($p > 0.05$) entre ambas

cohortes con respecto a género, prevalencia de síntomas abdominales o LCS detectadas en la colonoscopia basal.

Durante una mediana de 36.5 ± 8.4 meses, 30 (2.1%) pacientes fueron diagnosticados de algún tipo de tumor localizado en el tracto gastrointestinal (TTGI), de estas lesiones 22 estaban localizadas en el tracto gastrointestinal superior y 8 eran CCR. Además, 85 (5.9%) pacientes fueron diagnosticados de algún tipo de cáncer localizado fuera del tracto gastrointestinal.

Los sujetos con niveles altos de CEA mostraron mayor riesgo de ser diagnosticados de CCR (HR 4.4, IC 95% 1.1-17.7) y cáncer localizado fuera del tracto gastrointestinal (HR 1.7, IC 95% 1.0-2.8). Sin embargo, no se apreciaron diferencias en el riesgo de detectar un TTGI localizado en tracto gastrointestinal alto en función de los niveles de CEA (HR 2.2, IC 95% 0.9-5.4).

Por otra parte, 100 (7.0 %) pacientes fallecieron durante el seguimiento. De ellos, 41 (2.9%) lo hicieron por causas no relacionadas con un diagnóstico de cáncer. Entre los restantes, 21 (1.5%) pacientes fallecieron por TTGI de las que 6 (0.4%) muertes estaban relacionadas con un diagnóstico de CCR. Treinta y ocho (2.7%) pacientes murieron por causas relacionadas con algún tipo de cáncer localizado fuera del tracto gastrointestinal.

Los sujetos con niveles elevados de CEA mostraron un mayor riesgo de muerte causada por CCR (HR 8.8, IC 95% 1.6-48.5) y lesiones malignas localizadas fuera del tracto gastrointestinal (HR 3.5, IC 95% 1.8-6.7). Nuevamente, no se apreciaron diferencias en el riesgo de fallecer por un TTGI localizado en el tracto gastrointestinal alto (HR 2.3, IC 95% 0.8-6.8).

Durante el primer año, 51 pacientes (3.6%) fueron diagnosticados de algún tipo de cáncer. Tres variables se asociaron de forma independiente con este desenlace: la presencia de anemia (OR 2.8, IC 95% 1.3-5.8), sangrado rectal (OR 0.3, IC 95% 0.1-0.7) y niveles de CEA > 3 ng / dL (OR 3.4, IC 95% 1.7-7.1).

Conclusión

Los pacientes con síntomas y un nivel sérico de CEA > 3 ng/dL a los que se realiza una colonoscopia que descarta CCR, poseen un aumento moderado del riesgo de detección de cáncer durante el primer año. En nuestra cohorte, aquellos pacientes que presentaban anemia y negaban la presencia de sangrado rectal entre sus síntomas mostraron significativamente mayor riesgo que el resto.

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Abstract: We aimed to assess the risk of cancer in patients with abdominal symptoms after a complete colonoscopy without colorectal cancer (CRC), according to the carcinoembryonic antigen (CEA) concentration, as well as its diagnostic accuracy. For this purpose, we performed a post-hoc analysis within a cohort of 1431 patients from the COLONPREDICT study, prospectively designed to assess the fecal immunochemical test accuracy in detecting CRC. Over 36.5 ± 8.4 months, cancer was detected in 115 (8%) patients. Patients with CEA values higher than 3 ng/mL revealed an increased risk of cancer (HR 2.0, 95% CI 1.3–3.1), CRC (HR 4.4, 95% CI 1.1–17.7) and non-gastrointestinal cancer (HR 1.7, 95% CI 1.0–2.8). A new malignancy was detected in 51 (3.6%) patients during the first year and three variables were independently associated: anemia (OR 2.8, 95% CI 1.3–5.8), rectal bleeding (OR 0.3, 95% CI 0.1–0.7) and CEA level >3 ng/mL (OR 3.4, 95% CI 1.7–7.1). However, CEA was increased only

in 31.8% (95% CI, 16.4–52.7%) and 50% (95% CI, 25.4–74.6%) of patients with and without anemia, respectively, who would be diagnosed with cancer during the first year of follow-up. On the basis of this information, CEA should not be used to assist in the triage of patients presenting with lower bowel symptoms who have recently been ruled out a CRC.

Keywords: biochemical diagnosis; carcinoembryonic antigen; colonoscopy; early cancer; gastrointestinal cancer; symptoms; tumor biomarkers

1. Introduction

Early colorectal cancer (CRC) diagnosis in primary healthcare is challenging. Most CRCs presenting symptoms, if any, are vague, and often shared among different types of cancer [1]. Furthermore, when most types of cancer develop specific symptoms, they have usually progressed to an advanced stage [2].

The quantitative fecal immunochemical test for hemoglobin (FIT) has shown its usefulness in the diagnosis of CRC both in a screening setting and in the assessment of patients with abdominal symptoms [3,4]. Hence, the National Institute for Health and Care Excellence (NICE) recommends FIT in primary healthcare to assist in the triage of patients presenting with lower bowel symptoms who do not meet the criteria for suspected cancer pathway referral [5].

In addition, carcinoembryonic antigen (CEA), a complex intracellular glycoprotein, is one of the most widely used tumor markers. Serum CEA is produced by approximately 90% of colorectal cancers (CRC), and its most common clinical use is monitoring CRC recurrence following curative resection [6]. However, serum CEA levels can also be elevated in other malignancies and have been proven to be useful in decision-making processes in selected clinical situations unrelated to CRC [7–9].

Based on the above, general practitioners sometimes incorporate serum CEA unsupported by evidence as part of health testing for asymptomatic individuals. Despite this, serum CEA is not recommended as a screening test [10]. CEA levels can also be elevated under benign conditions (i.e., cirrhosis, ulcerative colitis), and even smoking appears to almost double the CEA serum concentration in healthy subjects [11]. Moreover, the incidence of other gastrointestinal neoplasia which could also elevate CEA levels is low, and serum CEA lacks sensitivity in early stages [12].

Although CRC is the most common gastrointestinal cancer (and the third most common cancer worldwide) [13], other less prevalent cancer diagnoses have been reported in patients with gastrointestinal symptoms, regardless of their FIT result, as a consequence of the previously commented on lack of specificity of symptoms related to cancer diagnosis [14]. Many of these low prevalence cancers could account for elevated serum CEA levels [7–9]. Therefore, the incidence of this group of malignancies in the patient with abdominal symptoms could be sufficiently high to consider assessing the value of CEA in this particular clinical situation.

Therefore, the aim of our study is to evaluate the risk of cancer detection and cancer related death in symptomatic patients that underwent a complete colonoscopy with no CRC according to the serum CEA concentration. We will also evaluate which variables are related to cancer diagnosis in the year after the initial evaluation, as well as the diagnostic accuracy of CEA for cancer detection.

2. Materials and Methods

2.1. Study Design

This is a post hoc cohort analysis performed within the COLONPREDICT study, which was designed to prospectively evaluate the accuracy of FIT for CRC diagnosis [15]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the

Clinical Research Ethics Committee of Galicia (Code 2011/038) under a resolution dated 11 April 2012. Patients provided written informed consent prior to inclusion.

We followed the Strengthening the Reporting of Observational studies in Epidemiology statement to conduct and report our study [16].

2.2. Study Population

The main characteristics of our cohort have been detailed elsewhere [15]. In short, we included in this analysis ambulatory patients referred consecutively from primary and secondary healthcare for the evaluation of gastrointestinal symptoms. Patients included in the study underwent a colonoscopy, serum CEA and a quantitative FIT. Patients were excluded from this post hoc analysis if a CRC was diagnosed in the baseline colonoscopy or if the colonoscopy was incomplete. We also excluded patients either with insufficient follow-up (less than 2 years) or any untreated cancer diagnosis before basal colonoscopy.

2.3. Measurements and Definitions

Serum CEA levels (ng/mL) were measured using a chemiluminescent microparticle immunoassay (UniCel DXI 800; Beckman Coulter, CA, USA). Abnormal levels were defined as levels above 3 ng/mL [15]. Fecal hemoglobin (f-Hb) was measured using OC-SensorTM (Eiken Chemical Co., Tokyo, Japan), as previously reported [17]. Results with f-Hb ≥ 20 µg/g were defined as positive [18].

All the colonoscopies were conducted by endoscopists who perform at least 200 colonoscopies per year [19]. Significant colonic lesion (SCL) was defined as histologically confirmed colitis (any etiology), colonic ulcer, advanced adenoma (any adenoma ≥ 10 mm, with high-grade dysplasia or villous histology), polyposis (>10 polyps of any histology), polyps ≥ 10 mm, bleeding angiodysplasia and complicated diverticular disease (diverticulitis, bleeding). Any diagnosed polyp during baseline colonoscopy was removed either upon that exploration or afterwards.

2.4. Follow-Up and Main Outcome

The main outcomes of the study are cancer detection and its related death. Electronic medical records were reviewed for all patients and cancer diagnoses of any etiology were recorded. We classified esophageal, gastric, intestinal, ampullary and colorectal cancer as gastrointestinal cancer (GIC), and we defined an upper GIC as any GIC located outside the colon. The cause and date of death were recorded. We classified the cause of death as (a) global death (death from any cause) and (b) global cancer (death from any cancer). We also divided the cause of death related with cancer into (a) related to GIC, which is further subdivided into (1) upper GIC and (2) CRC, and (b) other types of cancer (non GIC). Secondary outcomes analyzed were cancer risk the first year after performing colonoscopy and the diagnostic accuracy of CEA for cancer detection in this period.

2.5. Statistical Analysis

Qualitative variables were expressed as absolute numbers and percentages, while quantitative ones were expressed as medians with their interquartile range. We calculated cumulative risk and number of cases per 1000 patient-years (risk density rate) with their 95% confidence interval (CI) according to the CEA concentration. Patients with normal and abnormal CEA levels were compared using the Fisher's Exact Test and the Mann Whitney U Test for qualitative and quantitative variables, respectively. We analyzed the differences between both groups in cumulative risk and risk density rate using the Chi-square test and Cochran-Mantel-Haenszel statistics expressed as the risk ratio (RR) and incidence ratio (IR), respectively, with their 95% CI. Cox proportional hazard models were used to estimate the adjusted (age, sex and advanced adenoma) hazard ratios (HR) of presenting a main outcome [20].

A multivariable logistic regression model was used to estimate the independent effect of abnormal serum CEA levels on the detection of any cancer during the first year after baseline

colonoscopy, as measured by adjusted odds ratio (OR) with a 95% CI. Variables that had a statistically significant association ($p < 0.05$) with the detection of a new malignancy using Chi-square and Cochran-Mantel-Haenszel statistics were included in the multivariable analysis.

Finally, we assessed the discriminatory ability of serum CEA to detect GIC and non-GIC cancer the first year of follow-up by means of the receiver operating characteristics (ROC) curve and its area under the curve (AUC). Furthermore, we assessed the sensitivity, specificity and positive (PPV) and negative (NPV) predictive value, (positive and negative likelihood ratio and diagnostic odds ratio (DOR) with their 95% CI, using a threshold of 3 ng/mL. Sensitivity analysis was performed using the threshold of 5 ng/mL [21]. Subgroup analysis was conducted to evaluate differences between patients with and without anemia (<11 g hemoglobin per 100 mL in men and <10 g hemoglobin per 100 mL in non-menstruating women), due to its potential association with cancer risk [22–25]. A p-value of <0.05 was deemed statistically significant. Statistical analysis was performed using SPSS statistical software, version 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Participants

A final sample of 1431 symptomatic patients were included in our analysis (Figure 1).

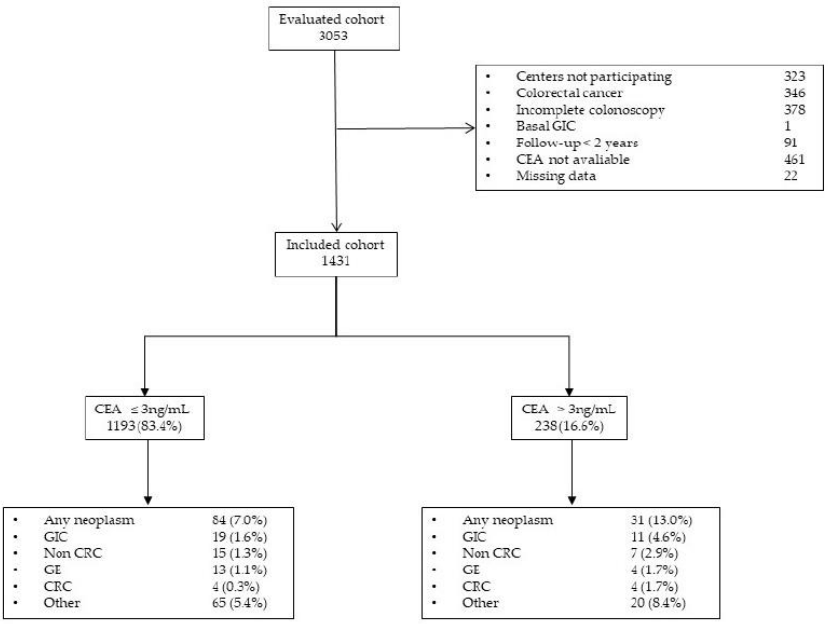

Figure 1. Study population flowchart. CEA = carcinoembryonic antigen; CRC = colorectal cancer; GE = gastroesophageal cancer; GIC = gastrointestinal cancer.

Of these, 238 (16.6%) had CEA values higher than 3 ng/mL. Patient cohort characteristics are provided in Table 1.

Table 1. Characteristics of the individuals included in the analysis.

Characteristics	Overall (n = 1431)	CEA ≤ 3ng/mL (n = 1193)	CEA > 3 ng/mL (n = 238)	p
Demographic				
Age, (years)	66.7 (20.0)	66.2 (19.5)	69.1 (22.0)	<0.01
Female sex, no. (%)	748 (52.3)	634 (53.1)	114 (47.9)	0.16
Primary healthcare referral, no. (%)	390 (27.3)	335 (28.1)	55 (23.1)	0.13
Previous colonoscopy, no. (%)	398 (27.8)	326 (27.3)	72 (30.3)	0.38
Daily using ASA, no. (%)	280 (19.6)	223 (18.7)	57 (23.9)	0.07
f-Hb concentration	33.0 (140.0)	33.0 (139.5)	31.0 (142.0)	0.8
Indications, no. (%)				
Rectal bleeding	796 (55.6)	675 (56.6)	121 (50.8)	0.12
Change of bowel habit	839 (58.6)	705 (59.1)	134 (56.3)	0.43
Anaemia [1]	338 (34.1)	279 (33.4)	59 (38.1)	0.27
Abdominal pain [1]	451 (45.6)	378 (45.3)	73 (47.1)	0.73
Weight loss [1]	240 (24.2)	197 (23.6)	43 (27.7)	0.26
Basal colonoscopy findings, no. (%)				
Benign anorectal lesion	612 (42.8)	521 (43.7)	91 (38.2)	0.13
Significant colonic lesions	277 (19.4)	233 (19.5)	44 (18.5)	0.79
Advanced adenoma	206 (14.4)	176 (14.8)	30 (12.6)	0.42
Follow-up, (months)	38.0 (10.0)	38.0 (10.0)	37.0 (11.0)	0.03

[1] Missing data in 441 subjects; ASA, acetyl salicylic acid; f-Hb, faecal hemoglobin.

3.2. Cancer Diagnosis

During a mean follow-up of 36.5 ± 8.4 months, cancer was detected in 115 (8.0%) patients. Thirty subjects were diagnosed with GIC, and of these 22 (1.5%) lesions were located outside the colon, while 8 (0.6%) were CRC. Furthermore, 85 patients (5.9%) were diagnosed with cancer located outside the gastrointestinal (GI) tract. Of these, twelve patients were diagnosed with lymphoproliferative syndromes (0.8%) and twelve with skin cancer (0.8%), whilst a solid organ neoplasm was diagnosed in fifty-seven patients (4.0%). Four patients showed cancer from an unknown origin.

The distribution of the different types of diagnosed cancer according to the time elapsed since baseline colonoscopy and CEA result is detailed in Supplementary Table S1.

3.3. Main Outcome

Patients with high CEA values showed an increased risk of death after adjusting for demographic variables and the presence of advanced adenoma (HR 2.6, 95% CI 1.7–3.9). These patients presented both a greater incidence of cancer diagnosis (HR 2.0, 95% CI 1.3–3.1) and cancer-related death (HR 3.7, 95% CI 2.2–6.2) during follow-up. The subgroup analysis also revealed a higher risk for both GIC (HR 2.7, 95% CI 1.3–5.7) and cancer located outside the GI tract (RR 1.7, 95% CI 1.0–2.8). The increased risk of GIC was related to an increased probability of CRC detection (HR 4.4, 95% CI 1.1–17.7) and CRC-related death (HR 8.8, 95% CI 1.6–48.5) in patients with an abnormal CEA concentration. In contrast, the risk of upper GIC and upper GIC-related death did not increase significantly. Table 2 and Figure 2 show the cumulative risk of cancer and related death calculated in Cox's multivariable regression analysis.

Table 2. Risk of cancer and death according to the carcinoembryonic antigen value.

EVENT	Risk	Overall (n = 1431)	CEA ≤ 3 ng/mL (n = 1193)	CEA > 3 ng/mL (n = 238)	RR/IR (95% CI)	p	HR (95% CI)	p
Gastrointestinal cancer	Cumulative [1]	2.1 (1.5–3.0)	1.6 (1.0–2.5)	4.6 (2.6–8.1)	2.9 (1.4–6.0)	<0.01	2.7 (1.3–5.7)	0.01
	Density [2]	6.9 (4.7–9.9)	5.1 (2.9–8.0)	16.1 (8.0–28.5)	3.1 (1.5–6.5)	<0.01		
	Cumulative death [1]	1.5 (1.0–2.2)	1.0 (0.6–1.7)	3.8 (2.0–7.0)	3.8 (1.6–8.8)	0.03	3.4 (1.4–8.1)	0.01
	Death density [2]	4.7 (2.9–7.3)	3.3 (1.8–5.5)	12.8 (5.8–24.4)	4.0 (1.7–9.4)	<0.01		
Upper gastrointestinal cancer [3]	Cumulative [1]	1.5 (1.0–2.3)	1.3 (0.8–2.1)	2.9 (1.4–5.9)	2.3 (1.0–5.7)	0.10	2.2 (0.9–5.4)	0.09
	Density [2]	5.1 (3.3–7.7)	4.0 (2.2–6.6)	10.2 (4.0–20.8)	2.5 (1.0–6.1)	0.04		
	Cumulative death [1]	1.0 (0.6–1.7)	0.8 (0.5–1.5)	2.1 (0.9–4.8)	2.5 (0.9–7.3)	0.16	2.3 (0.8–6.8)	0.13
	Death density [2]	3.3 (1.8–5.5)	2.6 (1.5–5.1)	7.3 (2.2–16.8)	2.6 (0.9–7.7)	0.06		
Colorectal cancer	Cumulative [1]	0.6 (0.3–1.1)	0.3 (0.1–0.9)	1.7 (0.7–4.2)	5.0 (1.3–19.9)	0.04	4.4 (1.1–17.7)	0.04
	Density [2]	1.8 (0.7–3.7)	1.1 (0.4-2.9)	5.8 (1.5–14.6)	5.3 (1.3–21.3)	<0.01		
	Cumulative death [1]	0.4 (0.2–0.9)	0.2 (0.0–0.6)	1.7 (0.7–4.2)	10.0 (1.8–54.4)	<0.01	8.8 (1.6–48.5)	<0.01
	Death density [2]	1.5 (0.4–2.9)	0.4 (0.0–1.8)	5.8 (1.5–14.6)	10.6 (1.9–57.8)	<0.01		
Non gastrointestinal cancer	Cumulative [1]	5.9 (4.8–7.3)	5.4 (4.3–5.5)	8.4 (5.5–12.6)	1.5 (1.0–2.5)	0.11	1.7 (1.0–2.8)	0.04
	Density [2]	19.7 (15.7–24.5)	17.9 (13.9–22.6)	29.6 (17.9–45.7)	1.7 (1.0–2.7)	0.05		
	Cumulative death [1]	2.7 (1.9–3.6)	1.8 (1.2–2.8)	6.7 (4.2–10.6)	3.6 (1.9–6.8)	< 0.01	3.5 (1.8–6.7)	<0.01
	Death density [2]	8.8 (6.2–11.7)	5.8 (3.7–9.1)	22.6 (13.1–36.9)	3.8 (2.0–7.3)	<0.01		
Cancer	Cumulative [1]	8.0 (6.7–9.6)	7.0 (5.7–8.6)	13.0 (9.3–18.0)	1.8 (1.3–2.7)	<0.01	2.0 (1.3–3.1)	<0.01
	Density [2]	27.0 (22.3–32.1)	23.4 (18.6–28.9)	46.8 (31.8–66.5)	2.0 (1.3–3.0)	<0.01		
	Cumulative death [1]	4.1 (3.2–5.3)	2.9 (2.0–4.0)	10.5 (7.2–15.0)	3.7 (2.2–6.1)	<0.01	3.7 (2.2–6.2)	<0.01
	Death density [2]	13.5 (10.2–17.2)	9.1 (6.2–12.8)	35.8 (23.0–52.6)	3.9 (2.3–6.5)	<0.01		
Death	Cumulative [1]	7.0 (5.8–8.4)	5.4 (4.2–6.8)	15.1 (11.1–20.2)	2.8 (1.9–4.1)	<0.01	2.6 (1.7–3.9)	<0.01
	Density [2]	22.6 (18.6–27.4)	17.2 (13.1–21.9)	51.5 (35.8–71.2)	3.0 (2.0–4.5)	<0.01		

[1] Cumulative risk is expressed as percentage and its 95% CI; [2] risk density rate is expressed per 1000 patient-years and its 95% CI; [3] defined as a cancer located outside the colon. CI = confidence interval; HR = adjusted hazard ratio; IR = incidence ratio; RR = risk ratio.

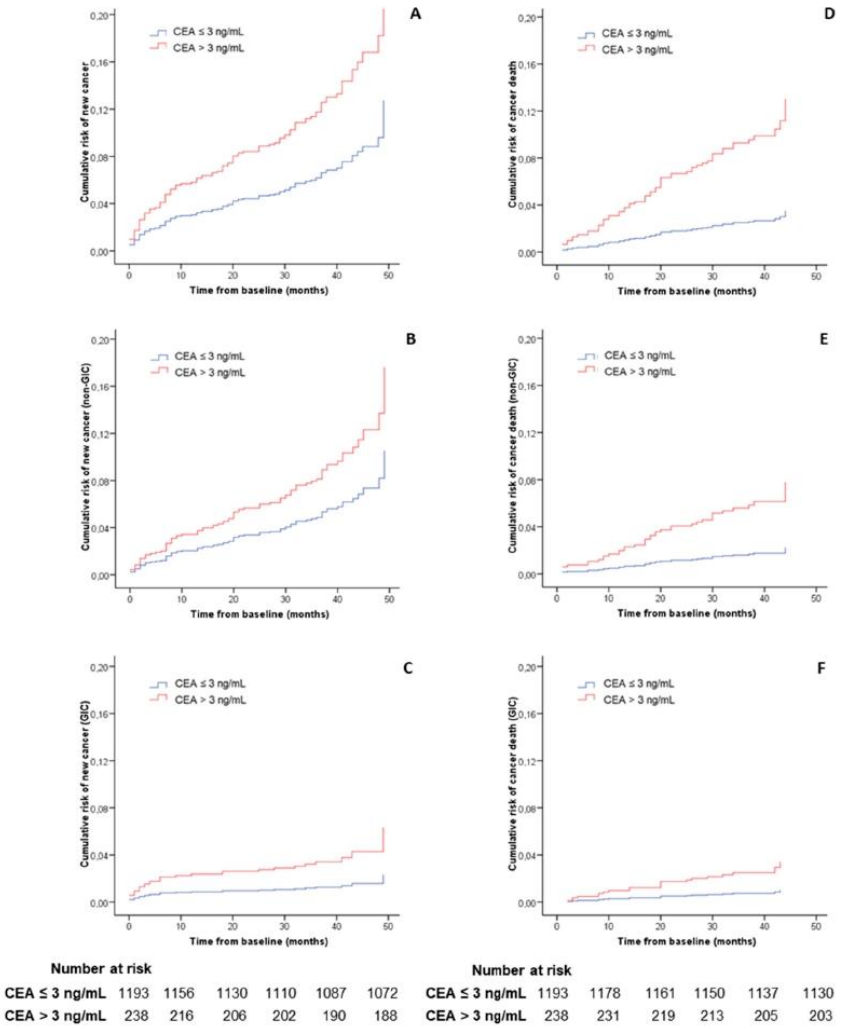

Figure 2. Cumulative risk of cancer and related death. Cumulative risk of cancer and related death during follow-up after baseline evaluation according to carcinoembryonic antigen value and adjusted by sex, age and the presence of advanced adenoma. The figure is calculated with a Cox's multivariable regression. (**A**) Risk of cancer diagnosis (global cancer); (**B**) risk of non-gastrointestinal cancer diagnosis; (**C**) risk of gastrointestinal cancer diagnosis; (**D**) risk of new cancer-related death; (**E**) risk of new non-gastrointestinal cancer death; (**F**) risk of new gastrointestinal cancer death. Number at risk was calculated for global cancer diagnosis and new cancer related death, respectively.

3.4. Risk of Cancer Diagnosis during the First Year of Follow-Up

A cancer was detected in 51 (3.6%) patients during the first year after baseline colonoscopy, which represented 44.3% of all diagnosed cancer during follow-up. Nineteen subjects were diagnosed with GIC over this period (63.3% of all diagnosed GIC in this study). Of these, 16 (84.2%) lesions were located outside the colon, while three (15.8%) were CRC. The percentage of CRC and GIC located outside the colon which were diagnosed over this period was 37.5% and 72.7%, respectively. Two thirds of gastroesophageal cancer were diagnosed during the first year. Only three variables were independently

associated with cancer detection: rectal bleeding (OR 0.3, 95% CI 0.1–0.7), anemia (OR 2.8, 95% CI 1.3–5.8) and CEA > 3 ng/mL (OR 3.4, 95% CI 1.7–7.1), as shown in Table 3.

Table 3. Factors associated with cancer detection the first year after baseline colonoscopy.

	New Cancer	Odds Ratio (95% CI)	Odds Ratio (95% CI) [1]
Sex			
Male (683)	28 (4.0%)	1	
Female (748)	23 (3.1%)	0.8 (0.4–1.3)	
Age			
≤70 years (846)	19(2.2%)	1	
>70 years (585)	32(5.5%)	2.4 (1.4–4.3)	
Primary healthcare referral			
No (1041)	35 (3.4%)	1	
Yes (390)	16 (4.1%)	1.2 (0.7–2.2)	
Rectal bleeding			
No (635)	37 (5.8%)	1	1
Yes (796)	14 (1.8%)	0.3 (0.2–0.6)	0.3 (0.1–0.7)
Change of bowel habit			
No (592)	25 (4.2%)	1	
Yes (839)	26 (3.1%)	0.7 (0.4–1.3)	
Anaemia			
No (652)	12 (1.8%)	1	1
Yes (338)	22 (6.5%)	3.5 (1.8–7.1)	2.8 (1.3–5.8)
Abdominal pain			
No (539)	21 (3.9%)	1	
Yes (451)	13 (2.9%)	0.7 (0.4–1.5)	
Weight loss			
No (750)	25 (3.3%)	1	
Yes (240)	9 (3.4%)	1.1 (0.5–2.4)	
Faecal immunochemical test			
≤10 μg/g (n = 948)	30 (3.2%)	1	
>10 μg/g (n = 483)	21 (4.3%)	1.4 (0.8–2.4)	
Carcinoembryonic antigen value			
≤3 ng/mL (n = 1193)	31 (2.3%)	1	1
>3 ng/mL (n = 238)	20(8.4%)	3.2 (1.9–5.6)	3.4 (1.7–7.1)
Advanced adenoma			
No (1225)	43 (3.5%)	1	
Yes (206)	8 (3.9%)	1.1 (0.5–2.3)	

[1] Variables with statistically significant differences were introduced in a multivariable logistic regression analysis stepwise (backward) to identify the prognostic factors associated with cancer detection the first year after baseline colonoscopy; as a result of this method, the dichotomous variable "Age" has finally not entered in the final equation. CI = confidence interval.

3.5. Diagnostic Accuracy of CEA for Cancer Diagnosis the First Year of Follow-Up

In our cohort, 652 (45.6%) patients did not have anemia, of whom 96 (14.7%) showed CEA values higher than 3 ng/mL. The AUC of CEA for cancer detection during the first year of follow-up was 0.53 (95% CI, 0.38–0.67) and 0.63 (95% CI, 0.42–0.84) for patients with and without anemia, respectively. At a 3 ng/mL threshold, the sensitivity and specificity for detecting a new cancer in patients without anemia was 50.0% (95% CI, 25.4–74.6%) and 85.9% (95% CI, 83.0–88.4%). For patients with anemia, the sensitivity and specificity for detecting a new cancer in patients was 31.8% (95% CI, 16.4–52.7%) and 83.5% (95% CI, 79.1–87.2%). The diagnostic accuracy of CEA to detect different types of cancer based on the presence of anemia using the thresholds of 3 and 5 ng/mL is shown in Table 4.

Table 4. Diagnostic accuracy of carcinoembryonic antigen for different types of cancer diagnosed in the first year during follow-up.

Threshold	Type of Cancer	Anaemia	Prevalence	%AT	Sensitivity [1]	Specificity [1]	NPV ‡,[1]	PPV [1]	AUC	LR+	LR−	DOR
CEA > 3 ng/mL	GI cancer	No	0.6	14.7	50.0 (15.0–85.0)	85.5 (82.6–88.0)	99.6 (98.7–99.9)	2.1 (0.6–7.3)	0.70 (0.41–0.99)	3.4	0.6	5.82
		Yes	3.0	17.5	30.0 (10.8–60.3)	82.9 (78.5–86.6)	97.5 (94.9–98.8)	5.1 (1.7–13.9)	0.57 (0.39–0.74)	1.8	0.8	2.08
	Upper GI cancer [2]	No	0.2	14.7	0.0 (0.0–79.3)	85.3 (82.3–87.8)	99.8 (99.0–99.96)	0.0 (0.0–3.8)	0.48 (0.44–0.53)	0.0	NA	NA
		Yes	3.0	17.5	30.0 (10.8–60.3)	82.9 (78.5–86.6)	97.5 (94.9–98.8)	5.1 (1.7–13.9)	0.57 (0.39–0.74)	1.8	0.8	2.08
	Colorectal cancer	No	0.5	14.7	66.7 (20.8–93.9)	85.5 (82.6–88.0)	99.8 (99.0–99.96)	2.1 (0.6–7.3)	0.77 (0.42–1.0)	4.6	0.4	11.80
		Yes	0.0	17.5	NA	NA	NA	NA	NA	NA	NA	NA
	Non-GI cancer	No	1.2	14.7	50.0 (21.5–78.5)	85.7 (82.8–88.5)	99.3 (98.2–99.7)	4.2 (1.6–10.2)	0.60 (0.32–0.87)	3.5	0.6	6.00
		Yes	3.6	17.5	33.3 (13.8–60.9)	83.1 (78.7–86.8)	97.1 (94.4–98.5)	6.8 (2.7–16.2)	0.49 (0.28–0.70)	2.0	0.8	2.46
	Cancer	No	1.8	14.7	50.0 (25.4–74.6)	85.9 (83.0–88.4)	98.9 (97.7–99.5)	6.3 (2.9–13.0)	0.63 (0.42–0.84)	3.6	0.6	6.11
		Yes	6.5	17.5	31.8 (16.4–52.7)	83.5 (79.1–87.2)	94.6 (91.3–96.7)	11.9 (5.9–22.5)	0.53 (0.38–0.67)	1.9	0.8	2.37
CEA >5 ng/mL	GI cancer	No	0.6	5.1	50.0 (15.0–85.0)	99.2 (93.3–96.6)	99.7 (98.8–99.9)	6.1 (1.7–19.6)	0.70 (0.41–0.99)	10.5	0.5	19.91
		Yes	3.0	8.6	20.0 (5.7–51.0)	91.8 (88.3–94.3)	97.4 (95.0–98.7)	6.9 (1.9–22.0)	0.57 (0.39–0.74)	2.4	0.9	2.79
	Upper GI cancer [2]	No	0.2	5.1	0.0 (0.0–79.3)	94.9 (93.0–96.4)	99.8 (99.1–99.97)	0.0 (0.0–10.4)	0.48 (0.44–0.53)	0.0	NA	NA
		Yes	3.0	8.6	20.0 (5.7–51.0)	91.8 (88.3–94.3)	97.4 (95.0–98.7)	6.9 (1.9–22.0)	0.57 (0.39–0.74)	2.4	0.9	2.79
	Colorectal cancer	No	0.5	5.1	66.7 (20.8–93.9)	95.2 (93.3–96.6)	99.8 (99.1–99.97)	6.1 (1.7–19.6)	0.77 (0.42–1.0)	14.0	0.4	39.88
		Yes	0.0	8.6	NA	NA	NA	NA	NA	NA	NA	NA
	Non-GI cancer	No	1.2	5.1	37.5 (13.7–69.4)	95.3 (93.4–96.7)	99.2 (98.1–99.7)	9.1 (3.1–23.6)	0.60 (0.32–0.87)	8.1	0.7	12.27
		Yes	3.6	8.6	16.7 (4.7–44.8)	91.7 (88.2–94.2)	96.8 (94.1–98.2)	6.9 (1.9–22.0)	0.49 (0.28–0.70)	2.0	0.9	2.21
	Cancer	No	1.8	5.1	41.7 (19.3–68.0)	95.6 (93.8–97.0)	98.9 (97.7–99.5)	15.2 (6.7–30.9)	0.63 (0.42–0.84)	9.5	0.6	15.61
		Yes	6.5	8.6	18.2 (7.3–38.5)	92.1 (88.6–94.6)	94.2 (91.0–96.3)	13.8 (5.5–30.6)	0.53 (0.38–0.67)	2.3	0.9	2.59

AUC = area under the curve; CEA = carcinoembryonic antigen; DOR = diagnostic odds ratio; GI = gastrointestinal; %AT = percentage of carcinoembryonic antigen above threshold; LR = likelihood ratio; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; +: positive; −: negative. [1] Values were expressed as percentages and their 95% confidence interval. [2] Defined as a cancer located outside the colon. ‡ Some NPV results were rounded to two decimals, as they could be incorrectly interpreted if they were rounded to one decimal (100.0).

4. Discussion

4.1. Statement of Principal Findings

In this study, we have evaluated the risk of cancer detection in patients with abdominal symptoms and a complete colonoscopy with no baseline CRC detected according to CEA concentration. The risk of cancer, GIC and CRC detection, but not upper-GIC, as well as their related death, is increased in patients with a CEA > 3 ng/mL. Moreover, we have determined three variables independently associated with cancer detection during the first year, as well as the diagnostic accuracy of CEA. In this sense, although specific, CEA values lack sensitivity to identify those patients who would be diagnosed with cancer during the first year of follow-up regardless of the presence of anemia.

4.2. Strengths and Weaknesses of Our Study

To our knowledge, this is the first cohort study offering information about the utility of CEA to assist in the triage of patients presenting with lower bowel symptoms who have recently been ruled out a CRC but may be suffering (or not) from other multiple types of cancer due the low specificity of digestive symptoms.

Important strengths of our study are (i) a sample size consisting of a significant number of consecutively recruited patients who underwent a colonoscopy, which guaranteed the absence of CRC and (ii) the availability of a sufficient monitoring period to detect different types of cancer. Both characteristics of our study together guarantee that these results reflect the effectiveness of CEA to predict a cancer diagnosis in the foreseeable future in a patient with abdominal symptoms after ruling out CRC.

Nonetheless, our study is not free from bias. The most important bias is a lack of pertinent background information, such as history of tobacco use or other benign conditions, which could account for a high CEA value without subsequent cancer diagnosis in some patients. This bias may have led to understating the role of CEA as a predictor of cancer. However, it should not have an impact on the assessment of CEA's sensitivity to detect cancer, only CEA's specificity.

Moreover, symptomatic patients usually present to primary healthcare, although sometimes they are allowed direct access to the specialist. Our results were obtained from a cohort comprised mainly of secondary healthcare patients. These are generally at a higher risk of being diagnosed with cancer than primary healthcare patients. Consequently, the assessment of CEA's diagnostic accuracy could be lower in a cohort made up solely of patients from that setting.

4.3. Strengths and Weaknesses in Relation to Other Studies

Until now, CEA has been revealed to be mainly related to CRC and our study is along those lines [6]. Even after selecting patients with abdominal symptoms who had undergone a colonoscopy without CRC, a high CEA value only significantly increased the risk of future CRC diagnosis and related death. In this regard, the incidence of CRC during follow-up is very low, within the admissible CRC range values [26].

CEA was previously found to have low sensitivity and specificity to detect CRC in asymptomatic patients. However, it was found that average-risk patients with raised CEA should be investigated, because approximately 9% present some type of cancer. Furthermore, those patients should also be followed up, as another 7% are subsequently diagnosed with some cancer during monitoring [9]. This high cancer incidence could be accounted for the selection process of those patients. Although that study was performed in asymptomatic patients, the reason for which CEA was determined could entail an increased risk of cancer diagnosis. In our prospective cohort, comprised of consecutive patients who complained about abdominal symptoms, 13% of patients were diagnosed with cancer at some time during follow-up. A large proportion of those cancers were detected in the first year of follow-up and were thus likely to be present at the time baseline colonoscopy was performed.

In the past, various CEA thresholds were used. The threshold of 5 ng/mL was the most common during CRC follow-up despite a recommendation to raise this to 10 ng/mL when used in this context as a single test [21]. In this work, we decided to explore a lower threshold, as we are using CEA as a triage test of a group of diseases whose prognosis would benefit from a prompt diagnosis.

4.4. Implications for Clinical Practice and Research

The time between the onset of symptoms and consultation with the physician is a significant proportion of the total time to most cancer diagnosis [27]. Unfortunately, the most frequent initial cancer symptoms are common features of benign conditions and are often shared between different types of cancer [28].

Despite previous work recommending a rational evaluation pathway for a patient with a raised CEA [6], our data reveals that CEA also has a poor sensitivity to detect cancer in the patient with abdominal symptoms. The CEA levels were only higher than 3 ng/mL in about one third and one half of patients—with and without anemia, respectively—who will later be diagnosed with cancer during follow-up. Therefore, even as an independent predictor for future cancer diagnosis in the patient with abdominal symptoms who have ruled out a CRC, the determination of serum CEA should not be used as triage tool to identify who could benefit from further diagnostic tests in this population.

4.5. Unanswered Questions and Future Research

This study has revealed a remarkably high incidence of non-gastrointestinal cancer in a cohort of patients with abdominal symptoms. Furthermore, the incidence of non-gastrointestinal cancer in the subgroup of patients with CEA below the threshold 3 ng/mL and FIT < 20 µg Hb/g feces exceed the threshold risk of cancer of 3% recommended by the 2015 version of the NICE guidelines for investigation [29]. Similarly, other authors have reported that abdominal symptoms are common at presentation in different types of cancer [30]. Further prospective studies are needed in order to better understand the relationship between the presence of some particular abdominal symptoms and the subsequent diagnosis of an apparently unrelated cancer.

4.6. Conclusion

This study assesses the value of CEA in a large cohort of patients with symptoms that could be compatible with multiple tumors after the most common digestive tumor (CRC) had been ruled out with a very reliable test (colonoscopy). In this situation, extremely frequent in clinical practice, some doctors request the determination of serum CEA level to decide whether to perform or not additional work up to assess the possibility of that patient having other types of cancer. Our work, with its limitations, suggests that this practice should be abandoned.

Supplementary Materials: The following are available online at http://www.mdpi.com/2075-4418/10/12/1036/s1. **Supplementary Table S1.** Time to cancer diagnosis based on CEA level and type of cancer.

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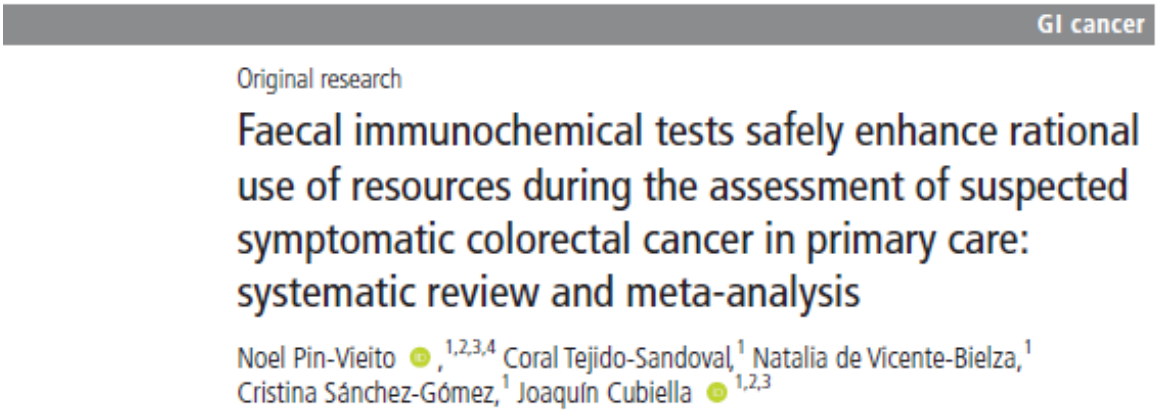
Supplementary Table 1. Time to cancer diagnosis based on CEA level and type of cancer.

Type of Cancer		CEA ≤ 3 ng/mL (*n* = 1193)									CEA > 3 ng/mL (*n* = 238)						
		Total[1]	Time to Diagnosis						Total[2]	Risk[3]	Time to Diagnosis						Total[5]	Risk[6]
			0–12 months[1]		13–24 months[1]		>24 months[1]				0-12 months[4]		13–24 months[4]		>24 months[4]			
H&N		1	1	100.0	0	0.0	0	0.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
GIC	Oesophageal	2	1	50.0	0	0.0	1	50.0	2	0.17	0	NA	0	NA	0	NA	0	0.00
	Gastric	15	7	63.6	2	18.2	2	18.2	11	0.92	4	100.0	0	0.0	0	0.0	4	1.68
	Small Bowell	3	1	50.0	0	0.0	1	50.0	2	0.17	1	100.0	0	0.0	0	0.0	1	0.42
	Ampullary	2	0	NA	0	NA	0	NA	0	0.00	2	100.0	0	0.0	0	0.0	2	0.84
	CRC	8	1	25.0	1	25.0	2	50.0	4	0.34	2	50.0	0	0.0	2	50.0	4	1.68
Hepatobiliary	Gallbladder	2	1	50.0	1	50.0	0	0.0	2	0.17	0	NA	0	NA	0	NA	0	0.00
	Pancreas	3	1	50.0	0	0.0	1	50.0	2	0.17	1	100.0	0	0.0	0	0.0	1	0.42
	Hepatocarcinoma	4	1	50.0	0	0.0	1	50.0	2	0.17	2	100.0	0	0.0	0	0.0	2	0.84
Skin	Basal cell	4	1	33.3	1	33.3	1	33.3	3	0.25	0	0.0	0	0.0	1	100.0	1	0.42
	Melanoma	1	1	100.0	0	0.0	0	0.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
	Unspecified	7	3	50.0	3	50.0	0	0.0	6	0.50	0	0.0	0	0.0	1	100.0	1	0.42
Ginaecology	Endometrial	2	0	0.0	0	0.0	2	100.0	2	0.17	0	NA	0	NA	0	NA	0	0.00
	Ovarian	4	1	50.0	0	0.0	1	50.0	2	0.17	2	100.0	0	0.0	0	0.0	2	0.84
Respiratory	Breast	8	0	0.0	2	40.0	3	60.0	5	0.42	0	0.0	2	66.7	1	33.3	3	1.26
	Lung	9	1	25.0	0	0.0	3	75.0	4	0.34	3	60.0	2	40.0	0	0.0	5	2.10
Urology	Kidney	5	0	0.0	2	66.7	1	33.3	3	0.25	1	50.0	0	0.0	1	50.0	2	0.84
	Urotelial	1	0	0.0	0	0.0	1	100.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
	Prostate	10	2	22.2	1	11.1	6	66.7	9	0.75	0	0.0	1	100.0	0	0.0	1	0.42
	Vesical	5	3	60.0	0	0.0	2	40.0	5	0.42	0	NA	0	NA	0	NA	0	0.00
Haematology	Leukemia	1	0	0.0	0	0.0	1	100.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
	Lymphoma	6	3	60.0	0	0.0	2	40.0	5	0.42	1	100.0	0	0.0	0	0.0	1	0.42
	Myeloma	3	1	33.3	0	0.0	2	66.7	3	0.25	0	NA	0	NA	0	NA	0	0.00
Other	Unspecified	2	0	0.0	1	100.0	0	0.0	1	0.08	1	100.0	0	0.0	0	0.0	1	0.42
	Glioblastoma	1	0	0.0	0	0.0	1	100.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
	Schwannoma	1	1	100.0	0	0.0	0	0.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
	Kaposi	1	0	0.0	1	100.0	0	0.0	1	0.08	0	NA	0	NA	0	NA	0	0.00
Cancer of unknown origin		4	0	0.0	3	75.0	1	25.0	4	0.34	0	NA	0	NA	0	NA	0	0.00
Total		115	31	36.9	18	21.4	35	41.7	84	7.04	20	64.5	5	16.1	6	19.4	31	13.03

CEA = carcinoembryonic antigen; CRC = colorectal cancer; GIC = gastrointestinal cancer; H&N = head and neck cancer; NA = not applicable; 1 number of cancer diagnosed for each period of time from baseline colonoscopy and their percentage with respect to total diagnosed cancer of the same type in patients with CEA ≤ 3 ng/mL; 2 Total number of each type diagnosed cancer in patients with CEA ≤ 3 ng/mL; 3 Incidence of each type of cancer in patients with CEA ≤ 3 ng/mL; 4 number of cancer diagnosed for each period of time from baseline colonoscopy and their percentage with respect to total diagnosed cancer of the same type in patients with CEA > 3 ng/mL; 5 Total number of each type diagnosed cancer in patients with CEA > 3 ng/mL; 6 Incidence of each type of cancer in patients with CEA > 3 ng/mL;.

Metodología y resultados - Artículo 5



GI cancer

Original research

Faecal immunochemical tests safely enhance rational use of resources during the assessment of suspected symptomatic colorectal cancer in primary care: systematic review and meta-analysis

Noel Pin-Vieito ,[1,2,3,4] Coral Tejido-Sandoval,[1] Natalia de Vicente-Bielza,[1] Cristina Sánchez-Gómez,[1] Joaquín Cubiella [1,2,3]

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Objetivo

Realizar una revisión sistemática y en caso de ser posible un metaanálisis de aquellos trabajos que han estudiado la precisión de SOH-i cuantitativo para detectar CCR en pacientes con síntomas digestivos en el entorno específico de atención primaria.

Métodos

Dos investigadores revisaron de forma independiente las bases de datos MEDLINE y EMBASE, ampliando la búsqueda a la bibliografía y autores de trabajos considerados relevantes. Se incluyeron todos los estudios transversales que aportaron información sobre la precisión diagnóstica de SOH-i para detectar CCR en pacientes que consultan en atención primaria por la aparición de síntomas digestivos.

La extracción de datos se realizó de forma independiente por dos investigadores y se evaluó la calidad de los artículos mediante la herramienta QUADAS-2 [151]. El sesgo de publicación se valoró por medio de un gráfico de embudo invertido (Funnel plot).

Se empleó el modelo normal bivariado para sintetizar la evidencia disponible [152]. Cuando este enfoque no fue posible, se utilizó un modelo de efectos aleatorios siguiendo el método de DerSimonian para dibujar curvas resumen (sROC) de las estimaciones de sensibilidad y especificidad a través del modelo de DerSimonian y Lair [155,156].

Se evaluó el rendimiento diagnóstico de SOH-i para diferentes puntos de corte a partir de la prevalencia de CCR y las probabilidades post-test mediante nomogramas de Fagan, calculando el número de colonoscopias necesarias para encontrar un CCR

(NNS), y el número de CCR perdidos por 1000 pacientes con una concentración de Hb-f por debajo de cada umbral seleccionado.

Se determinó la existencia de heterogeneidad por medio del estadístico Q de Cochran, evaluando sus causas por medio de procedimientos de meta-regresión y tomando el índice de inconsistencia (I^2) como medida del grado de la misma [158]. A este respecto, la marca comercial de SOH-i, el lugar donde se reclutaron los pacientes de cada estudio (unidad de colonoscopia o centro de atención primaria) y el estándar de referencia utilizado para el seguimiento de los pacientes con resultados de SOH-i por debajo del umbral, fueron variables tenidas en cuenta como potenciales sesgos de confusión en la evaluación de la precisión de SOH-i.

El efecto umbral se valoró por medio de la correlación de Spearman ($p<0.1$ se considera significativo).

Resultados

Se incluyeron veintitrés estudios observacionales que cumplieron los criterios de inclusión [86, 170-191], acumulando una muestra de 69,536 pacientes con un rango de edad mediana entre 58 y 72 años. La prevalencia de CCR fue variable entre 0.3 y 6.2%.

La sensibilidad global de SOH-i para detectar CCR, estimada a partir de los estudios que utilizaron un umbral ≥10 μg Hb / g en heces (15 estudios; n = 48,872 pacientes) fue 87.2% (IC 95% 81.0%-91.6%), y disminuyó hasta un 84.1% (IC 95% 78.6%-88.4%) en aquellos estudios que utilizaron un umbral ≥20 μg Hb / g heces (cinco estudios; n = 24,187 pacientes). Por el contrario, la especificidad aumentó desde 84.4% (IC 95% 79.4%-88.3%) a 86.6% (IC 95% 75.6%-93.1%) en esos dos grupos de estudios respectivamente.

Por otra parte, seis estudios (n = 34,691 pacientes) evaluaron la precisión diagnóstica de SOH-i utilizando el umbral de ≥150 μg Hb / g heces, mostrando una sensibilidad y especificidad del 64.1% (IC 95% 57.8%-69.9%) y 95.0% (IC 95% 91.2%-97.2%) respectivamente.

Se apreció una elevada heterogeneidad entre los diversos estudios utilizados en el metaanálisis. Las variables "patrón de referencia para el diagnóstico de CCR" (colonoscopia o seguimiento), "lugar de reclutamiento de los pacientes" (centro de atención primaria o unidad de colonoscopia) y "prevalencia de CCR" (CCR <3% o CCR ≥3%) influyeron de forma significativa en el cálculo de ambos estimadores de precisión de SOH-i para la detección de CCR (sensibilidad y especificidad). Además, la marca comercial de SOH-i (OC-Sensor o HM-JACKarc) también demostró ser un predictor significativo de heterogeneidad en el cálculo de la especificidad. A pesar de esta significativa variabilidad entre los diversos estudios, la magnitud del cambio que supone en el cálculo de los estimadores de sensibilidad y especificidad y sus intervalos de confianza para cada subgrupo analizado no fue clínicamente relevante.

También se calculó el número de falsos negativos de SOH-i y el número de colonoscopias que es necesario realizar para encontrar un CCR entre aquellos sujetos con un valor de Hb-f superior a cada umbral escogido para un rango de prevalencia de CCR entre 1% y 5% (esperable en el entorno de atención primaria). Por ejemplo, el número de CCR que se perderían por cada 1000 pacientes evaluados mediante SOH-i en una población con una prevalencia de CCR del 2% (falsos negativos del test) aumentaría de cuatro a cinco si utilizamos el umbral de 20 μg Hb / g en heces en lugar de 10 μg Hb / g heces mientras que el número de colonoscopias necesarias para diagnosticar un CCR disminuiría de seis a cuatro. Por otro lado, en una población de

esta prevalencia de CCR (2%), se espera que el NNS disminuya de diez a cuatro si se utiliza el umbral de 150 µg Hb / g en heces en lugar de 10 µg de Hb / g en heces.

Algunos estudios evaluados en este metaanálisis han ofrecido información sobre la precisión de SOH-i para detectar LCS. Sin embargo, la prevalencia de este tipo de lesiones varió ampliamente (4.4%-13.6%) anticipando una alta heterogeneidad entre los diversos estudios, lo que unido al reducido número de los mismos ha restringido la posibilidad de realizar análisis para varios puntos de corte, así como estimaciones robustas de la precisión de SOH-i para detectar este tipo de lesiones.

Conclusión

Este metaanálisis confirma que el test de SOH-i es la prueba de elección para evaluar pacientes que consultan en su centro de salud por la aparición de síntomas digestivos compatibles con un cáncer colorrectal.

Faecal immunochemical tests safely enhance rational use of resources during the assessment of suspected symptomatic colorectal cancer in primary care. Systematic review and meta-analysis

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Key words

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ABSTRACT

Objective: Implementation of faecal immunochemical tests (FIT) as a triage test in primary healthcare may improve the efficiency of referrals without missing cases of colorectal cancer (CRC). We aim to summarize the performance characteristics of FITs for CRC in symptomatic patients presenting to primary healthcare.

Design: We performed a systematic literature review of Medline and EMBASE databases from May 2018 to November 2020. Previous related systematic searches were also adapted to this aim and completed with reference screening. We identified studies performed on adult patients consulting for abdominal symptoms in primary care which reported data such that the FIT diagnostic performance parameters for CRC could be obtained. Bivariate models were used to synthesize available evidence. Meta-regression analysis was performed to evaluate the causes of heterogeneity.

Results: Twenty-three studies (69,536 participants) were included (CRC prevalence 0.3%-6.2%). Six studies (n=34,691) assessed FIT as rule in test (threshold of ≥150 µg Hb/g faeces) showing a sensitivity of 64.1% (95% CI 57.8-69.9) and a specificity of 95.0% (95% CI 91.2-97.2). A threshold of 10 µg/g (15 studies; n=48,872) resulted in a sensitivity of 87.2 % (95% CI 81.0-91.6) and a specificity of 84.4% (95% CI 79.4-88.3) for CRC. At a 20 µg Hb/g faeces threshold (five studies; n=24,187) less than one additional CRC would be missed per 1000 patients investigated compared to 10 µg Hb/g faeces threshold (CRC prevalence 2%).

Conclusion: FIT is the test of choice to evaluate patients with new-onset lower gastrointestinal symptoms in primary healthcare.

What is already known about this subject?

- CRC detection in symptomatic patients is a challenge for healthcare systems given the low specificity of symptoms. This results in overuse of colonoscopy resources and delay in diagnosis.
- FIT may be effective in the stratification of CRC risk in patients with abdominal symptoms seen in primary healthcare.

What are the new findings?

- A 150 µg Hb/g of faeces threshold identifies more than half of CRC with high specificity.
- In low CRC prevalent populations, CRC risk in patients with f-Hb< 10 µg/g of faeces equals the risk of colonoscopy severe complications and the CRC risk in asymptomatic subjects.

How might it impact clinical practice in the foreseeable future?

- The evaluation of patients consulting with new-onset lower gastrointestinal symptoms in primary healthcare with FITs enables rational use of the available resources.
- In the near future, we will have to address two questions: how to detect FIT negative CRC and whether FIT evaluation in symptomatic patients improves CRC prognosis.

INTRODUCTION

A significant percentage of colorectal cancers (CRC) are diagnosed in symptomatic patients, after the implementation of CRC screening programmes.[1] Unfortunately, most symptoms are nonspecific at presentation as they are shared among non-malignant conditions and different types of cancer, which produces additional difficulties and delay in diagnosis.[2] Moreover, concordance between patient-reported and doctor-reported symptoms is low,[3] and most patients with abdominal symptoms do not have significant colorectal disease.[4]

In the last few years, evidence has proven that faecal immunochemical tests for haemoglobin (FIT) may be effective in evaluating patients with abdominal symptoms to identify patients at low risk of CRC.[5] Furthermore, the amount of faecal haemoglobin (f-Hb) detected has been shown to be related to severity of disease,[6] and constitutes a better CRC risk predictor than demographic (age and sex), clinical (presence of symptoms) and family history or lifestyle factors.[7]

For these reasons, the National Institute for Health and Care Excellence (NICE) recommended (DG30) in 2017 the use of FIT to guide referral for suspected CRC in patients without rectal bleeding who complain with certain unaccounted for low-risk symptoms.[8] Furthermore, implementation of FIT as a triage test in primary care with appropriate safety netting, may improve the efficiency of referrals without missing cases of relevant bowel disease. This is even more important nowadays, in regions with additional capacity issues due to the COVID-19 pandemic.[9]

Notwithstanding the above, a recent systematic review revealed that few countries recommend FIT in primary healthcare as an adjunct to clinical assessment.[10] There is limited evidence of the use of FITs in this setting as most studies supporting DG30 recommendation were performed in secondary care.[5] This could increase the concerns of general practitioners to use FITs to aid their decision-making process when dealing with a patient with symptoms suggesting CRC. Several studies have recently been published evaluating FIT in symptomatic patients seen in primary healthcare. We therefore aim to perform a systematic review to assess the diagnostic accuracy of FIT for CRC detection in patients presenting with recent onset gastrointestinal symptoms in primary healthcare, with special interest on the clinical effectiveness for triaging referrals in this setting.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct and report this systematic review.[11]

Data sources and searches

MEDLINE (via PubMed) and EMBASE (via Ovid) databases were searched from May 2018 to November 2020 without restrictions on language or publication status. Published search strategies in related systematic reviews were consulted and updated. [5,12] The reference lists of all relevant articles extracted were also reviewed to identify additional potentially interesting articles following an iterative process. Furthermore, we also included all studies identified by previous systematic reviews that satisfied the inclusion criteria of this research (Appendix 1-Supplementary file).

Study selection

Three authors (CT, NV and CSG) independently screened titles and abstracts and assessed full text articles of studies considered relevant. We included any cohort study which met all the following criteria: 1) adult subjects (older than 18 years) consulting for abdominal symptoms in primary healthcare, 2) FIT diagnostic performance parameters for CRC and/or significant colonic lesions (SCL) available and 3) thresholds used to determine a positive result expressed as micrograms of haemoglobin per gram of faeces (µg Hb/g). We included in this systematic review studies that reported colon evaluation (either by endoscopic or imaging techniques) or longitudinal follow-up of controls with medical records or cancer registry and a minimum monitoring time of three months as reference standard. A previous study showed that the different follow-up periods (3, 6, 12 months) did not affect FIT diagnostic performance for CRC detection.[13]

We excluded studies if two by two tables with absolute numbers of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) test results could not be constructed. Case-control studies, conference abstracts, studies with hospital inpatients and those including screening, or mixed (with and without symptoms) population were also excluded. Those studies conducted on symptomatic patients who were recruited in colonoscopy units, were only included if authors explicitly state that they were performed on patients referred solely from primary healthcare facilities.

Outcome assessment

Our primary and secondary outcomes were FIT diagnostic performance estimates to detect CRC and significant colonic lesion (SCL) respectively, at a cut-off

value of limit of detection (LoD), 10 µg Hb/g faeces, 20 µg Hb/g faeces and 150 µg Hb/g faeces.

Data extraction

Two reviewers (CT and NV) extracted data and extractions were verified by a second reviewer (CSG). Any disagreement was consulted with a third reviewer (NPV/JC). In addition to test performance outcome measures, information on study details (author, year of publication, aim and setting, period of recruitment and type of cohort), participant characteristics (inclusion and exclusion criteria, demographic characteristics, symptoms, acceptability defined as the proportion of participants who returned a FIT sample), target reported (prevalence of CRC and SCL as well as the definition used), FITs characteristics (brand, analyzer used, faecal haemoglobin concentration [f-Hb] used as threshold) and reference standard used (bowel examination and follow up length when applicable) were considered relevant.

Quality assessment

The potential risks of bias were evaluated for each study included using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2).[14] An inverted funnel scatterplot was used to detect publication bias.

Statistical analysis

To avoid threshold effect, studies were classified by f-Hb threshold for a positive test result. Threshold effect is a specific cause of heterogeneity in meta-analyses of diagnostic test accuracy. It occurs when different criteria (cut-off values or thresholds) are used between studies to assess whether a test result is positive or negative. We calculated pooled estimates of sensitivity, specificity and likelihood ratios using a bivariate random-effects model when at least four studies with similar characteristics were available.[15] When necessary, a hierarchical summary receiver operating characteristic (HSROC) curve presenting summary estimates of sensitivities and specificities along with their corresponding 95% confidence interval (CI) and prediction region was also generated for each subgroup of studies.[16] If this approach was not possible, a random-effects model was applied following DerSimonian´s method and summary sensitivity and specificity estimates were reported by plotting a summary receiver operating characteristics (sROC) curve using DerSimonian and Lair's model.[17] We evaluated the diagnostic yield of FIT according to the CRC prevalence and the post-test probabilities of CRC assessed through Fagan nomograms. We calculated the number of necessary colonoscopies to find one CRC (number necessary

to scope - NNS), and the number of missed CRC per 1000 patients with a f-Hb value below a chosen threshold.

The percentage of total variation across studies attributable to heterogeneity rather than chance was assessed statistically using the inconsistency index I^2, and values greater than 50% represent substantial heterogeneity.[18] Threshold effect was assessed through Spearman's rank correlation (P<0.1 was considered to be statistically significant).

FIT brand, the location where the patient was recruited (colonoscopy unit or primary health facility) or the reference standard used to follow up on patients with negative FIT results, are variables which may affect the assessment of FIT accuracy. Thus, when the number of studies allowed, we performed a bivariate random-effects meta-regression to evaluate the impact of these variables on our results. Visual inspection of ROC space was used to enable identification of those studies with major differences from each subgroup based on threshold and sensitivity analysis was performed after removing keynote outliers when those differences can be accounted for through bias. We used Stata V.14.0 (StataCorp, College Station, Texas), and MetaDisc software for statistical analyses.[19]

Patient and public involvement

We consulted a European association of colorectal cancer patients and their relatives during the development of the study protocol (https://europacolonespana.org) to assess the general public acceptability as well as any concern about using FITs as a triage tool for symptomatic patients with suspected CRC in primary care. Feedback was used to select the most relevant information collected in this systematic review from a general public point of view. These data will be included in a friendly designed poster to be shown in primary care centres, patient association websites and disseminated through press releases.

RESULTS

Study Selection

The literature search in MEDLINE and EMBASE identified 4620 potentially relevant articles, of which 170 full-text articles were evaluated and 22 articles met the inclusion criteria (Figure 1 and Appendix 2). The reasons for excluding the articles were as follow: secondary literature (41), studies mixing symptomatic and asymptomatic subjects (76), research performed outside primary healthcare (97), uncertainty with the index test (53), the reference standard (21) or the outcome definition (13). These were supplemented by one article from a manual search published one month from the search date, providing a total of 23 studies included in this systematic review (Table 1 and Supplementary table 1).[13,20-41] Furthermore, additional information of the same patients evaluated in the studies of Khan et al,[38] and Chapman et al,[31] is respectively reported in another two secondary published studies.[42,43] Partial information reported in the studies of Hogberg et al,[40] and McSorley et al,[37] can also be found in other studies included in this review,[34,29] and this has been considered in the quantitative synthesis.

Table 1. Characteristics of the studies included in the meta-analysis.

Author, year	Country	Type	n	Age	Sex	CRC		SCL		Symptoms										FIT brand	Reference standard€		
										AbPa		ReBl		ChBoHa		WeLo		Anaemia			Performed BI		Censor date/Follow-up time¥
				Median	% Fem	N	%	N	%	N	%	N	%	N	%	N	%	N	%		N	%	
Recruited in primary care																							
Hogberg, 2010 [20]	SWE	Pro	303	ND	ND	1	0.3	9	3.0	250	82.5	47	15.5	70	23.1	ND	ND	51	16.8	AFB	ND	54.0	31/05/08
Mowat, 2015 [21]	UK (Sco)		755	64	54.7	28	3.7	103	13.6	83	11.0	258	34.2	323	42.8	7	0.9	67	8.9	OC-S	755	100.0£	NA
Elias, 2016 [22]	NL		810	61	54.9	37	4.6	141	17.4	ND	80.7	ND	43.6	ND	65.5	ND	19.2	ND	5.5	COS	810	100.0£	3 months
Hogberg, 2016 [23]	Sweden		373	63	64.6	8	2.1	26	6.8	207	58.0	92	25.3	161	45.7	46	13.5	62	21.0	AFB	185	49.6	2 years
Juul, 2018 [24]	Denmark		3462	ND	56.1	54	1.6	153	4.4	1579	45.6	0	0.0	1867	53.9	ND	ND	424	12.3	OC-S	834	24.1	3 months
Ayling, 2020 [35]	UK (Eng)		894	60	55.7	8	0.9	23	2.6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	OC-S	217	24.3	31/01/20
Mowat, 2019 [29]	UK (Sco)		5372	65	56.4	103	1.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	1926	35.9	01/11/18
Keenan, 2019 [30]	NZ		185	59	50.8	2	1.0	7	3.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Ngaio	67	36.2	1 year
Chapman, 2019 [31]	UK (Eng)		810	ND	55.7	40	4.9	108	13.3	ND	ND	0	0.0	ND	58.2	ND	ND	288	37.8	OC-S	ND	ND	22/09/17
Pin-Vieito, 2020 [33]	ESP		5623	61	53.4	80	1.4	ND	ND	1008	ND	ND	ND	ND	ND	ND	ND	ND	ND	OC-S	ND	ND	2 years
Nicholson, 2018 [13]	UK (Eng)		238	58	57.0	7	2.9	20	8.4	45	18.9	23	9.7	59	24.8	4	1.7	62	26.1	HM-J	75	31.5	21-23 months
Hogberg, 2020 [34]	SWE		5683	64	59.9	107	1.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	AFB	ND	ND	2 years
Nicholson, 2020 [27]	UK (Eng)	Ret	9896	60	58.6	105	1.1	682	6.9	ND	25.2	ND	19.7	ND	50.6	ND	ND	ND	28.2	HM-J	ND	ND	6-36 months
McSorley, 2020 [37]	UK (Sco)		4841	66	52.7	266	5.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	4841	100.0£	NA
Bailey, 2020 [39]	UK (Eng)		5733	67.4#	56.0	106	1.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	OC-S	ND	ND	31/12/18
Hogberg, 2020 [40]	SWE		15789	65	60.9	304	1.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Mix$^{\Psi}$	ND	ND	2 years
Recruited in colonoscopy unit																							
Widlak, 2018 [25]	UK (Eng)	Pro	562	68	49.0	35	6.2	173	31.0	164	29.0	232	41.0	369	66.0	87	15.0	121	22.0	HM-J	562	100.0	NA
Turvill, 2018 [26]	UK (Eng)		515	69	50.0	27	5.0	76	15.0	134	26.0	187	36.0	409	79.0	ND	14.0	ND	18.0	HM-J	515	100.0	NA
D'Souza, 2019 [32]	UK (Eng)		298	60.6#	51.4	12	4.0	27	9.1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	298	100.0	NA
D'Souza, 2020 [36]	UK (Eng)		9822	65	54.9	329	3.3	1177	12.0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	HM-J	9822	100.0	NA
Khan, 2020 [38]	UK (Eng)		928	72	59.5	47	5.1	ND	ND	69	7.4	94	10.1	609	65.6	70	7.5	189	20.4	HM-J	928	100.0	NA
Laszlo, 2020 [41]	UK (Eng)		3596	67	53.1	90	2.5	444	12.3	427	11.9	970	27.0	1835	51.0	312	8.7	684	19.0	OC-S	3596	100.0	NA
Ayling, 2019[28]	UK (Eng)	Ret	178	71	51.2	7	3.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	178	100	OC-S	178	100.0	NA

AbPa, abdominal pain; AFB, Actim Faecal Blood; BI, bowel image; ChBoHa, Change of bowel habit; COS, Clearview One Step; CRC, colorectal cancer; En, England; ESP, Spain; Fem, Female; HM-J, HM-JACKarc; Jun, June; NA, Not applicable; ND, No data; Ngaio, Ngaio Diagnostics; NL, Netherlands; Nov, November; NZ, New Zealand; OC-S, OC-Sensor; Pro, prospective; ReBl, Rectal bleeding; SCL, significant colonic lesion; Ret, retrospective; Scot, Scotland; SWE, Sweden; UK, United Kingdom; WeLo, Weight loss; £, Colonoscopy was performed as reference standard in 100% of patients; €, The studies performed on patients recruited in primary care facilities used follow-up by means of review of clinical records and cross-databases as reference standard. However, a variable fraction of the cohort performed different bowel imaging investigations, mainly colonoscopy, computer tomography colonography, plain computer tomography and/or sigmoidoscopy; ¥, follow up end date or monitoring time; Ψ, This study used various FIT: Actim Faecal Blood in Örebro, Analyz FOB in Kronoberg, Västerbotten, and Västernorrland, Chemtrue FOB Test in Jämtland Härjedalen and Diaquick FOB also in Kronoberg; # Mean age.

Study characteristics

The total number of participants was 69,536. Sample sizes ranged from 178 to 15,789. Median age ranged from 58 to 72 years and the proportion of women from 49.0% to 64.6%. CRC and SCL prevalence ranged from 0.3% to 6.2% and 2.6% to 31.0%, respectively. Twelve studies provided information on the FIT's accuracy for SCL detection. SCL definition varied widely between the different studies. Most authors defined it as the sum of CRC plus high risk and/or advanced adenoma plus Inflammatory bowel disease, [13,21-24,27,29-32,35,36] although diverticulitis significant diverticular disease or complicated diverticular disease were also included in three studies.[22, 26. 31] With respect to the reference standard for CRC and/or SCL, colonoscopy was performed as reference standard in 100% of patients recruited in colonoscopy units and in a variable percentage in patients recruited in primary healthcare. In this subgroup of studies, the CRC diagnosis was based either on different bowl imaging investigations (colonoscopy, computer tomography colonography, plain computer tomography and/or sigmoidoscopy) or in follow-up with a variable length of time (3 to 36 months). Full details of these studies are shown in Table 1 and the Supplementary table 1.

Quality Assessment

Overall results of the quality assessment from the 23 articles are reported in Figure 2 by means of the QUADAS-2 instrument. Eight studies were retrospective in design.[13,27,28,33,34,37,39,40] Of the thirteen articles using longitudinal follow-up as reference standard, eight articles were at high-risk of bias because they used heterogenous monitoring periods less than two years.[13,20,24,27,30,31,35,39] Ten articles had a high risk of selection bias, as their cohorts had either been recruited in colonoscopy units or comprised solely of patients referred to colonoscopy, thus having an increased risk of CRC.[21,22,25,26,28,32,36-38,41] Two studies included frozen stool samples,[22,28] and another two, which assessed the accuracy of a quantitative FIT (HM-JACKarc), evaluated more than one sample for each patient and considered a positive result if any of those samples had a positive outcome.[13,27] One study collected the stool sample for FIT through a digital rectal examination.[38] A number of studies had 'patient selection' applicability concerns. In many cases, a low proportion of patients who were either invited or agreed to participate in the study were included in the analysis.[21,22,25,26,36,41] Other studies also had a very low number of patients.[13,20,23,28,30,32]

Overall Accuracy of FIT based on positivity threshold to detect CRC

The LoD value depended on the FIT brand used and ranged from 2 µg Hb/g faeces to 7 µg Hb/g faeces.The overall pooled sensitivity and specificity of FITs for CRC for studies which used the LoD as threshold (11 studies; n=41,338 patients) were 93.4% (95% CI 88.0-96.4) and 76.9% (95% CI 67.7-84.0), respectively. Sensitivity for CRC decreased from 87.2% (95% CI 81.0-91.6) for studies with a threshold of ≥10 µg Hb/g faeces (15 studies; n=48,872 patients) to 84.1% (95% CI 78.6-88.4) for studies with a threshold ≥20 µg Hb/g faeces (five studies; n=24,187 patients), and specificity increased from 84.4% (95% CI 79.4-88.3) to 86.6% (95%CI 75.6-93.1). Furthermore, six studies (n=34,691 patients) evaluated the diagnostic accuracy of FIT with a threshold of ≥150 µg Hb/g faeces showing a sensitivity and specificity of 64.1% (95%CI 57.8-69.9) and 95.0% (95%CI 91.2-97.2), respectively (Table 2). Appendix 3 shows pooled sensitivity and specificity for faecal immunochemical test studies based on a cut-off value (Supplementary file).

Table 2. Diagnostic accuracy parameters based on quantitative FIT threshold concentration to detect colorectal cancer and significant colonic lesion.

Target	Studies (n)	Sensitivity†	I^2‡	Specificity†	I^2‡	Positive LR§	I^2‡	Negative LR§	I^2‡	Diagnostic OR§	I^2‡	*P**	AUC
> LoD µg Hb/g faeces													
CRC	11	93.4 (88.0-96.4)	83.6	76.9 (67.7-84.0)	99.6	4.03 (2.91-5.60)	99.2	0.09 (0.05-0.15)	81.2	46.64 (28.08-77.49)	100.0	< 0.01	0.93 (0.90-0.95)
SCL$^{\Psi}$	7	70.4 (68.4-72.3)	95.3	78.4 (77.8-78.9)	99.7	3.31 (2.31-4.77)	98.5	0.36 (0.28-0.46)	87.1	9.33 (7.26-11.99)	70.2	< 0.01	0.81 (0.79-0.82)
≥ 10 µg Hb/g faeces													
CRC	15	87.2 (81.0-91.6)	92.4	84.4 (79.4-88.3)	99.7	5.57 (4.28-7.26)	99.6	0.15 (0.10-0.22)	97.2	36.77 (23.51-57.51)	100.0	0.16	0.92 (0.90-0.94)
CRC$^{¥}$	13	88.9 (85.8-91.4)	37.0	84.0 (81.4-86.3)	97.4	5.54 (4.71-6.53)	93.5	0.13 (0.10-0.17)	43.6	41.91 (28.85-60.87)	99.7	0.58	0.93 (0.91-0.95)
SCL	8	69.1 (60.5-76.5)	93.6	87.2 (83.4-90.2)	98.2	5.38 (4.39-6.59)	88.0	0.35 (0.23-0.45)	90.6	15.18 (11.41-20.19)	100.0	0.33	0.82 (0.79-0.85)
≥ 20 µg Hb/g faeces													
CRC	5	84.1 (78.6-88.4)	94.4	86.6 (75.6-93.1)	99.9	6.29 (3.46-11.47)	99.8	0.18 (0.14-0.23)	95.1	34.37 (19.99-59.10)	100.0	0.51	0.90 (0.87-0.92)
CRC$^{¥}$	4	81.8 (76.4-86.1)	00.0	90.3 (86.5-93.2)	98.8	8.44 (5.85-12.18)	96.0	0.20 (0.15-0.27)	00.0	41.81 (23.41-76.67)	98.8	0.80	0.89 (0.86-0.91)
SCL$^{\Psi}$	2	47.0 (43.3-50.8)	0.0	94.1 (93.6-94.6)	0.0	8.00 (7.15-8.96)	0.0	0.56 (0.52-0.60)	0.0	14.22 (11.98-16.87)	0.0	NA	NA
≥ 150 µg Hb/g faeces													
CRC	6	64.1 (57.8-69.9)	87.1	95.0 (91.2-97.2)	99.7	12.70 (7.65-21.10)	99.0	0.38 (0.33-0.44)	89.2	33.56 (21.32-52.82)	98.1	0.02	0.82 (0.78-0.85)
CRC$^{¥}$	5	62.9 (55.5-69.6)	72.9	96.2 (94.6-97.3)	97.9	16.58 (12.36-22.23)	88.5	0.39 (0.32-0.46)	72.9	42.95 (32.33-57.04)	98.9	0.10	0.88 (0.85-0.91)
SCL$^{\Psi}$	3	35.9 (33.8-38.1)	94.7	97.5 (97.3-97.8)	95.7	13.05 (10.3-16.55)	70.2	0.67 (0.57-0.78)	94.6	20.48 (17.03-24.63)	35.5	0.67	0.83 (0.62-1.00)

† Values are expressed as percentages and its 95% confidence interval; ‡ Values are expressed as percentages; § Values are expressed as absolute numbers and its 95% confidence interval; *Significance of the threshold effect using the Spearman rank correlation (P<0.1 is considered statistically significant); ¥, Sensitivity analysis: diagnostic accuracy parameters for colorectal cancer detection after removing keynote outliers; Ψ Diagnostic accuracy parameters were estimated with DerSimonian method. AUC, area under the curve; CRC, colorectal cancer; FIT, faecal immunochemical test for haemoglobin; I2, inconsistency index; LoD, limit of detection; LR, likelihood ratio; NA, not applicable; OR, Odds Ratio; SCL, significant colonic lesion.

Evaluation of Heterogeneity

We found substantial heterogeneity between studies when calculating the summary performance estimates of FITs for CRC using the bivariate model (Table 2 and Appendix 3). The type of reference standard used (colonoscopy or follow up), the place of recruitment (primary care facility or colonoscopy unit) and CRC prevalence (CRC <3% or CRC ≥3%) were significant predictors of heterogeneity for both sensitivity and specificity. Moreover, FIT brand (OC-Sensor or HM-JACKarc) was also a significant predictor of heterogeneity for specificity (Figure 3). However, the magnitude of change for the pooled summary estimates and their confidence intervals in each subgroup was small (Supplementary Table 2). Supplementary Figure 1 shows ROC space plots. When we removed keynote outliers in the sensitivity analysis the magnitude of change between the summary estimates and their confidence intervals in each subgroup based on a cut-off value was again small. However, pooled sensitivity estimates were more homogeneous. Instead, pooled specificity estimates remained with high heterogeneity (Table 2).

Threshold effect was unsurprisingly detected in the subgroup of studies using cut-off values at LoD due to the differences in the threshold defined by each brand. Moreover, a threshold effect was also found in the subgroup of studies at a cut-off value of ≥ 150 µg Hb/g faeces. In addition to explicit threshold effect, implicit threshold effect may arise due to several biases (i.e., different spectrum of patients) which may determine differences in sensitivity and specificity between studies. Once outliers were removed, heterogeneity related to implicit threshold effect in this subgroup was also controlled (Table 2).

Diagnostic yield for CRC

Figure 4 shows the expected NNS and the number of missed CRC per 1000 patients according to the CRC prevalence expected in primary care (1-5%). The post-test probabilities of CRC were assessed through Fagan nomograms (Supplementary Figure 2). As an example, the number of missed CRC per 1000 patients if a patient has a 'negative' FIT result in population with a CRC prevalence of 2% is expected to increase from four to five when using the threshold of 20 µg Hb/g faeces instead of 10 µg Hb/g faeces. On the other hand, at the same CRC prevalence, the NNS is expected to decrease from ten to four if the 150 µg Hb/g faeces threshold is used instead of 10 µg Hb/g faeces.

Overall Accuracy of FIT based on positivity threshold to detect SCL

The overall pooled sensitivity and specificity of FITs for SCL for studies which used the limit of detection (LoD) as threshold (seven studies; n=22,624 patients) were 70.4% (95% CI 68.4-72.3) and 78.4% (95% CI 77.8-78.9), respectively. If we consider all SCLs as target instead of solely CRC, FIT sensitivity decreased from 87.2% (95% CI 81.0-91.6) for studies with a threshold of ≥ 10 µg Hb/g faeces (fifteen studies; n=48,872 patients) to 69.1% (95% CI 60.5-76.5) at the same threshold (seven studies; n=20,407 patients), and specificity increased from 84.4% (95% CI 79.4-88.3) to 87.2% (95%CI 83.4-90.2). Furthermore, three studies (n=20,528 patients) assessed the diagnostic accuracy of FIT with a threshold of ≥150 µg Hb/g faeces showing a sensitivity and specificity of 35.9% (95%CI 33.8-38.1) and 97.5% (95%CI 97.3-97.8), respectively (Table 2). SCL prevalence ranged widely between 4.4% and 13.6% anticipating high heterogeneity when assessing summary sensitivity and specificity FIT estimates for SCL detection, which combined with reduced number of studies restricted the possibility of subgroup analysis (Table 2 and Appendix 3).

Publication bias

Supplementary Figure 3 shows various funnel plots where each study is represented by one point on the plot drawn based on the natural logarithm of its diagnostic odds ratio (X-axis) and the value of its standard error (Y-axis). The existence of a symmetric figure around an axis traced by the pooled dOR value suggests the absence of publication bias.

DISCUSSION

Statement of principal findings

Our results confirm that FITs are the test of choice to evaluate patients with new-onset lower gastrointestinal symptoms in primary healthcare. The high sensitivity for CRC shown at the 10 µg Hb/g faeces threshold means that any result below has a negative predictive value for CRC greater than 99.6%-99.9% at CRC prevalence most commonly reported in primary healthcare. The risk of CRC detection in patients with a negative FIT equals the risk of colonoscopy-associated side effects and the CRC prevalence in asymptomatic adults aged 50-69.[44,45] Moreover, the minor differences between sensitivities for CRC shown at 10 µg Hb/g faeces and 20 µg Hb/g faeces thresholds mean that if we choose the higher threshold, less than one additional CRC would be missed per 1000 patients investigated. Finally, pooled estimates of sensitivity for CRC suggest that more than 60% of CRC would be identified at a f-Hb threshold of 150 µg Hb/g faeces. This threshold has recently been proposed in several large studies as a rule in criteria for urgent evaluation.[13,31,36,37,39,41] Furthermore, the NNS range is between two and seven for a CRC prevalence between 1% and 3% at this threshold, which constitutes an appropriate criterion for colonoscopy prioritization.

Strengths and weaknesses

This is the first systematic review and meta-analysis evaluating the diagnostic performance of FIT in symptomatic patients in primary healthcare. The high number of patients included and consistency in relation to previously published systematic reviews in various settings reinforce the validity of these findings.[5,46] However, studies included in this systematic review are not free from bias, which could affect our results. On the one hand, verification bias arises in diagnostic and prognostic studies when the reference test may have been performed preferably in those patients with 'positive' index tests, as occurs in those studies performed on patients recruited in primary care facilities. Besides, we have found a large heterogeneity in the reference standard used, the length of follow-up in case bowel imaging was not performed and, finally, in the definition of SCL across the studies included. This finding highlights the need of common definition both for a reference standard for CRC diagnosis and for SCL.

Conversely, those studies performed on patients recruited in colonoscopy units are at risk of clinical spectrum bias, because they could lack representation of the whole clinical spectrum of CRC in the study population. Instead of presenting vague symptoms, patients from those studies are more likely to have developed specific symptoms related to advanced stages, and therefore higher f-Hb concentration.[6] In both cases, sensitivity

could be overestimated. Furthermore, the low ratio between eligible patients and those included in the final analysis may bring risks of representativeness in a number of studies. Although this could also involve selection bias, it would be necessary to compare the characteristics between both subgroups to know in which way the evaluation of FIT diagnostic performance estimates could be affected.

However, these biases may not have a significant impact on the results of this meta-analysis. As stated previously in the methods section of this manuscript, all patients who did not undergo colonoscopy as a reference standard were monitored and any CRC causing symptoms would worsen in the following months leading to diagnosis even if the FIT test proved to be a false negative.[13] IWe are aware that a short follow-up period could overestimate FIT sensitivity for CRC as long as patients with a positive result would perform a confirmation test. However, in the heterogeneity analysis the magnitude of change for the pooled summary estimates related to the reference standard used was small (Supplementary Table 2), suggesting that the reference test had little effect on the diagnostic performance. Furthermore, despite the high risk of selection bias, the patients included in this meta-analysis should be representative of the population consulting in primary care whose clinical situation constitutes a cause of concern for their physician, which is the clinical spectrum where FIT should prove useful.

As expected, this meta-analysis showed high heterogeneity when calculating pooled estimates of specificity. This is because f-Hb can be detected in a number of benign and malignant conditions other than CRC.[47] The major variability in the prevalence of some of these conditions (i.e., NSAID enteropathy), together with the absence of randomized or consecutive sampling in most studies included in this review determine the presence of heterogeneity. Instead, those conditions which could account for the presence of f-Hb over the detection limit should only affect FIT sensitivity to detect CRC by serendipity.[48] Thus, after removing those studies with higher selection bias, pooled estimates of sensitivity revealed low heterogeneity.

Strengths and weaknesses in relation to other studies

This systematic review could not detect information to compare the accuracy of quantitative and qualitative tests. Several studies offered information on the precision of different brands of qualitative tests, but different cut-off points were used and there are not enough studies to perform an analysis by the different subgroups. However, it is interesting to highlight that several qualitative FIT brands with diverse cut-off values were indirectly compared in the study of Hogberg et al,[40] which shows that sensitivity to detect CRC was always higher than 80% despite cut-off values ranging between 2 µg

Hb/g faeces and 50 µg Hb/g faeces. This information, combined with sensitivity evaluated at a cut-off value of 150 µg Hb/g faeces, and the minor differences between pooled estimates of sensitivity and specificity assessed at 10 µg Hb/g faeces and 20 µg Hb/g faeces for any demographic subgroup,[33] strongly suggest that f-Hb should be evaluated for any patient who has been requested a colonoscopy for symptom evaluation to effectively handle the colonoscopy waiting list, as priority. We specifically evaluated the 150 µg Hb/g faeces threshold because several studies have evaluated recently this cut-off due to its reduced number of positive results, high specificity and positive predictive value.[13,31,36,37,39,41] The likelihood of cancer increases with increasing f-Hb concentrations, and consequently, FIT could be used to rule-in cancer or prioritise patients for investigation.[36]

This systematic review cannot recommend any specific quantitative FIT assay either. Although the meta-regression analysis suggests statistically significant differences between OC-Sensor and HM-JACKarc at a cut-off value of 10 µg Hb/g faeces, these are clinically irrelevant and could be partially justified by the different methodology used in the design of their respective studies. Moreover, to the best of our knowledge only one study in this setting directly compared both FIT brands on the same patients,[43] and although large variations were found between the different devices, the correlation of the f-Hb results between both was gradually higher as the threshold was increased; 91.7% at a cut-off value of 10 µg Hb/g faeces. Thus, considering that approximately 90% of CRC may be detected above that threshold, it is unlikely that further information will show clinically significant differences between both FIT assays.

The small number of studies conducted in primary care, together with heterogeneity makes it difficult to evaluate publication bias. However, it is unlikely that the most important conclusions of this review will be refuted by additional data. At the time of writing this manuscript, another two studies reporting information are available and their results are in line with this work's conclusions. [49,50]

Unanswered questions and future research

Three relevant questions remain to be answered and are critical in the implementation of FIT in primary healthcare. The first is related to the "*FIT negative CRCs*". It is relevant to know what the factors are that account for a negative result, either related to the patient or to the CRC, to reduce the false negative results. The information available is limited to description of the characteristics of the 47 CRC with a negative result in five studies.[13,29,37,41,42] On the other hand, if FIT-based strategies are implemented, it is necessary to establish a safety netting strategy to avoid delays in CRC

diagnosis that could worsen the prognosis. A re-evaluation of the symptoms and referral to secondary healthcare in case they persist could be a reasonable option until we have further evidence.[51] We have additional potential options: CRC prediction models and the combination of noninvasive biomarkers including the microbiota, but these options are complex and not validated in primary healthcare.[52-55]

The second question is related to the effect of FIT on CRC prognosis. The main objective of any diagnostic strategy is to improve the prognosis of the disease detected. The information regarding CRC prognosis detected after a positive FIT in symptomatic subjects in primary healthcare is still limited. We have evidence from two retrospective studies that suggest that CRC survival is improved in cancers detected through a FIT-based strategy when compared with a clinical evaluation strategy. [1,56] The reason for these findings is not clear but could be related either to a reduction in diagnostic delay or, on the contrary, to an opportunistic CRC screening. A specifically designed study is, however, required to answer this relevant question.

Another relevant implication is the effect of a screening program in the evaluation of patients with symptoms in primary care. On one hand, including FIT in primary care can facilitate opportunistic screening, increasing inequities in the health system and reducing its efficiency.[57] On the other hand, the establishment of a population-based CRC screening program reduces the risk of CRC among the population that adheres to it. This point raises the hypothesis that the diagnostic approach in patients with recent onset gastrointestinal symptoms could be different if they are invited and adherent to a population-based CRC screening program.[58]

Conclusion

In this systematic review and meta-analysis, we confirmed that implementation of FIT as a triage test in primary care may improve the efficiency of referrals. Thus, FIT is the test of choice to evaluate patients with new-onset lower gastrointestinal symptoms in this setting. Use of this test as 'rule in' at a cut-off value of 150 µg Hb/g faeces identifies more than half of CRCs using few resources while a f-Hb concentration below 20 µg Hb/g faeces rules out more than 85% of CCR at the expected prevalence in this setting (1% to 3%). However, appropriate safety netting is still necessary.

FIGURE LEGENDS AND FOOTNOTES

Figure 1. Summary of evidence search and selection.

Figure 2. Quality Assessment of Diagnostic Accuracy Studies (QUADAS).

Figure 3. Forest plot of multiple univariable meta-regression and subgroup analyses.

Meta-regression to assess the effect of covarying factors on summary measures of performance: 'Brand', Yes: OC-Sensor vs No: HM-JACKarc; 'CRCprev', Yes: CRC prevalence < 3% vs No: CRC prevalence ≥ 3%; 'PrimaryCare', Yes: recruitment performed in primary care facilities vs No: recruitment performed in colonoscopy units; 'Colonoscopy', Yes: follow up performed as reference standard vs No: colonoscopy performed as reference standard.

Figure 4. Number of patients necessary to scope to find one CRC and number of missed CRC per 1000 patients.

Figures are calculated according to the post-test probabilities of CRC assessed by means of Fagan nomograms for different thresholds and CRC prevalence.

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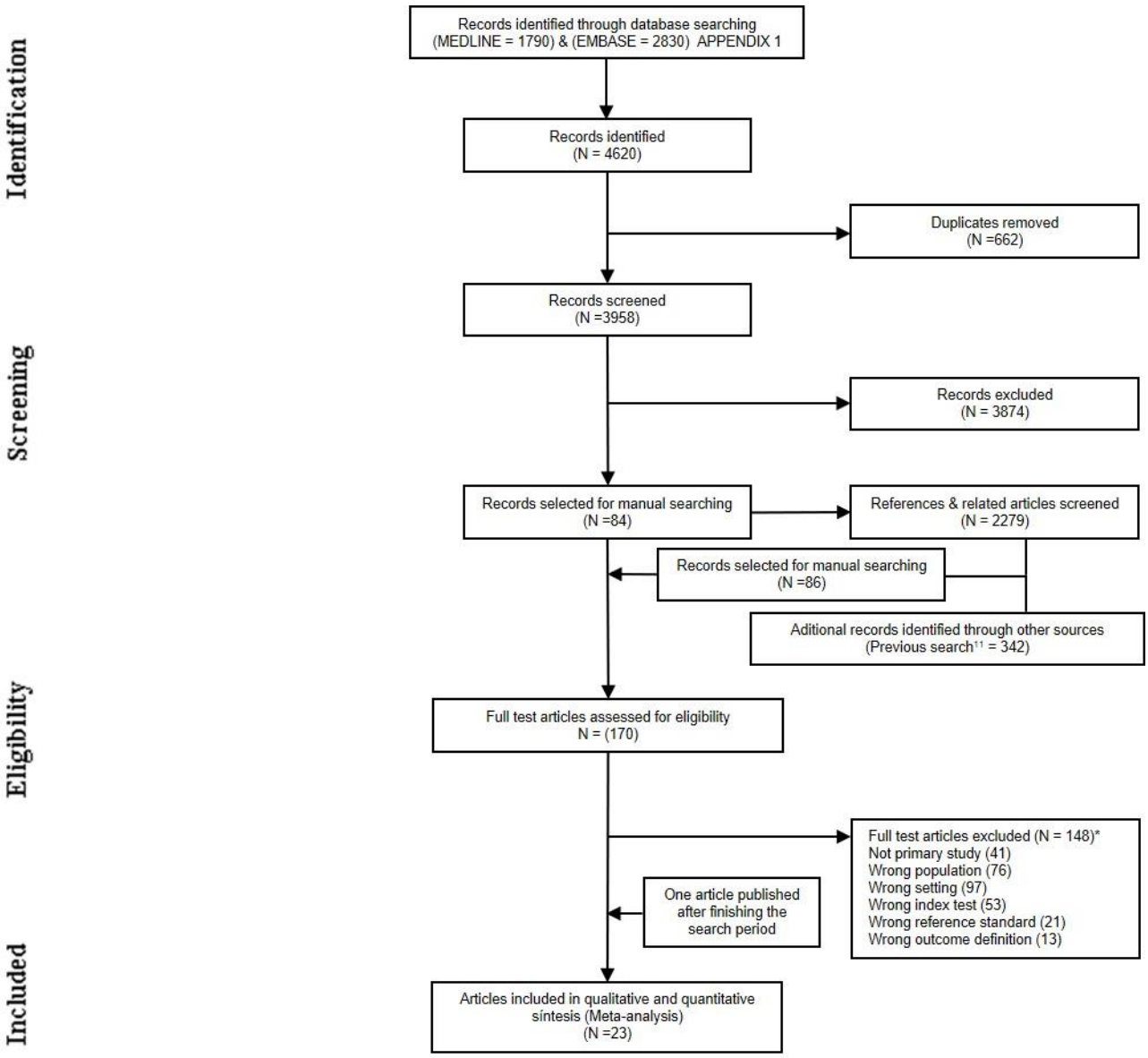
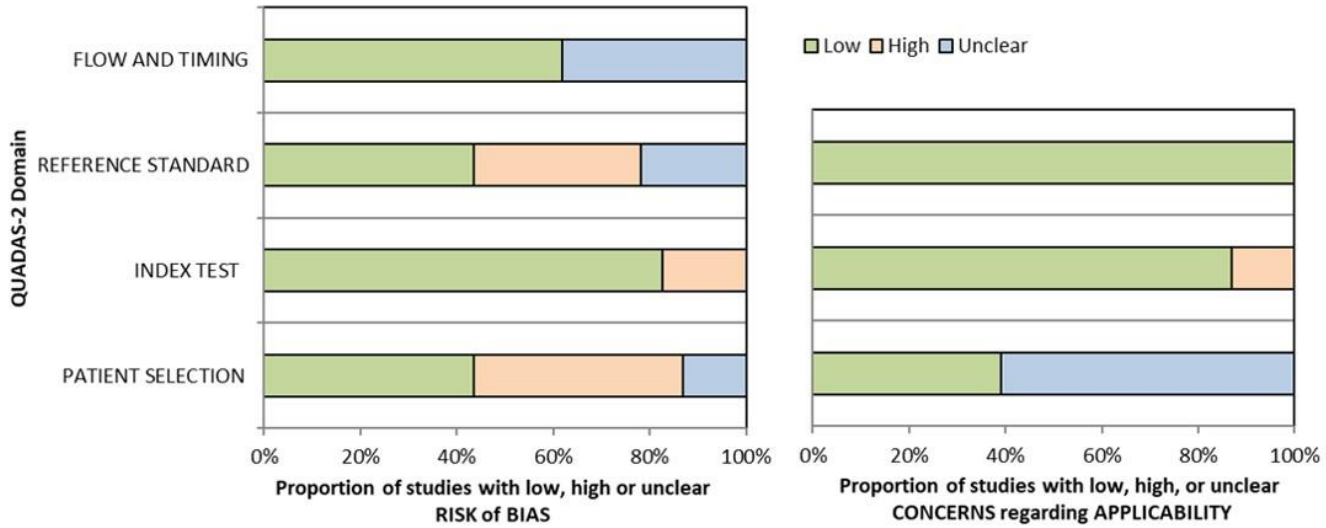
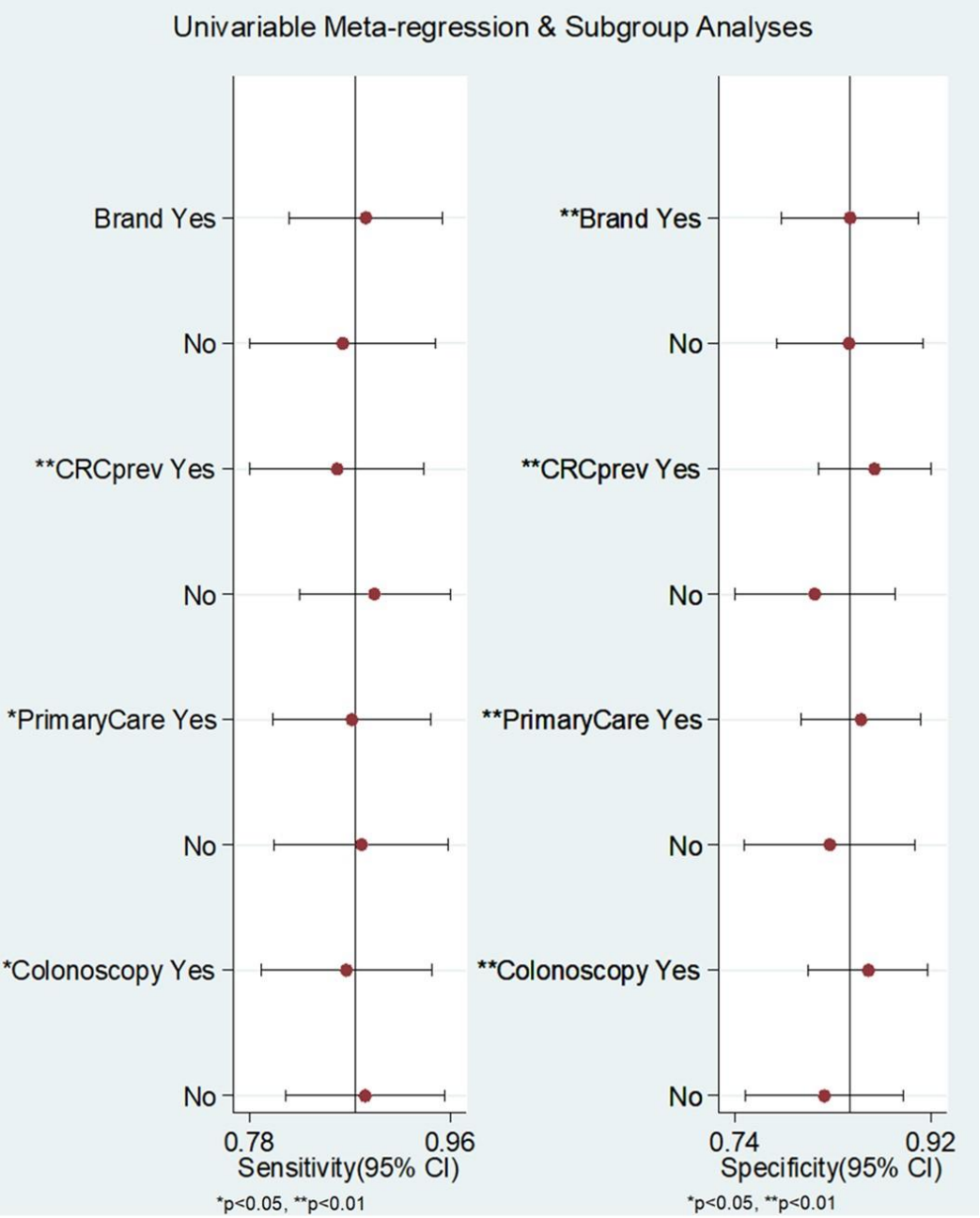
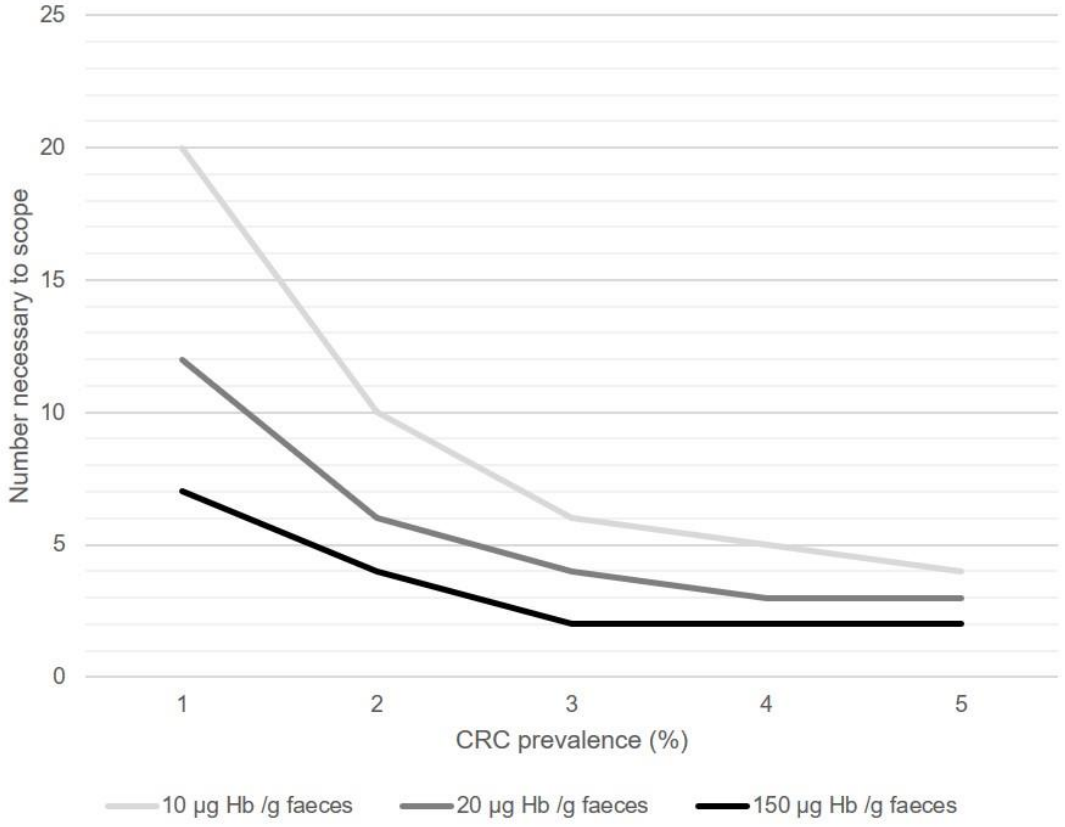

Identification
Screening
Eligibility
Included
Records identified through database searching (MEDLINE = 1790) & (EMBASE = 2830) APPENDIX 1
Records identified (N = 4620)
Duplicates removed (N =662)
Records screened (N =3958)
Records excluded (N = 3874)
Records selected for manual searching (N =84)
References & related articles screened (N = 2279)
Records selected for manual searching (N =86)
Aditional records identified through other sources (Previous search[11] = 342)
Full test articles assessed for eligibility N = (170)
Full test articles excluded (N = 148)*
Not primary study (41)
Wrong population (76)
Wrong setting (97)
Wrong index test (53)
Wrong reference standard (21)
Wrong outcome definition (13)
One article published after finishing the search period
Articles included in qualitative and quantitative síntesis (Meta-analysis) (N =23)

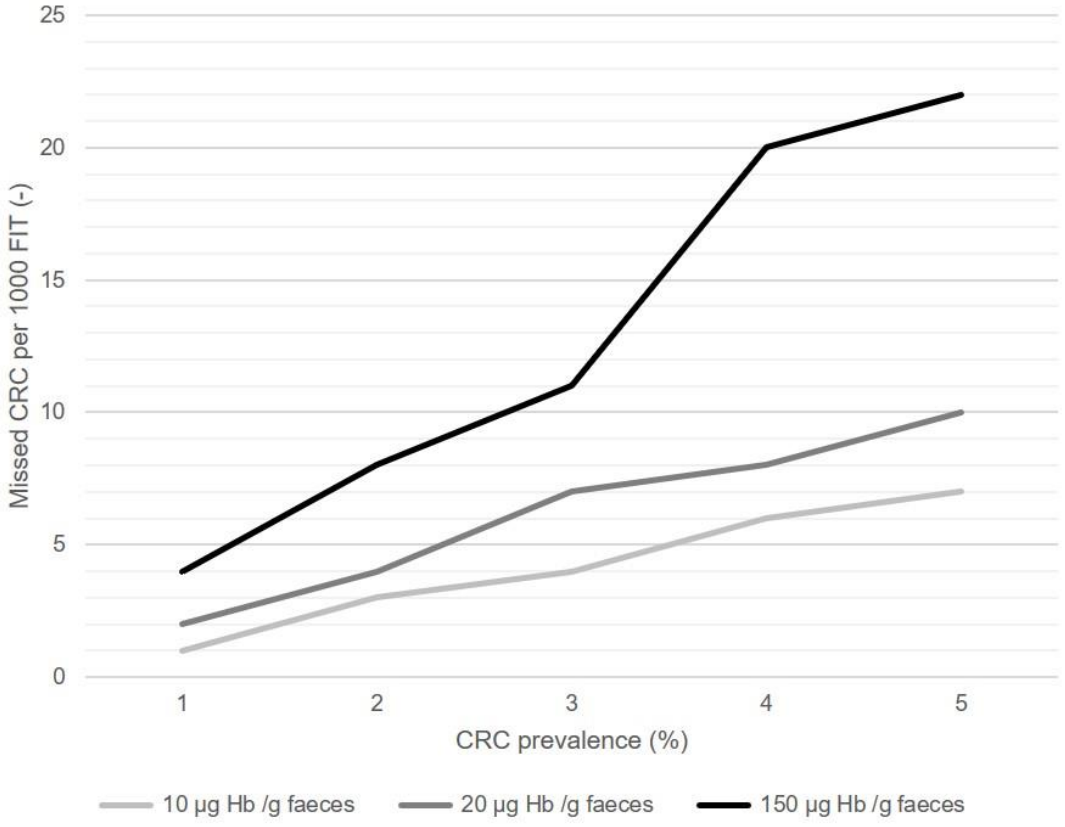
Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Hogberg 2010	☺	☺	☹	☺	?	☺	☺
Mowat 2015	☹	☺	☺	☺	?	☺	☺
Elias 2016	☹	☹	☺	☺	?	☺	☺
Hogberg 2016	☺	☺	?	☺	?	☺	☺
Juul 2018	☺	☺	☹	☺	☺	☺	☺
Widlak 2018	☹	☺	☺	☺	?	☺	☺
Turvill 2018	☹	☺	☺	☺	?	☺	☺
Nicholson 2018	☺	☹	☹	?	?	☹	☺
Ayling 2019	☹	☹	☺	?	?	☺	☺
Mowat 2019	☺	☺	?	☺	☺	☺	☺
Keenan 2019	?	☺	☹	☺	?	☺	☺
Chapman 2019	☺	☺	☹	☺	☺	☺	☺
D'Souza 2019	☹	☺	☺	☺	?	☺	☺
Pin-Vieito 2020	☺	☺	?	?	☺	☺	☺
Hogberg 2020	?	☺	?	?	☺	☺	☺
Ayling 2020	☺	☺	☹	☺	☺	☺	☺
Nicholson 2020	☺	☹	☹	?	☺	☹	☺
D'Souza 2020	☹	☺	☺	☺	?	☺	☺
McSorley 2020	☹	☺	☺	?	☺	☺	☺
Khan 2020	☹	☺	☺	☺	☺	☹	☺
Bailey 2020	☺	☺	☹	?	☺	☺	☺
Hogberg Nov 2020	?	☺	?	?	☺	☺	☺
Lazlo 2020	☹	☺	☺	☺	?	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk




Univariable Meta-regression & Subgroup Analyses
Brand Yes
No
**CRCprev Yes
No
*PrimaryCare Yes
No
*Colonoscopy Yes
No
0.78
0.96
Sensitivity(95% CI)
*p<0.05, **p<0.01
**Brand Yes
No
**CRCprev Yes
No
**PrimaryCare Yes
No
**Colonoscopy Yes
No
0.74
0.92
Specificity(95% CI)
*p<0.05, **p<0.01


25
20
15
10
5
0
Number necessary to scope
1
2
3
4
5
CRC prevalence (%)
10 µg Hb /g faeces
20 µg Hb /g faeces
150 µg Hb /g faeces


25
20
15
10
5
0
Missed CRC per 1000 FIT (-)
1
2
3
4
5
CRC prevalence (%)
10 µg Hb /g faeces
20 µg Hb /g faeces
150 µg Hb /g faeces

SUPPLEMENTARY MATERIAL

Appendix 1. Search strategy

We avoided the routine use of any study design terms or methodology search filters. A previously published filter designed to simplify the identification of FIT-related studies in MEDLINE based on the last name of first and corresponding authors of "FIT in symptomatic patients" related studies was also used to complete our data sources.

MEDLINE (Pubmed) May 1, 2018 to November 10, 2020

1. immunochem* [tiab] or immuno-chem* [tiab] or immunohistochem* [tiab] or immuno-histochem* [tiab] or immunol* [tiab] or immunochromatographic [tiab] or immuno-chromatographic [tiab] or immunoassay [tiab] or "immuno assay" [tiab] (76214)

2. fecal [tiab] or faecal [tiab] or feces [tiab] or faeces [tiab] or stool* [tiab] (23882)

3. ifobt or "faecal haemoglobin" or "fecal hemoglobin" or fobt or (FIT and hemoglobin) or (FIT and haemoglobin) (475)

4. occult blood or occult hemoglobin or occult haemoglobin (1252)

5. OC-Sensor or "OC Sensor" or HM-JACKarc or "HM JACKarc" or "FOB Gold" or HM-JACK or HM JACK or Ridascreen or jack-arc or jackarc or FOBgold (64)

6. ("Atef SH" [au]) OR ("Bachir NM" [au]) OR ("Barber MD" [au]) OR ("Boereboom CL" [au]) OR ("Calogero A" [au]) OR ("Ferraris R" [au]) OR ("Hata K" [au]) OR ("Adelstein BA" [au]) OR ("Ahlquist DA" [au]) OR ("Ahmed S" [au]) OR ("Akbari A" [au]) OR ("Allameh Z" [au]) OR ("Allard J" [au]) OR ("Allison JE" [au]) OR ("Alvarez-Urturi C" [au]) OR ("Annibale B" [au]) OR ("Armitage N" [au]) OR ("Ashraf I" [au]) OR ("Astin M" [au]) OR ("Auge JM" [au]) OR ("Azlie S" [au]) OR ("Ballal MS" [au]) OR ("Ballantyne GH" [au]) OR ("Bampton PA" [au]) OR ("Barrett P" [au]) OR ("Barrison IG" [au]) OR ("Bassett ML" [au]) OR ("Bates T" [au]) OR ("Bernardini S" [au]) OR ("Bessa X" [au]) OR ("Bhargava A" [au]) OR ("Bini EJ" [au]) OR ("Bjerregaard NC" [au]) OR ("Bjornsson ES" [au]) OR ("Bosch LJ" [au]) OR ("Brault J" [au]) OR ("Brenner H" [au]) OR ("Brodersen J" [au]) OR ("Burch JA" [au]) OR ("Cade D" [au]) OR ("Cai QC" [au]) OR ("Capurso G" [au]) OR ("Carlsson L" [au]) OR ("Carroll M" [au]) OR ("Castells A" [au]) OR ("Castiglione G" [au]) OR ("Celestino A" [au]) OR ("Chang HJ" [au]) OR ("Chen HH" [au]) OR ("Chen LS" [au]) OR ("Chiang TH" [au]) OR ("Chiu HM" [au]) OR ("Church JM" [au]) OR ("Ciatto S" [au]) OR ("Cilona A" [au]) OR ("Clarke N" [au]) OR ("Collins JF" [au]) OR ("Corley DA" [au]) OR ("Corte C" [au]) OR ("Crotta S" [au]) OR ("Cubiella J" [au]) OR ("Dancourt V" [au]) OR ("Daveson AJ" [au]) OR ("de Vet HC" [au]) OR ("Dent OF" [au]) OR ("Diaz-Ondina M" [au]) OR ("Dilshad AT" [au]) OR ("Doi Y" [au]) OR ("Dominitz JA" [au]) OR ("Dutta AK" [au]) OR ("Eckardt VF" [au]) OR ("Elsafi SH" [au]) OR ("Eskeland SL" [au]) OR ("Ewald N" [au]) OR ("Faivre J" [au]) OR ("Falkson CB" [au]) OR ("Farkouh M" [au]) OR ("Farrands PA" [au]) OR ("Fauzi A" [au]) OR ("Favre H" [au]) OR ("Fenocchi E" [au]) OR ("Fisher DA" [au]) OR ("Flashman K" [au]) OR ("Fletcher RH" [au]) OR ("Fraser CG" [au]) OR ("Freedman A" [au]) OR ("Freitas BR" [au]) OR ("Friedman A" [au]) OR ("Fu R" [au]) OR ("Gandhi S" [au]) OR ("Garman KS" [au]) OR ("Gibson P" [au]) OR ("Gillberg A" [au]) OR ("Godber IM" [au]) OR ("Gopalswamy N" [au]) OR ("Goulston KJ" [au]) OR ("Greenberg PD" [au]) OR ("Guardiola J" [au]) OR ("Guittet L" [au]) OR ("Haddy RI" [au]) OR ("Hamilton W" [au])

OR ("Han DS" [au]) OR ("Harmston C" [au]) OR ("Harrison AJ" [au]) OR ("Hatch QM" [au]) OR ("Haug U" [au]) OR ("Hazazi R" [au]) OR ("Heresbach D" [au]) OR ("Herrero J" [au]) OR ("Hewett DG" [au]) OR ("Hewitson P" [au]) OR ("Hill AG" [au]) OR ("Hippisley-cox J" [au]) OR ("Hirai HW" [au]) OR ("Hirayama Y" [au]) OR ("Hirobe K" [au]) OR ("Hoepffner N" [au]) OR ("Hogberg C" [au]) OR ("Hol L" [au]) OR ("Holden DJ" [au]) OR ("Holloway RH" [au]) OR ("Hope RL" [au]) OR ("Howden CW" [au]) OR ("Hreinsson JP" [au]) OR ("HU H-" [au]) OR ("Huang G" [au]) OR ("Hundt S" [au]) OR ("Hunt RH" [au]) OR ("Imperiale TF" [au]) OR ("Ioannidis JP" [au]) OR ("Ioannou GN" [au]) OR ("Ip S" [au]) OR ("Iwase N" [au]) OR ("Jamil S" [au]) OR ("Jeanson A" [au]) OR ("Jellema P" [au]) OR ("Jimbo M" [au]) OR ("Jin P" [au]) OR ("Kadakia SC" [au]) OR ("Kalimutho M" [au]) OR ("Kalra L" [au]) OR ("Kato J" [au]) OR ("Kaul A" [au]) OR ("Kemppainen M" [au]) OR ("Kepczyk MT" [au]) OR ("Khakimov N" [au]) OR ("Khasanova G" [au]) OR ("kim BC" [au]) OR ("Klewandrowski K" [au]) OR ("Ko CW" [au]) OR ("Koga Y" [au]) OR ("Kok L" [au]) OR ("Kolligs F" [au]) OR ("Konrad C" [au]) OR ("Koo JH" [au]) OR ("Kovarova JT" [au]) OR ("Kozlowski T" [au]) OR ("Krivec S" [au]) OR ("Kubisch H" [au]) OR ("Lanoy G" [au]) OR ("Lansdorp-Vogelaar I" [au]) OR ("Launois R" [au]) OR ("Lawson N" [au]) OR ("Lee FI" [au]) OR ("Lee JK" [au]) OR ("Lee TJ" [au]) OR ("Lee YC" [au]) OR ("Leicester RJ" [au]) OR ("Leis VM" [au]) OR ("Letsou G" [au]) OR ("Levi Z" [au]) OR ("Levy BT" [au]) OR ("Li R" [au]) OR ("Li ZC" [au]) OR ("Lieberman DA" [au]) OR ("Macrae FA" [au]) OR ("Mansouri D" [au]) OR ("Mansson J" [au]) OR ("Manus B" [au]) OR ("Marshall JK" [au]) OR ("Marshall TP" [au]) OR ("Matsumura Y" [au]) OR ("Maw A" [au]) OR ("McDonald CA" [au]) OR ("McDonald PJ" [au]) OR ("McDonald R" [au]) OR ("McDonald RL" [au]) OR ("Meijer GA" [au]) OR ("Mesquita MA" [au]) OR ("Miyoshi H" [au]) OR ("Moran A" [au]) OR ("Morikawa T" [au]) OR ("Morini S" [au]) OR ("Mowat C" [au]) OR ("Murakami R" [au]) OR ("Murphy J" [au]) OR ("Nagaoka S" [au]) OR ("Nakama H" [au]) OR ("Narula N" [au]) OR ("Niedermaier T" [au]) OR ("Niv Y" [au]) OR ("Olsson L" [au]) OR ("Oono Y" [au]) OR ("Oort FA" [au]) OR ("Ostrow JD" [au]) OR ("Ou C-" [au]) OR ("Parente FR" [au]) OR ("Park DD" [au]) OR ("Park JG" [au]) OR ("Park Y" [au]) OR ("Paz-Valiñas L" [au]) OR ("Peacock O" [au]) OR ("Petty MT" [au]) OR ("Pfeifer RM" [au]) OR ("Piperno A" [au]) OR ("Pochapin MB" [au]) OR ("Pongprasobchai S" [au]) OR ("Pye G" [au]) OR ("Quintero E" [au]) OR ("Rae AJ" [au]) OR ("Rai S" [au]) OR ("Rajasekhar PT" [au]) OR ("Ransohoff DF" [au]) OR ("Rao J" [au]) OR ("Rao SK" [au]) OR ("Rees CJ" [au]) OR ("Rentier B" [au]) OR ("Riboe DG" [au]) OR ("Rigas B" [au]) OR ("Ritchie MC" [au]) OR ("Robertson R" [au]) OR ("Robinson MH" [au]) OR ("Rockey DC" [au]) OR ("Rodriguez-Alonso L" [au]) OR ("Rodriguez-Moranta F" [au]) OR ("Rosman AS" [au]) OR ("Rozen P" [au]) OR ("Rubeca T" [au]) OR ("Saccomanno S" [au]) OR ("Saito H" [au]) OR ("Saldanha JD" [au]) OR ("Saquib N" [au]) OR ("Saratzis A" [au]) OR ("Scales CD" [au]) OR ("Schwartz S" [au]) OR ("Scriven AJ" [au]) OR ("Segal WN" [au]) OR ("Selinger RR" [au]) OR ("Selvachandran SN" [au]) OR ("Sequist TD" [au]) OR ("Shah R" [au]) OR ("Sharma VK" [au]) OR ("Shashideep S" [au]) OR ("Shastri YM" [au]) OR ("Shaw AG" [au]) OR ("Sheng J" [au]) OR ("Sieg A" [au]) OR ("Singh H" [au]) OR ("Singhal S" [au]) OR ("Skaife P" [au]) OR ("Smith A" [au]) OR ("Sohn DK" [au]) OR ("Songster CL" [au]) OR ("Sontag SJ" [au]) OR ("St John DJ" [au]) OR ("Stapley S" [au]) OR ("Steele RJ" [au]) OR ("Stegeman I" [au]) OR ("Stein J" [au]) OR ("Stelling HP" [au]) OR ("Stockbrugger RW" [au]) OR ("Stray N" [au]) OR ("Stubbs RS" [au]) OR ("Subramanian S" [au]) OR ("Sung JJ" [au]) OR ("Symonds EL" [au]) OR ("Tan V" [au]) OR ("Tannous B" [au]) OR ("Tao S" [au]) OR ("Tarpay Ad" [au]) OR ("Tate JJ" [au]) OR ("Thompson M" [au]) OR ("Tsoi KK" [au]) OR ("van Turenhout ST" [au]) OR ("Vega P" [au]) OR ("Weller D" [au]) OR ("Whitlock EP" [au]) OR ("Wu MS" [au]) OR ("Yansong J" [au]) OR ("Young GP" [au]) OR ("Zullo A" [au]) OR ("Terhaar sive Droste JS" [au]) OR

("Thomas WM" [au]) OR ("Thompson MR" [au]) OR ("Thomson AD" [au]) OR ("Tibble J" [au]) OR ("Tonus C" [au]) OR ("Trickett JP" [au]) OR ("Donaldson DR" [au]) OR ("Trojan J" [au]) OR ("Turunen MJ" [au]) OR ("Adlercreutz H" [au]) OR ("van Rijn AF" [au]) OR ("van Rossum LG" [au]) OR ("Vandvik P" [au]) OR ("van Roon AH" [au]) OR ("Vart G" [au]) OR ("Vasilyev S" [au]) OR ("Syrjanen K" [au]) OR ("Vaughan-Shaw PG" [au]) OR ("Wheeler JM" [au]) OR ("Vilkin A" [au]) OR ("Vironen J" [au]) OR ("Kellokumpu I" [au]) OR ("Wanebo HJ" [au]) OR ("de Wijkerslooth TR" [au]) OR ("Williams JA" [au]) OR ("Winawer SJ" [au]) OR ("Wong WM" [au]) OR ("Wong BC" [au]) OR ("Wong CK" [au]) OR ("Sadowski DC" [au]) OR ("Dube C" [au]) OR ("Wong MC" [au]) OR ("Woo HY" [au]) OR ("Park H" [au]) OR ("Wu D" [au]) OR ("Li JN" [au]) OR ("Guoxiang L" [au]) OR ("Jufang S" [au]) OR ("Yoshinaga M" [au]) OR ("Zhu MM" [au]) OR ("Widlak MM" [au]) OR ("Arasaradnam R" [au]) OR ("Ran ZH" [au]) OR ("Wen-xian Z" [au]) (32922)

7. #1 AND #2 (1416)

8. #1 AND #6 (1254)

9. #2 AND #6 (568)

10. #3 OR #4 OR #5 OR #7 OR #8 OR #9 (3943)

11. #10 NOT DNA [ti] NOT MicroRNA [ti] NOT (COVID [tiab] OR SARS* [tiab] OR coronavirus [tiab]) NOT #10 filter "review" "editorial" "guideline" (3552)

12. colon* OR gastrointestinal OR colorectal OR bowel OR intestinal OR gut (193824)

13. #11 AND #12 (1790)

Embase (Ovid) May 1, 2018 to November 10, 2020

1. (immunochem# or immuno-chem# or immunohistochem# or immuno-histochem# or immunol# or immunochromatographic or immuno-chromatographic or immunoassay or "immuno assay").mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (40118)

2. (fecal or faecal or feces or faeces or stool#).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (81005)

3. (ifobt or "faecal haemoglobin" or "fecal hemoglobin" or fobt or (FIT and hemoglobin) or (FIT and haemoglobin)).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (4670)

4. (occult blood or occult hemoglobin or occult haemoglobin).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (4721)

5. OC-Sensor or "OC Sensor" or HM-JACKarc or "HM JACKarc" or "FOB Gold" or HM-JACK or HM JACK or Ridascreen or jack-arc or jackarc or FOBgold limit to yr="2018 -Current"; original articles (390)

6. (colon# or gastrointestinal or colorectal or bowel or intestinal or gut).mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] limit to yr="2018 -Current"; original articles (521912)

7. #1 AND #2 (1652)

8. #7 OR #3 (6267)

9. #8 OR #4 OR #5 (10050)

10. #9 AND #6 (5496)

11. #10 NOT (DNA OR MicroRNA OR COVID OR SARS# OR coronavirus .m_titl limit to yr="2018 -Current"; original articles) (5374)

12. Remove duplicates from #11 (3987)

13. #12 limit to human and embase (2830)

Appendix 2. RATIONAL FOR EXCLUSION OF 148 STUDIES

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Ahmed S, Leslie A, Thaha MA, Carey FA, Steele RJ. Lower gastrointestinal symptoms are not predictive of colorectal neoplasia in a faecal occult blood screen-positive population. *Br J Surg*. 2005;92(4):478-481. doi:10.1002/bjs.4879	Yes	No	Yes	Yes	Yes	Yes	Screening setting. No data about FIT accuracy.
Almilaji O, Smith C, Surgenor S, et al. Refinement and validation of the IDIOM score for predicting the risk of gastrointestinal cancer in iron deficiency anaemia. *BMJ Open Gastroenterol*. 2020;7(1):e000403. doi:10.1136/bmjgast-2020-000403	Yes	No	No	Yes	Yes	No	To refine and validate a model for predicting the risk of GI cancer in iron deficiency anaemia and to develop an app to facilitate use in clinical practice.
Arasaradnam RP, Bhala N, Evans C, et al. Faecal immunochemical testing in the COVID-19 era: balancing risk and costs [published correction appears in Lancet Gastroenterol Hepatol. 2020 Jun 19;:]. *Lancet Gastroenterol Hepatol*. 2020;5(8):717-719. doi:10.1016/S2468-1253(20)30185-0	No	NA	NA	NA	NA	NA	Comment
Auge JM, Fraser CG, Rodriguez C, et al. Clinical utility of one versus two faecal immunochemical test samples in the detection of advanced colorectal neoplasia in symptomatic patients. Clin Chem Lab Med. 2016;54(1):125-132. doi:10.1515/cclm-2015-0388	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Auge JM, Rodriguez C, Espanyol O, et al. An evaluation of the SENTiFIT 270 analyser for quantitation of faecal haemoglobin in the investigation of patients with suspected colorectal cancer. Clin Chem Lab Med. 2018;56(4):625-633. doi:10.1515/cclm-2017-0605	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Bailey SE, van Melle MA, Nicholson BD. Faecal immunochemical (rule-in) testing in general practice. *Br J Gen Pract*. 2019;69(681):178. doi:10.3399/bjgp19X702173	No	NA	NA	NA	NA	NA	Letter
Bampton PA, Holloway RH. A prospective study of the gastroenterological causes of iron deficiency anaemia in a general hospital. *Aust N Z J Med*. 1996;26(6):793-799. doi:10.1111/j.1445-5994.1996.tb00627.x	Yes	Yes	No	No	Yes	Yes	Secondary care. No data about FIT accuracy
Benton SC, Fraser CG. Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration - can a repeat test be used? [published online ahead of print, 2020 Oct 27]. *Ann Clin Biochem*. 2020;4563220967569. doi:10.1177/0004563220967569	No	NA	NA	NA	NA	NA	Editorial

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Bjerregaard NC, Tøttrup A, Sørensen HT, Laurberg S. Evaluation of the Danish national strategy for selective use of colonoscopy in symptomatic outpatients without known risk factors for colorectal cancer. *Scand J Gastroenterol*. 2007;42(2):228-236. doi:10.1080/00365520600815662	Yes	Yes	No	No	yes	Yes	Secondary care; Haemoccult Sensa. Unknown cut-off
Bjerregaard NC, Tøttrup A, Sørensen HT, Laurberg S. Detection of colorectal cancer in symptomatic outpatients without visible rectal bleeding: Validity of the fecal occult blood test. *Clin Epidemiol*. 2009;1:119-124. Published 2009 Aug 9. doi:10.2147/clep.s7097	Yes	Yes	No	No	yes	Yes	Secondary care; Haemoccult Sensa. Unknown cut-off
Borges LV, Mattar R, Silva JMKD, Silva ALWD, Carrilho FJ, Hashimoto CL. FECAL OCCULT BLOOD: A COMPARISON OF CHEMICAL AND IMMUNOCHEMICAL TESTS. Arq Gastroenterol. 2018;55(2):128-132. doi:10.1590/S0004-2803.201800000-22	Yes	Yes	No	Yes	Yes	Yes	Secondary care. Patients older than 14 years of both genders who had indications for colonoscopy and who attended at the Clinics Hospital of the University of São Paulo Medical School.
Bretthauer M, Kalager M, Weinberg DS. From Colorectal Cancer Screening Guidelines to Headlines: Beware!. *Ann Intern Med*. 2019;170(10):734. doi:10.7326/L19-0086	No	NA	NA	NA	NA	NA	Letter
Byun UH, Anderson N, Upton A, Frankish P. Faecal immunochemical tests for occult blood testing should not be used outside of bowel screening: an audit of a large general practice. *J Prim Health Care*. 2019;11(3):259-264. doi:10.1071/HC18068	Yes	Yes	Yes	Unclear	Unclear	Yes	Unknown FIT & Unclear number of samples & Unclear indication in a percentage of patients.
Chandrapalan S, Arasaradnam RP. The role of fecal markers in the investigation of patients with chronic diarrhea. *Pol Arch Intern Med*. 2019;129(6):408-413. doi:10.20452/pamw.14787	No	NA	NA	NA	NA	NA	Review
Chang WY, Chiu HM. Bringing fecal immunochemical test into play in symptomatic population: Exploring the feasibility of fecal immunochemical test-symptom combined approach. *J Gastroenterol Hepatol*. 2020;35(6):911-912. doi:10.1111/jgh.15100	No	NA	NA	NA	NA	NA	Editorial
Chapman C, Thomas C, Morling J, et al. Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham. Colorectal Dis. 2020;22(6):679-688. doi:10.1111/codi.14944	Yes	Yes	Yes	Yes	Yes	Yes	Data were completed in Bailey's study
Chapman C, Banerjea A, Ng Oet al. PTU-076 The 'getting fit' project in Nottingham: a comparison of haemoglobin levels as measured by OC sensor and HM jack in two week wait referrals. Gut 2017; 66(Suppl 2): A88–A89.	No	Yes	Yes	Yes	Yes	Yes	Poster; Repeated data

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Chapman CJ, Banerjea A, Humes DJ, et al. Choice of faecal immunochemical test matters: comparison of OC-Sensor and HM-JACKarc, in the assessment of patients at high risk of colorectal cancer [published online ahead of print, 2020 Oct 29]. Clin Chem Lab Med. 2020;cclm-2020-1170. doi:10.1515/cclm-2020-1170	No	Yes	Yes	Yes	Yes	Yes	Same data of another study. Compares OC-Sensor and HM-JACKarc
Chen CH, Yan SL, Yang TH, et al. The Relationship between the Methylated Septin-9 DNA Blood Test and Stool Occult Blood Test for Diagnosing Colorectal Cancer in Taiwanese People. *J Clin Lab Anal.* 2017;31(1):e22013. doi:10.1002/jcla.22013	Yes	No	No	Yes	Yes	Yes	No data about FIT accuracy. Secondary care
Chen M-Y, Chang H-C, Chong L-W, et al. Relatively low risk and nonaggressive stage of colorectal cancer in individuals with negative baseline fecal immunochemical test results: A cohort study. Adv Dig Med. 2020;1–8. https://doi.org/10.1002/aid2.13169	Yes	No	No	Yes	Yes	Yes	Screening setting
Chen KC, Chung CS, Hsu WF, et al. Identification of risk factors for neoplastic colonic polyps in young adults with bloody stool in comparison with those without symptom. *J Gastroenterol Hepatol.* 2018;33(7):1335-1340. doi:10.1111/jgh.14070	Yes	No	No	No	Yes	Yes	Secondary care. No data about FIT accuracy
Christopher J, Flint TR, Ahmed H, et al. Straight-to-test for the two-week-wait colorectal cancer pathway under the updated NICE guidelines reduces time to cancer diagnosis and treatment. *Ann R Coll Surg Engl.* 2019;101(5):333-339. doi:10.1308/rcsann.2019.0022	Yes	Yes	Yes	No	No	No	No data about FIT accuracy
Chuter C, Keding A, Holmes H, Turnock D, Turvill J. Getting the best out of faecal immunochemical tests and faecal calprotectin. *Frontline Gastroenterol.* 2019;11(5):414-416. Published 2019 Dec 24. doi:10.1136/flgastro-2019-101381	No	Yes	No	Yes	Yes	Yes	Letter; Repeated data
Cilona A, Zullo A, Hassan C, Ridola L, Annese M. Is faecal-immunochemical test useful in patients with iron deficiency anaemia and without overt bleeding?. Dig Liver Dis. 2011;43(12):1022-1024. doi:10.1016/j.dld.2011.08.002	Yes	Yes	Unclear	Unclear	Yes	Yes	Consecutive patients with iron deficiency anaemia and without either overt bleeding or thalassaemia minor referred to our Endoscopic Units for diagnostic work-up. No FIT brand
Clark SK. Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using faecal immunochemical testing in Nottingham, Chapman et al. Colorectal Dis. 2020 Jun;22(6):608-608. doi: 10.1111/codi.15101	No	NA	NA	NA	NA	NA	Editorial

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Cross AJ, Wooldrage K, Robbins EC, et al. Whole-colon investigation vs. flexible sigmoidoscopy for suspected colorectal cancer based on presenting symptoms and signs: a multicentre cohort study. *Br J Cancer.* 2019;120(2):154-164. doi:10.1038/s41416-018-0335-z	Yes	No	No	No	Yes	Yes	No data about FIT accuracy
Cubiella J, Salve M, Díaz-Ondina M, et al. Diagnostic accuracy of the faecal immunochemical test for colorectal cancer in symptomatic patients: comparison with NICE and SIGN referral criteria. Colorectal Dis. 2014;16(8):O273-O282. doi:10.1111/codi.12569	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Cubiella J, Vega P, Salve M, et al. Development and external validation of a faecal immunochemical test-based prediction model for colorectal cancer detection in symptomatic patients. BMC Med. 2016;14(1):128. Published 2016 Aug 31. doi:10.1186/s12916-016-0668-5	Yes	Yes	No	Yes	Yes	Yes	Secondary and primary care
Cunin L, Khan AA, Ibrahim M, Lango A, Klimovskij M, Harshen R. FIT negative cancers: A right-sided problem? Implications for screening and whether iron deficiency anaemia has a role to play [published online ahead of print, 2020 Mar 18]. *Surgeon.* 2020;S1479-666X(20)30035-4. doi:10.1016/j.surge.2020.02.003	No	Yes	yes	yes	Yes	Yes	Same data than Khan´s study
de Klerk CM, Woudstra AJ, Fransen MP, Bossuyt PM, Dekker E. Invitees do not adequately act on alarm symptoms in colorectal cancer screening with fecal immunochemical tests. *Eur J Gastroenterol Hepatol.* 2019;31(1):141-142. doi:10.1097/MEG.0000000000001275	Yes	No	No	Yes	No	No	No data about FIT accuracy. Abstract
de Klerk CM, van der Vlugt M, Bossuyt PM, Dekker E. A large proportion of fecal immunochemical test-positive participants in colorectal cancer screening is symptomatic. *United European Gastroenterol J.* 2018;6(3):471-479. doi:10.1177/2050640617733922	Yes	No	No	Yes	No	No	No data about FIT accuracy
Digby J, Strachan JA, Mowat C, Steele RJC, Fraser CG. Appraisal of the faecal haemoglobin, age and sex test (FAST) score in assessment of patients with lower bowel symptoms: an observational study. *BMC Gastroenterol.* 2019;19(1):213. Published 2019 Dec 11. doi:10.1186/s12876-019-1135-5	No	Yes	Yes	Yes	Yes	Yes	Same data than Mowat´s study
Digby J, Strachan JA, McCann R, Steele RJ, Fraser CG, Mowat C. Measurement of faecal haemoglobin with a faecal immunochemical test can assist in defining which patients attending primary care with rectal bleeding require urgent referral. *Ann Clin Biochem.* 2020;57(4):325-327. doi:10.1177/0004563220935622	No	Yes	Yes	Yes	Yes	Yes	Repeated data

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Digby J, Steele RJ, Strachan JA, et al. Do other variables add value to assessment of the risk of colorectal disease using faecal immunochemical tests for haemoglobin?. *Ann Clin Biochem*. 2019;56(4):472-479. doi:10.1177/0004563219839423	No	Yes	Yes	Yes	Yes	Yes	Same data than Mowat´s study
Digby J, Mowat C, Steele R, *et al* OC-020 Validation of the utility of a faecal immunochemical testfor haemoglobin (fit) in patients presenting to primary care with new bowel symptoms *Gut* 2017;**66:**A10-A11.	No	Yes	Yes	Yes	Yes	Yes	Poster; Repeated data
Digby J, Cleary S, Gray L, et al. Faecal haemoglobin can define risk of colorectal neoplasia at surveillance colonoscopy in patients at increased risk of colorectal cancer. United European Gastroenterol J. 2020;8(5):559-566. doi:10.1177/2050640620913674	Yes	No	Yes	Yes	Yes	Yes	Surveillance
Dillon R, Croner LJ, Bucci J, et al. Analytical validation of a novel multiplex test for detection of advanced adenoma and colorectal cancer in symptomatic patients. *J Pharm Biomed Anal*. 2018;154:85-94. doi:10.1016/j.jpba.2018.02.038	Yes	No	No	No	No	Yes	No data about FIT accuracy
D'Souza N, Brzezicki A, Abulafi M. Faecal immunochemical testing in general practice. *Br J Gen Pract*. 2019;69(679):60-61. doi:10.3399/bjgp19X700853	No	NA	NA	NA	NA	NA	Editorial
Falkson CB, Bates T. Faecal occult blood screening for patients with gastrointestinal symptoms. *Br J Surg*. 1993;80(10):1326. doi:10.1002/bjs.1800801036	Yes	Yes	No	No	Unclear	Yes	Secondary care; Haemoccult; no follow up
Farrands PA, O'Regan D, Taylor I. An assessment of occult blood testing to determine which patients with large bowel symptoms require urgent investigation. *Br J Surg*. 1985;72(10):835-837. doi:10.1002/bjs.1800721020	Yes	Yes	No	No	Unclear	Yes	Secondary care; Haemoccult; no follow up
Farrugia A, Widlak M, Evans C, Smith SC, Arasaradnam R. Faecal immunochemical testing (FIT) in symptomatic patients: what are we missing?. Frontline Gastroenterol. 2020;11(1):28-33. doi:10.1136/flgastro-2018-101174	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Farrugia A, Widlak MM, Smith S, Waugh N, Arasaradnam RP. Letter: faecal immunochemical testing for adults with symptoms of colorectal cancer-ready for prime time?. *Aliment Pharmacol Ther*. 2020;52(8):1419. doi:10.1111/apt.16068	No	NA	NA	NA	NA	NA	Letter
Fernández-Bañares F, Clèries R, Boadas J, et al. Prediction of advanced colonic neoplasm in symptomatic patients: a scoring system to prioritize colonoscopy (COLONOFIT study). *BMC Cancer*. 2019;19(1):734. Published 2019 Jul 25. doi:10.1186/s12885-019-5926-4	Yes	Yes	Yes	No	Yes	Yes	to derive a predictive score of advanced colonic neoplasia in symptomatic patients in fast-track programs. No data about FIT accuracy.

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Fraser CG. Faecal immunochemical tests (FIT) in the assessment of patients presenting with lower bowel symptoms: Concepts and challenges. *Surgeon*. 2018;16(5):302-308. doi:10.1016/j.surge.2018.01.004	No	NA	NA	NA	NA	NA	Review
Fraser CG. Faecal immunochemical tests for haemoglobin (FIT) in the assessment of patients with lower abdominal symptoms: current controversies. *Gastroenterol Hepatol*. 2019;42(4):263-270. doi:10.1016/j.gastrohep.2018.09.007	No	NA	NA	NA	NA	NA	Review
Godber IM, Todd LM, Fraser CG, MacDonald LR, Younes HB. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. *Clin Chem Lab Med*. 2016;54(4):595-602. doi:10.1515/cclm-2015-0617	Yes	No	Yes	Yes	Yes	Yes	Mixed population; symptomatic & follow up
Gopalswamy N, Stelling HP, Markert RJ, Maimon HN, Wahlen SD, Haddy RI. A comparative study of eight fecal occult blood tests and HemoQuant in patients in whom colonoscopy is indicated. *Arch Fam Med*. 1994;3(12):1043-1048. doi:10.1001/archfami.3.12.1043	Yes	No	Unclear	No	Yes	Yes	Mixed population; Unknown cut-off
Greenberg PD, Bertario L, Gnauck R, et al. A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol*. 2000;95(5):1331-1338. doi:10.1111/j.1572-0241.2000.02032.x	Yes	No	No	No	Yes	Yes	Secondary care; Mixed population; Unknown cut-off
Guimarães DP, Fregnani JH, Reis RM, et al. Comparison of a New-generation Fecal Immunochemical Test (FIT) With Guaiac Fecal Occult Blood Test (gFOBT) in Detecting Colorectal Neoplasia Among Colonoscopy-referral Patients. Anticancer Res. 2019;39(1):261-269. doi:10.21873/anticanres.13106	Yes	No	No	Yes	Yes	Yes	Mixed population
Gutiérrez-Stampa MA, Aguilar Gama V, Bujanda L. Utilidad del test de sangre oculta en heces para el diagnóstico del cáncer colorrectal en la práctica clínica en atención primaria [Utility of faecal occult blood test for the diagnosis of colorectal cancer in clinical practice in primary care]. *Aten Primaria*. 2020;52(4):286-287. doi:10.1016/j.aprim.2019.07.009	No	Yes	Yes	Yes	Yes	Yes	Letter; Repeated data
Gutierrez-Stampa MA, Aguilar V, Sarasqueta C, Cubiella J, Portillo I, Bujanda L. Impact of the faecal immunochemical test on colorectal cancer survival. *BMC Cancer*. 2020;20(1):616. Published 2020 Jul 1. doi:10.1186/s12885-020-07074-y	Yes	No	Yes	Yes	Yes	Yes	No data about FIT accuracy

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Hamarneh Z, Symonds EL, Kholmurodova F, Cock C. Older age, symptoms, or anemia: Which factors increase colorectal cancer risk with a positive fecal immunochemical test?. *J Gastroenterol Hepatol*. 2020;35(6):1002-1008. doi:10.1111/jgh.14888	Yes	No	No	Yes	Yes	Yes	This study aimed to examine factors that may increase neoplasia risk associated with a positive FIT, specifically age, gastrointestinal symptoms, or IDA. Only FIT positive patients.
Hazazi R, Rozen P, Leshno M, et al. Can patients at high risk for significant colorectal neoplasms and having normal quantitative faecal occult blood test postpone elective colonoscopy?. *Aliment Pharmacol Ther*. 2010;31(4):523-533. doi:10.1111/j.1365-2036.2009.04202.x	Yes	No	No	Yes	Yes	Yes	Screening setting
Herrero JM, Vega P, Salve M, Bujanda L, Cubiella J. Symptom or faecal immunochemical test based referral criteria for colorectal cancer detection in symptomatic patients: a diagnostic tests study. *BMC Gastroenterol*. 2018;18(1):155. Published 2018 Oct 25. doi:10.1186/s12876-018-0887-7	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Hippisley-Cox J, Coupland C. Identifying patients with suspected colorectal cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract*. 2012;62(594):e29-e37. doi:10.3399/bjgp12X616346	Yes	Yes	Yes	No	Yes	Yes	No data about FIT accuracy
Hirata I, Hoshimoto M, Saito O, et al. Usefulness of fecal lactoferrin and hemoglobin in diagnosis of colorectal diseases. World J Gastroenterol. 2007;13(10):1569-1574. doi:10.3748/wjg.v13.i10.1569	Yes	Yes	Unclear	No	Yes	Yes	Secondary care. Patients scheduled to undergo colorectal endoscopy.
Hoepffner N, Shastri YM, Hanisch E, et al. Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study. Aliment Pharmacol Ther. 2006;23(1):145-154. doi:10.1111/j.1365-2036.2006.02702.x	Yes	No	No	Yes	Yes	Yes	Mixed population
Högberg C, Karling P, Rutegård J, Lilja M. Patient-reported and doctor-reported symptoms when faecal immunochemical tests are requested in primary care in the diagnosis of colorectal cancer and inflammatory bowel disease: a prospective study. *BMC Fam Pract*. 2020;21(1):129. Published 2020 Jul 1. doi:10.1186/s12875-020-01194-x	No	Yes	Yes	Yes	Yes	Yes	Same data than another Hogberg´s study included in the review
Högberg C, Karling P, Rutegård J, Lilja M, Ljung T. Immunochemical faecal occult blood tests in primary care and the risk of delay in the diagnosis of colorectal cancer. *Scand J Prim Health Care*. 2013;31(4):209-214. doi:10.3109/02813432.2013.850205	Yes	No	No	Yes	Yes	Yes	Only CRC patients

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Högberg C, Samuelsson E, Lilja M, Fhärm E. Could it be colorectal cancer? General practitioners' use of the faecal occult blood test and decision making--a qualitative study. *BMC Fam Pract*. 2015;16:153. Published 2015 Oct 26. doi:10.1186/s12875-015-0371-1	Yes	No	Yes	No	No	No	Semi-structured individual interviews were conducted with eleven purposely selected GPs and registrars in Region Jämtland Härjedalen, Sweden, and subjected to qualitative content analysis. No data about FIT accuracy.
Högberg C, Söderström L, Lilja M. Faecal immunochemical tests for the diagnosis of symptomatic colorectal cancer in primary care: the benefit of more than one sample. *Scand J Prim Health Care*. 2017;35(4):369-372. doi:10.1080/02813432.2017.1397255	Yes	No	No	Yes	Yes	Yes	Only CRC patients
Holden CA, Frank O, Caruso J, et al. From participation to diagnostic assessment: a systematic scoping review of the role of the primary healthcare sector in the National Bowel Cancer Screening Program. *Aust J Prim Health*. 2020;26(3):191-206. doi:10.1071/PY19181	Yes	No	No	Yes	Yes	Yes	Screening setting
Imperiale TF, Gruber RN, Stump TE, Emmett TW, Monahan PO. Performance Characteristics of Fecal Immunochemical Tests for Colorectal Cancer and Advanced Adenomatous Polyps: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2019;170(5):319-329. doi:10.7326/M18-2390	No	NA	NA	NA	NA	NA	Review
James T, Nicholson BD, Marr Rm, et al. Faecal immunochemical testing (FIT): Sources of analytical variation based on three years of routine testing in the context of DG30. medRxiv 2020.04.15.20066191; doi:10.1101/2020.04.15.20066191	Yes	No	Yes	Yes	No	No	Data obtained from independent verification studies and clinical testing of the HM-JACKarc FIT method were analysed to derive analytical performance characteristics. No data about FIT accuracy
Jeanson A, Jamart J, Maisin JM, et al. Assessment of the new immunological test Hemoblot for detecting occult blood in faeces. *Eur J Cancer Prev*. 1994;3(5):407-412. doi:10.1097/00008469-199409000-00004	Yes	Yes	No	No	Yes	Yes	Secondary care; Mixed population; Unknown cut-off
Jellema P, van der Windt DA, Bruinvels DJ, et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. *BMJ*. 2010;340:c1269. Published 2010 Mar 31. doi:10.1136/bmj.c1269	No	NA	NA	NA	NA	NA	Review
Juul J, Vedsted P, Bro F. Development of an Intervention for Implementing Immunochemical Faecal Occult Blood Test in General Practice. *Quality in Primary Care* 2016; 24 (6): 289-292	Yes	No	No	No	No	No	No data about FIT accuracy

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Juul JS, Bro F, Hornung N, et al. Implementation of immunochemical faecal occult blood test in general practice: a study protocol using a cluster-randomised stepped-wedge design. *BMC Cancer*. 2016;16:445. Published 2016 Jul 11. doi:10.1186/s12885-016-2477-9	Yes	No	No	No	No	No	No data about FIT accuracy
Kalimutho M, Del Vecchio Blanco G, Cretella M, et al. A simplified, non-invasive fecal-based DNA integrity assay and iFOBT for colorectal cancer detection. *Int J Colorectal Dis*. 2011;26(5):583-592. doi:10.1007/s00384-010-1128-x	Yes	No	No	Yes	Yes	Yes	The purpose of the endoscopy was for screening and to investigate symptoms
Kalra L, Hamlyn AN. Comparative evaluation of investigations for colorectal carcinoma in symptomatic patients. *Postgrad Med J*. 1988;64(755):666-668. doi:10.1136/pgmj.64.755.666	Yes	Yes	No	No	Yes	Yes	Haemoccult. No data about FIT specificity
Kamarudin M. Low-risk bowel cancer symptoms: is it time for FIT?. *Br J Gen Pract*. 2019;69(684):356-357. doi:10.3399/bjgp19X704501	No	NA	NA	NA	NA	NA	Review
Karl J, Wild N, Tacke M, et al. Improved diagnosis of colorectal cancer using a combination of fecal occult blood and novel fecal protein markers. Clin Gastroenterol Hepatol. 2008;6(10):1122-1128. doi:10.1016/j.cgh.2008.04.021	Yes	No	No	Yes	Yes	Yes	Screening setting
Katsoula A, Paschos P, Haidich AB, Tsapas A, Giouleme O. Diagnostic Accuracy of Fecal Immunochemical Test in Patients at Increased Risk for Colorectal Cancer: A Meta-analysis. *JAMA Intern Med*. 2017;177(8):1110-1118. doi:10.1001/jamainternmed.2017.2309	No	NA	NA	NA	NA	NA	Review
Kaul A, Shah A, Magill FH, Hawkins SA, Skaife P. Immunological faecal occult blood testing: a discriminatory test to identify colorectal cancer in symptomatic patients. Int J Surg. 2013;11(4):329-331. doi:10.1016/j.ijsu.2013.02.013	Yes	Yes	Unclear	Yes	Yes	Yes	all consecutive consenting patients attending the rapid access colorectal service were prospectively studied.
Kemppainen M, Häkkinen I, Räihä I, Pomoell R, Sourander L. Finding colorectal tumours with an immunological faecal occult blood test in symptomatic primary health care patients. *Age Ageing*. 1994;23(5):365-370. doi:10.1093/ageing/23.5.365	Yes	Yes	Yes	No	Yes	Yes	Guaiac plus FIT. Unknown cut-off
Kim NH, Lee MY, Park JH, et al. A Combination of Fecal Immunochemical Test Results and Iron Deficiency Anemia for Detection of Advanced Colorectal Neoplasia in Asymptomatic Men. *Yonsei Med J*. 2017;58(5):910-917. doi:10.3349/ymj.2017.58.5.910	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population
Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. Am J Med. 2003;115(2):111-114. doi:10.1016/s0002-9343(03)00294-8	Yes	No	Yes	Yes	Yes	Yes	Mixed population

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Kok L, Elias SG, Witteman BJ, et al. Diagnostic accuracy of point-of-care fecal calprotectin and immunochemical occult blood tests for diagnosis of organic bowel disease in primary care: the Cost-Effectiveness of a Decision Rule for Abdominal Complaints in Primary Care (CEDAR) study. *Clin Chem*. 2012;58(6):989-998. doi:10.1373/clinchem.2011.177980	No	Yes	Yes	Yes	Yes	Yes	Repeated data
Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. *BMJ Open*. 2013;3(10):e003989. Published 2013 Oct 30. doi:10.1136/bmjopen-2013-003989	Yes	No	Yes	Yes	Yes	Yes	Mixed population
Lee MW, Pourmorady JS, Laine L. Use of Fecal Occult Blood Testing as a Diagnostic Tool for Clinical Indications: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2020;115(5):662-670. doi:10.14309/ajg.0000000000000495	No	NA	NA	NA	NA	NA	Review
Leicester RJ, Lightfoot A, Millar J, Colin-Jones DG, Hunt RH. Accuracy and value of the Hemoccult test in symptomatic patients. *Br Med J (Clin Res Ed)*. 1983;286(6366):673-674. doi:10.1136/bmj.286.6366.673	Yes	Yes	No	No	Unclear	Yes	Secondary care; Haemoccult; no follow up
Li S, Wang H, Hu J, et al. New immunochemical fecal occult blood test with two-consecutive stool sample testing is a cost-effective approach for colon cancer screening: results of a prospective multicenter study in Chinese patients. *Int J Cancer*. 2006;118(12):3078-3083. doi:10.1002/ijc.21774	Yes	No	No	No	yes	Yes	Secondary care; Mixed population; Unknown cut-off
Li W, Zhao LZ, Ma DW, et al. Predicting the risk for colorectal cancer with personal characteristics and fecal immunochemical test. *Medicine (Baltimore)*. 2018;97(18):e0529. doi:10.1097/MD.0000000000010529	Yes	No	No	No	Yes	Yes	A risk prediction model for CRC based on a series of symptoms and signs related to enteric diseases in combination with a FIT. No data about FIT accuracy
Loktionov A, Soubieres A, Bandaletova T, et al. Biomarker measurement in non-invasively sampled colorectal mucus as a novel approach to colorectal cancer detection: screening and triage implications. *Br J Cancer*. 2020;123(2):252-260. doi:10.1038/s41416-020-0893-8	Yes	Yes	No	No	Yes	Yes	No data about FIT accuracy
Loveday C, Sud A, Jones ME, et al. Prioritisation by FIT to mitigate the impact of delays in the 2-week wait colorectal cancer referral pathway during the COVID-19 pandemic: a UK modelling study [published online ahead of print, 2020 Aug 27]. *Gut*. 2020;gutjnl-2020-321650. doi:10.1136/gutjnl-2020-321650	Yes	Yes	Yes	Yes	Yes	Yes	Data about FIT accuracy from D´Souza´s study

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Lué A, Hijos G, Sostres C, et al. The combination of quantitative faecal occult blood test and faecal calprotectin is a cost-effective strategy to avoid colonoscopies in symptomatic patients without relevant pathology. Therap Adv Gastroenterol. 2020;13:1756284820920786. Published 2020 May 18. doi:10.1177/1756284820920786	Yes	Yes	No	Yes	Yes	Yes	Secondary and primary care
Maclean W, Limb C, Mackenzie P, Whyte MB, Benton SC, Rockall T, Jourdan I. Adoption of faecal immunochemical testing for 2-week-wait colorectal patients during the COVID-19 pandemic: an observational cohort study reporting a new service at a regional centre. Colorectal Dis. 2020 Oct 17. doi: 10.1111/codi.15408. Epub ahead of print. PMID: 33068489.	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Maclean W, Singh R, Mackenzie P, et al. The two-week rule colorectal cancer pathway: an update on recent practice, the unsustainable burden on diagnostics and the role of faecal immunochemical testing. *Ann R Coll Surg Engl.* 2020;102(4):308-311. doi:10.1308/rcsann.2020.0019	Yes	Yes	Yes	No	No	No	No data about FIT accuracy
Mashlab S, Large P, Laing W, et al. Anaemia as a risk stratification tool for symptomatic patients referred via the two-week wait pathway for colorectal cancer. *Ann R Coll Surg Engl.* 2018;100(5):350-356. doi:10.1308/rcsann.2018.0030	Yes	Yes	Yes	No	Yes	Yes	No data about FIT accuracy
Masood U, Dhamoon AS, Murthy U. Influence of Varying Quantitative Fecal Immunochemical Test Positivity Thresholds on Colorectal Cancer Detection. Ann Intern Med. 2019;170(10):736. doi:10.7326/L19-0094	No	No	No	No	No	No	Commentary
Mattar R, Marques SB, Minata MK, Silva-Etto JMKD, Sakai P, DE Moura EGH. DIAGNOSTIC ACCURACY OF ONE SAMPLE OR TWO SAMPLES QUANTITATIVE FECAL IMMUNOCHEMICAL TESTS FOR INTESTINAL NEOPLASIA DETECTION. Arq Gastroenterol. 2020;57(3):316-322. doi:10.1590/S0004-2803.202000000-58	Yes	Yes	Unclear	Yes	Yes	Yes	Referred to colonoscopy. Setting not detailed
McDonald PJ, Digby J, Innes C, et al. Low faecal haemoglobin concentration potentially rules out significant colorectal disease. Colorectal Dis. 2013;15(3):e151-e159. doi:10.1111/codi.12087	Yes	No	Yes	Yes	Yes	Yes	Primary care; Mixed population
McKinney R, Chapman C, Morling J, Weller J, Tangri A, Simpson JA, et al. Keeping FIT: early clinical outcomes of a novel two week wait pathway for colorectal cancer using faecal immunochemical testing. Colorectal Dis 2019;21(2):10. conference Abstract	No	Yes	Yes	Yes	Yes	Yes	Poster; Repeated data
Miyoshi H, Oka M, Sugi K, et al. Accuracy of Detection of colorectal neoplasia using an immunochemical occult blood test in symptomatic referred patients: comparison of retrospective and prospective studies. *Internal Medicine*. 2000; 39: 701-706.	Yes	No	No	No	Yes	Yes	Referred population; Unknown cut-off

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Mozdiak E, Weldeselassie Y, McFarlane M, et al. Systematic review with meta-analysis of over 90 000 patients. Does fast-track review diagnose colorectal cancer earlier?. *Aliment Pharmacol Ther.* 2019;50(4):348-372. doi:10.1111/apt.15378	No	NA	NA	NA	NA	NA	Review
Nakama H, Zhang B, Fattah AS, Zhang X. Colorectal cancer in iron deficiency anemia with a positive result on immunochemical fecal occult blood. *Int J Colorectal Dis.* 2000;15(5-6):271-274. doi:10.1007/s003840000255	Yes	Yes	Yes	No	Yes	Yes	Subgroup of asymptomatic with anaemia. Unknown cut-off
Nakama H, Kayano T, Katsuura T, et al. Comparison of predictive value for colorectal cancer in subjects with and without rectal bleeding. *Hepatogastroenterology.* 1999;46(27):1730-1732.	Yes	No	No	No	No	Yes	Not a symptomatic population
Nakama H, Zhang B, Abdul Fattah AS, Kamijo N, Fukazawa K. Relationships between a sign of rectal bleeding and the results of an immunochemical occult blood test, and colorectal cancer. *Eur J Cancer Prev.* 2000;9(5):325-328. doi:10.1097/00008469-200010000-00006	Yes	No	No	No	No	Yes	Not a symptomatic population
Narula N, Ulic D, Al-Dabbagh R, et al. Fecal occult blood testing as a diagnostic test in symptomatic patients is not useful: a retrospective chart review. Can J Gastroenterol Hepatol. 2014;28(8):421-426. doi:10.1155/2014/189652	Yes	No	Yes	No	Yes	Yes	Mixed population;gFOBT
Navarro M, Hijos G, Sostres C, et al. Reducing the Cut-Off Value of the Fecal Immunochemical Test for Symptomatic Patients Does Not Improve Diagnostic Performance. Front Med (Lausanne). 2020;7:410. Published 2020 Sep 2. doi:10.3389/fmed.2020.00410	Yes	Yes	Unclear	Yes	Yes	Yes	Referred to colonoscopy. Setting not detailed
Navarro M, Hijos G, Ramirez T, Omella I, Carrera-Lasfuentes P, Lanas Á. Fecal Hemoglobin Concentration, a Good Predictor of Risk of Advanced Colorectal Neoplasia in Symptomatic and Asymptomatic Patients. Front Med (Lausanne). 2019;6:91. Published 2019 May 3. doi:10.3389/fmed.2019.00091	Yes	No	Yes	Yes	Yes	Yes	Mixed population
Nicholson BD, East JE, Oke J, Roberts NW, James T, Shine B. Letter: extending FIT from DG30 to NG12 patients. Letter: faecal immunochemical testing for adults with symptoms of colorectal cancer - ready for prime time? Authors' reply: a unified approach to safety netting negative FITs is required. *Aliment Pharmacol Ther.* 2020;52(8):1420-1421. doi:10.1111/apt.16082	No	NA	NA	NA	NA	NA	Letter
Niedermaier T, Balavarca Y, Brenner H. Stage-Specific Sensitivity of Fecal Immunochemical Tests for Detecting Colorectal Cancer: Systematic Review and Meta-Analysis. *Am J Gastroenterol.* 2020;115(1):56-69. doi:10.14309/ajg.0000000000000465	No	NA	NA	NA	NA	NA	Letter

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Niv Y, Sperber AD. Sensitivity, specificity, and predictive value of fecal occult blood testing (Hemoccult II) for colorectal neoplasia in symptomatic patients: a prospective study with total colonoscopy. *Am J Gastroenterol*. 1995;90(11):1974-1977.	Yes	Yes	No	No	yes	Yes	Secondary care; Haemoccult II; no follow up
Oono Y, Iriguchi Y, Doi Y, et al. A retrospective study of immunochemical fecal occult blood testing for colorectal cancer detection. *Clin Chim Acta*. 2010;411(11-12):802-805. doi:10.1016/j.cca.2010.02.057	Yes	Yes	Unclear	Yes	Yes	Yes	patients thought to be symptomatic for a range of colorectal disorders following either point-of-care rapid test or physician examination were referred to the Tokyo Metropolitan Cancer Detection Center and scheduled for colonoscopy;
Oort FA, Terhaar Sive Droste JS, Van Der Hulst RW, et al. Colonoscopy-controlled intra-individual comparisons to screen relevant neoplasia: faecal immunochemical test vs. guaiac-based faecal occult blood test. *Aliment Pharmacol Ther*. 2010;31(3):432-439. doi:10.1111/j.1365-2036.2009.04184.x	Yes	No	No	Yes	Yes	Yes	Mixed population
Oort FA, van Turenhout ST, Coupé VM, et al. Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study. *BMC Cancer*. 2011;11:434. Published 2011 Oct 10. doi:10.1186/1471-2407-11-434	Yes	No	No	Yes	Yes	Yes	Mixed population
Ou CH, Kuo FC, Hsu WH, et al. Comparison of the performance of guaiac-based and two immunochemical fecal occult blood tests for identifying advanced colorectal neoplasia in Taiwan. J Dig Dis. 2013;14(9):474-483. doi:10.1111/1751-2980.12077	Yes	No	No	Yes	Yes	Yes	Mixed population
Parente F, Marino B, Ilardo A, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. *Eur J Gastroenterol Hepatol*. 2012;24(10):1145-1152. doi:10.1097/MEG.0b013e328355cc79	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Park CH, Jung YS, Kim NH, Park JH, Park DI, Sohn CI. Usefulness of risk stratification models for colorectal cancer based on fecal hemoglobin concentration and clinical risk factors. Gastrointest Endosc. 2019;89(6):1204-1211.e1. doi:10.1016/j.gie.2019.02.023	Yes	No	No	Yes	Yes	Yes	Screening setting

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Peabody J, Saldivar JS, Swagel E, Fugaro S, Paculdo D, Tran M. Primary care variability in patients at higher risk for colorectal cancer: evaluation of screening and preventive care practices. *Curr Med Res Opin*. 2018;34(5):851-856. doi:10.1080/03007995.2017.1417244	Yes	No	No	No	No	No	to evaluate physician practice variation in patients with a higher risk of CRC. To identify the physician characteristics and the types of patients that were associated with missed screening opportunities. No data about FIT accuracy.
Peacock O, Watts ES, Hanna N, Kerr K, Goddard AF, Lund JN. Inappropriate use of the faecal occult blood test outside of the National Health Service colorectal cancer screening programme. *Eur J Gastroenterol Hepatol*. 2012;24(11):1270-1275. doi:10.1097/MEG.0b013e328357cd9e	Yes	No	No	No	Unclear	Yes	Mixed population; Haemoccult
Pye G, Marks CG, Martin S, Marks V, Jackson J, Hardcastle JD. An evaluation of Fecatwin/Feca EIA; a faecal occult blood test for detecting colonic neoplasia. *Eur J Surg Oncol*. 1989;15(5):446-448.	Yes	Yes	No	No	Yes	Yes	Secondary care; Guaiac plus FIT. Unknown cut-off
Pye G, Jackson J, Thomas WM, Hardcastle JD. Comparison of Coloscreen Self-Test and Haemoccult faecal occult blood tests in the detection of colorectal cancer in symptomatic patients. *Br J Surg*. 1990;77(6):630-631. doi:10.1002/bjs.1800770612	Yes	Yes	No	No	Yes	Yes	Secondary care; Unknown cut-off
Quyn AJ, Steele RJ, Digby J, et al. Application of NICE guideline NG12 to the initial assessment of patients with lower gastrointestinal symptoms: not FIT for purpose?. *Ann Clin Biochem*. 2018;55(1):69-76. doi:10.1177/0004563217707981	No	No	No	Yes	Yes	Yes	Mixed population;
Rodríguez-Alonso L, Rodríguez-Moranta F, Ruiz-Cerulla A, et al. An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical faecal occult blood test. Dig Liver Dis. 2015;47(9):797-804. doi:10.1016/j.dld.2015.05.004	Yes	Yes	No	Yes	Yes	Yes	Referrals originated from general practitioners and community gastroenterologists, as well as from the hospital environment.
Rodriguez-Alonso L, Rodriguez-Moranta F, Ruiz-Cerulla A, et al. The use of faecal immunochemical testing in the decision-making process for the endoscopic investigation of iron deficiency anaemia. *Clin Chem Lab Med*. 2020;58(2):232-239. doi:10.1515/cclm-2019-0203	No	Yes	No	Yes	Yes	Yes	Mixed (Tertiary care & Primary care)
Rodriguez-Alonso L, Rodriguez-Moranta F, Arajol C, et al. Proton pump inhibitors reduce the accuracy of faecal immunochemical test for detecting advanced colorectal neoplasia in symptomatic patients. *PLoS One*. 2018;13(8):e0203359. Published 2018 Aug 31. doi:10.1371/journal.pone.0203359	No	Yes	No	Yes	Yes	Yes	Mixed (Tertiary care & Primary care)

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Rozen P, Comaneshter D, Levi Z, et al. Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Cancer*. 2010;116(9):2115-2125. doi:10.1002/cncr.25012	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Senore C, Haug U. Faecal immunochemical tests have the potential for correctly ruling out colorectal cancer in symptomatic patients. *BMJ Evid Based Med*. 2018;23(3):113-114. doi:10.1136/bmjebm-2018-110901	No	NA	NA	NA	NA	NA	Comment
Shastri YM, Loitsch S, Hoepffner N, et al. Comparison of an established simple office-based immunological FOBT with fecal tumor pyruvate kinase type M2 (M2-PK) for colorectal cancer screening: prospective multicenter study. *Am J Gastroenterol*. 2008;103(6):1496-1504. doi:10.1111/j.1572-0241.2008.01824.x	Yes	No	No	No	Yes	Yes	Mixed population. Unknown cut-off
Sieg A, Scheida M, John MR, et al. Validity of new immunological human fecal hemoglobin and albumin tests in detecting colorectal neoplasms--an endoscopy-controlled study. *Z Gastroenterol*. 1998;36(6):485-490.	Yes	Yes	No	Yes	Yes	Yes	Secondary care
Sieg A, Thoms C, Lüthgens K, John MR, Schmidt-Gayk H. Detection of colorectal neoplasms by the highly sensitive hemoglobin-haptoglobin complex in feces. *Int J Colorectal Dis*. 1999;14(6):267-271. doi:10.1007/s003840050226	Yes	Yes	Yes	No	Yes	Yes	No relevant index test
Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. *Cancer*. 2006;107(9):2152-2159. doi:10.1002/cncr.22230	Yes	No	No	No	Yes	Yes	Mixed population. Unknown cut-off
Singhal S, Verma A, Anand K. Colonoscopy for colorectal cancer screening above age 75: outcomes in symptomatic african american and Hispanic adults. *J Gastrointest Cancer*. 2011;42(4):212-216. doi:10.1007/s12029-010-9190-8	Yes	Yes	Yes	No	Yes	Yes	To evaluate the outcome of colonoscopies in symptomatic adults ≥75 years of age. No data about FIT accuracy
Sokoro A, Singh H. Fecal Occult Blood Test for Evaluation of Symptoms or for Diagnostic Testing. *Am J Gastroenterol*. 2020;115(5):679-680. doi:10.14309/ajg.0000000000000560	No	NA	NA	NA	NA	NA	Editorial
Stonestreet J, Chandrapalan S, Woolley D, Uthman U, Arasaradnam RP. Systematic review and meta-analysis : diagnostic accuracy of faecal immunochemical testing for haemoglobin (FIT) in detecting colorectal cancer for both symptomatic and screening population. *Acta Gastroenterol Belg*. 2019;82(2):291-299.	No	NA	NA	NA	NA	NA	Review

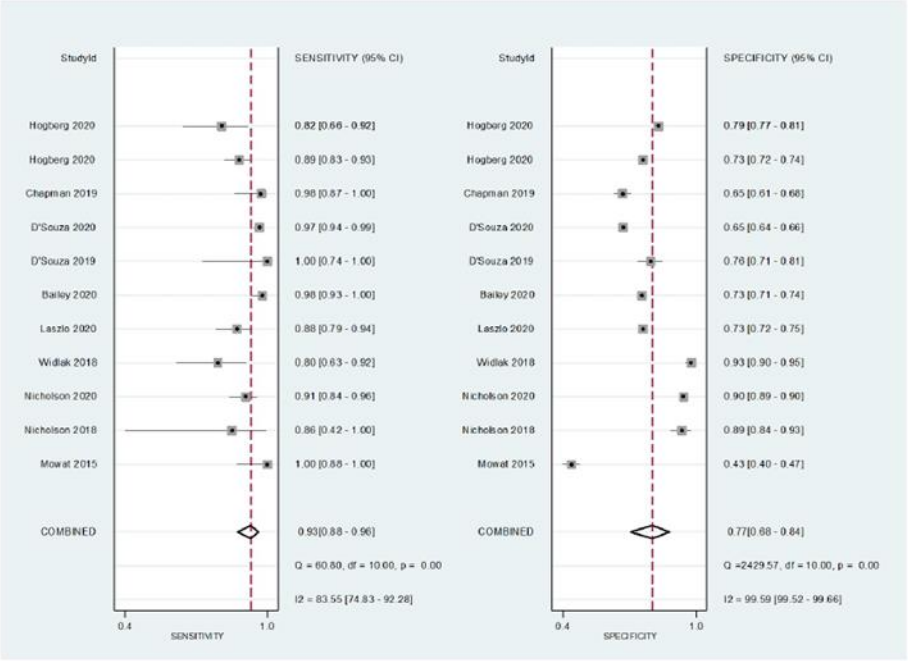
Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Steele RJ, McDonald PJ, Digby J, et al. Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity. *United European Gastroenterol J*. 2013;1(3):198-205. doi:10.1177/2050640613489281	Yes	No	No	Yes	Yes	Yes	Screening setting
St John DJ, Young GP, Alexeyeff MA, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. *Gastroenterology*. 1993;104(6):1661-1668. doi:10.1016/0016-5085(93)90643-q	Yes	No	No	No	Yes	Yes	Mixed population; Case-control
Symonds EL, Pedersen SK, Baker RT, et al. A Blood Test for Methylated BCAT1 and IKZF1 vs. a Fecal Immunochemical Test for Detection of Colorectal Neoplasia. *Clin Transl Gastroenterol*. 2016;7(1):e137. Published 2016 Jan 14. doi:10.1038/ctg.2015.67	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Szilagyi A, Xue X. Evaluation of a fecal immunochemistry test prior to colonoscopy for outpatients with various indications. Clin Exp Gastroenterol. 2017;10:285-292. Published 2017 Nov 10. doi:10.2147/CEG.S147928	Yes	No	Yes	Yes	Yes	Yes	Mixed population
Tate JJ, Northway J, Royle GT, Taylor I. Faecal occult blood testing in symptomatic patients: comparison of three tests. *Br J Surg*. 1990;77(5):523-526. doi:10.1002/bjs.1800770516	Yes	Yes	Yes	No	No	Yes	Guaiac plus FIT. Unknown cut-off. Double-contrast barium enema examination
Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. *Cancer Epidemiol Biomarkers Prev*. 2011;20(2):272-280. doi:10.1158/1055-9965.EPI-10-0848	No	Yes	No	Yes	Yes	Yes	Secondary care
Thomas WM, Hardcastle JD, Jackson J, Pye G. Chemical and immunological testing for faecel occult blood: a comparison of two tests in symptomatic patients. *Br J Cancer*. 1992;65(4):618-620. doi:10.1038/bjc.1992.125	Yes	Yes	Yes	No	Yes	Yes	No relevant index test; Unknown cut-off
Tsapournas G, Hellström PM, Cao Y, Olsson LI. Diagnostic accuracy of a quantitative faecal immunochemical test vs. symptoms suspected for colorectal cancer in patients referred for colonoscopy. Scand J Gastroenterol. 2020;55(2):184-192. doi:10.1080/00365521.2019.1708965	Yes	Yes	No	Yes	Yes	Yes	Referred from primary care or local hospitals
van de Veerdonk W, Hoeck S, Peeters M, Van Hal G. Towards risk-stratified colorectal cancer screening. Adding risk factors to the fecal immunochemical test: Evidence, evolution and expectations. *Prev Med*. 2019;126:105746. doi:10.1016/j.ypmed.2019.06.004	No	NA	NA	NA	NA	NA	Review

Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
van Melle M, Yep Manzano SIS, Wilson H, Hamilton W, Walter FM, Bailey SER. Faecal immunochemical test to triage patients with abdominal symptoms for suspected colorectal cancer in primary care: review of international use and guidelines. *Fam Pract*. 2020;37(5):606-615. doi:10.1093/fampra/cmaa043	No	NA	NA	NA	NA	NA	Review
van Turenhout ST, Oort FA, van der Hulst RW, et al. Prospective cross-sectional study on faecal immunochemical tests: sex specific cut-off values to obtain equal sensitivity for colorectal cancer?. *BMC Gastroenterol*. 2014;14:217. Published 2014 Dec 21. doi:10.1186/s12876-014-0217-7	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Vasilyev S, Smirnova E, Popov D, et al. A New-Generation Fecal Immunochemical Test (FIT) Is Superior to Quaiac-based Test in Detecting Colorectal Neoplasia Among Colonoscopy Referral Patients. *Anticancer Res*. 2015;35(5):2873-2880.	Yes	No	No	No	Yes	Yes	Secondary care; Mixed population; Unclear indication for colonoscopy
Vironen J, Kellokumpu S, Andersson LC, Kellokumpu I. Comparison of a peanut agglutinin test and an immunochemical faecal occult blood test in detecting colorectal neoplasia in symptomatic patients. *Scand J Clin Lab Invest*. 2004;64(2):140-145. doi:10.1080/00365510410004876	Yes	Yes	No	No	Yes	Yes	Secondary care; Unclear indication for colonoscopy; Unknown cut-off
von Wagner C, Verstraete W, Hirst Y, Nicholson BD, Stoffel ST, Laszlo H. Public preferences for using quantitative faecal immunochemical test versus colonoscopy as diagnostic test for colorectal cancer: evidence from an online survey. *BJGP Open*. 2020;4(1):bjgpopen20X101007. Published 2020 May 1. doi:10.3399/bjgpopen20X101007	Yes	No	No	No	No	No	To elicit public preferences for FIT versus colonoscopy (CC) and its delivery in primary care. No data about FIT accuracy
von Wagner C, Stoffel S, Freeman M, et al. Attitudes towards faecal immunochemical testing in patients at increased risk of colorectal cancer: an online survey of GPs in England. *Br J Gen Pract*. 2018;68(676):e757-e764. doi:10.3399/bjgp18X699413	Yes	No	No	No	No	No	to investigate general practitioneers attitudes and willingness to use a FIT over an urgent 2-week wait (2WW) referral. No data about FIT accuracy
Von Wagner C, Stoffel ST, Freeman M, et al. General practitioners' awareness of the recommendations for faecal immunochemical tests (FITs) for suspected lower gastrointestinal cancers: a national survey. *BMJ Open*. 2019;9(4):e025737. Published 2019 Apr 11. doi:10.1136/bmjopen-2018-025737	Yes	No	No	No	No	No	Cross-sectional online survey of GPs hosted by an English panel of Primary health care professionals. No data about FIT accuracy
Yoshinaga M, Motomura S, Takeda H, Yanagisawa Z, Ikeda K. Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. *Am J Gastroenterol*. 1995;90(7):1076-1079.	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population

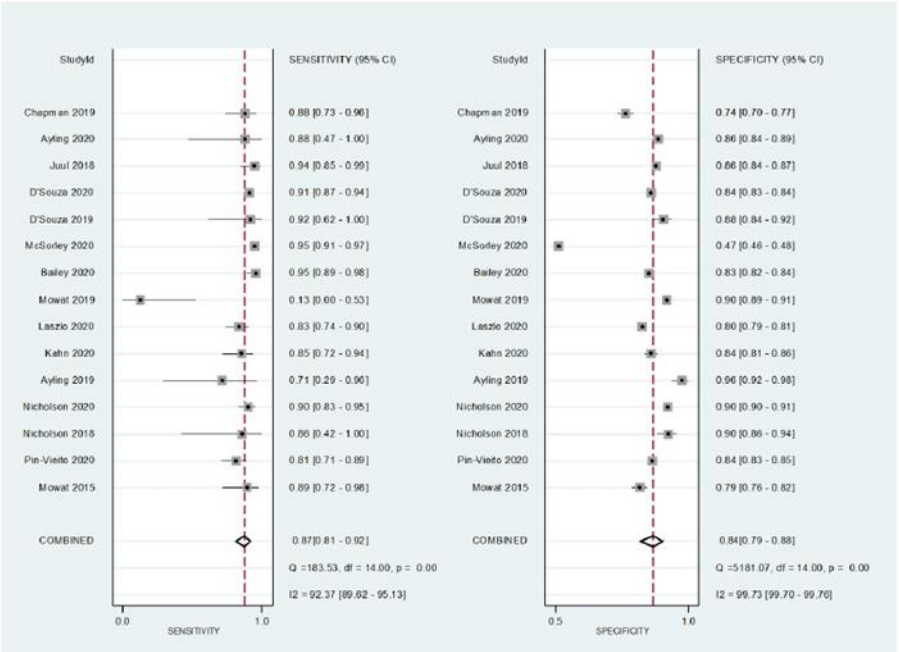
Study	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Comments
Widlak MM, Thomas CL, Thomas MG, et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther. 2017;45(2):354-363. doi:10.1111/apt.13865	Yes	Yes	No	Yes	Yes	Yes	All the referrals were seen in colorectal and dedicated gastroenterology clinics at University Hospitals Coventry and Warwickshire National Health Service Trust.
Wong WM, Lam SK, Cheung KL, et al. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. *Cancer*. 2003;97(10):2420-2424. doi:10.1002/cncr.11369	Yes	No	No	No	Yes	Yes	Mixed population
Woo HY, Mok RS, Park YN, et al. A prospective study of a new immunochemical fecal occult blood test in Korean patients referred for colonoscopy. Clin Biochem. 2005;38(4):395-399. doi:10.1016/j.clinbiochem.2005.01.003	Yes	No	No	Yes	Yes	Yes	Secondary care; Mixed population
Young GP, St John DJ, Cole SR, et al. Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin. *J Med Screen*. 2003;10(3):123-128. doi:10.1177/096914130301000305	Yes	Yes	No	No	Yes	Yes	Secondary care; Mixed population; Unknown cut-off
Wu D, Luo HQ, Zhou WX, Qian JM, Li JN. The performance of three-sample qualitative immunochemical fecal test to detect colorectal adenoma and cancer in gastrointestinal outpatients: an observational study. PLoS One. 2014;9(9):e106648. Published 2014 Sep 8. doi:10.1371/journal.pone.0106648	Yes	No	No	No	Yes	Yes	Secondary care; Mixed patients

Appendix 3. Forest plot showing pooled sensitivity and specificity for faecal immunochemical tests for the detection of colorectal cancer and significant colonic lesion based on cut-off value.

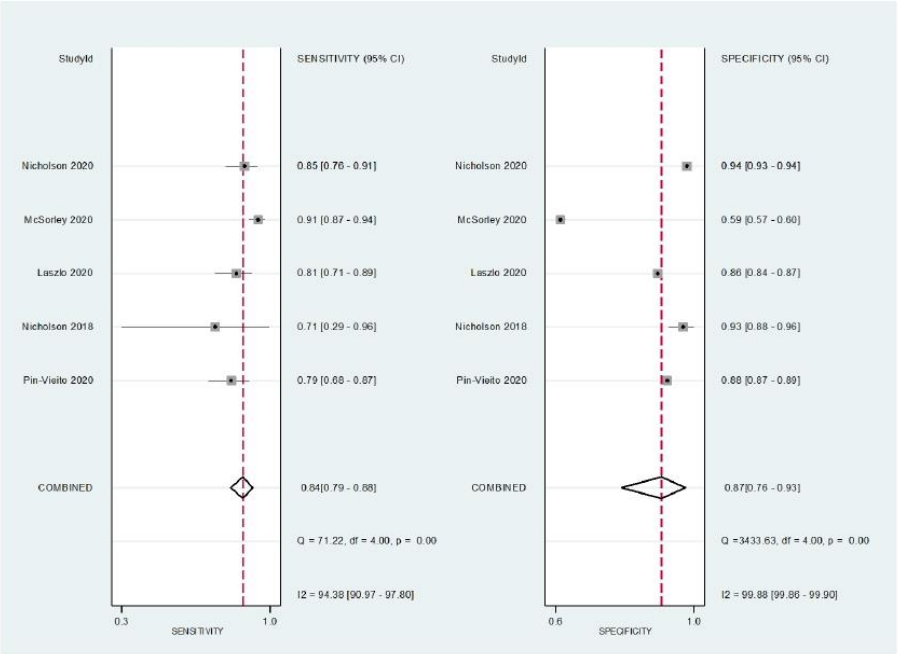
A) Cut-off value above the limit of detection (colorectal cancer)



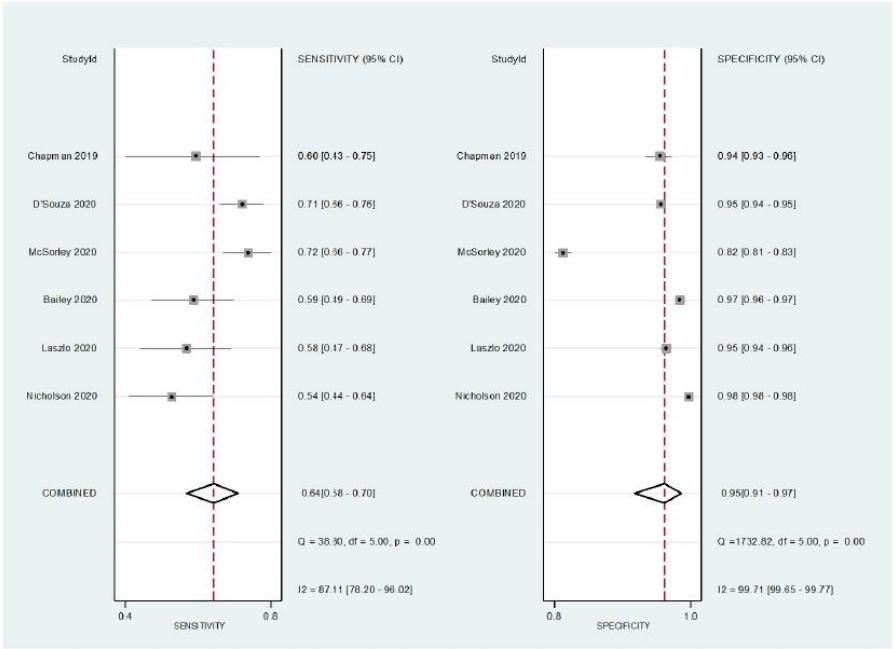
B) Cut-off value at 10 µg Hb/g faeces (colorectal cancer)



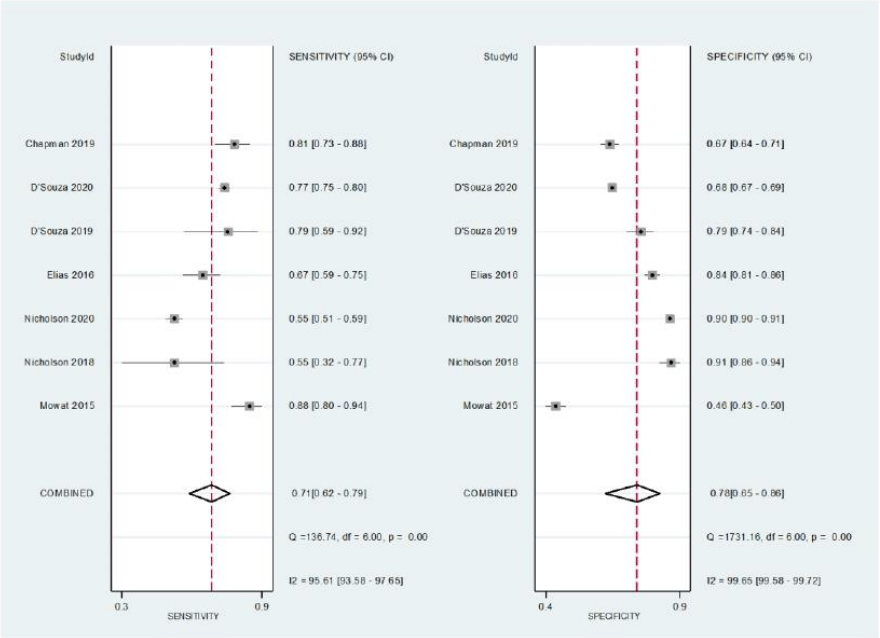
C) Cut-off value at 20 µg Hb/g faeces (colorectal cancer)



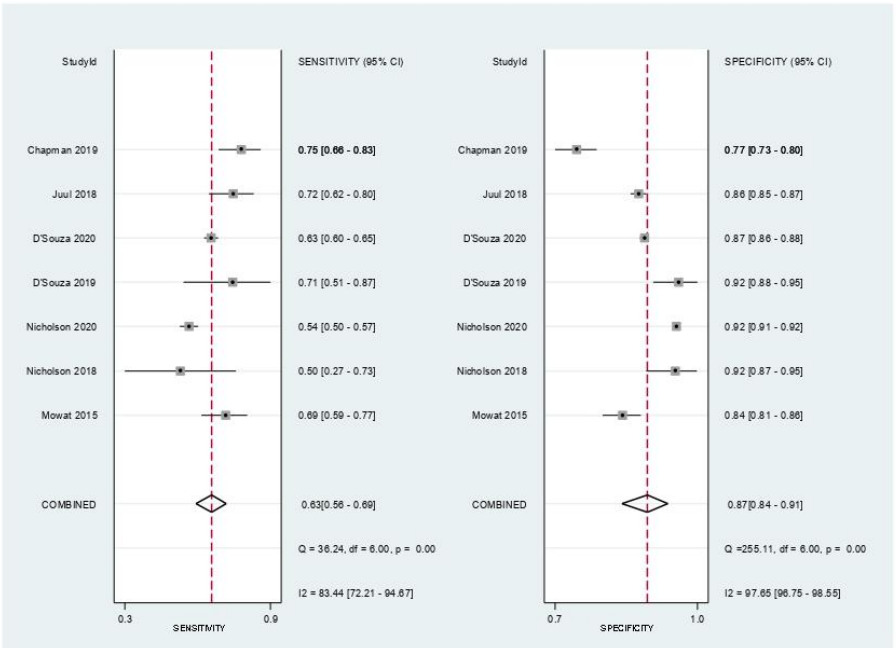
D) Cut-off value at 150 µg Hb/g faeces (colorectal cancer)



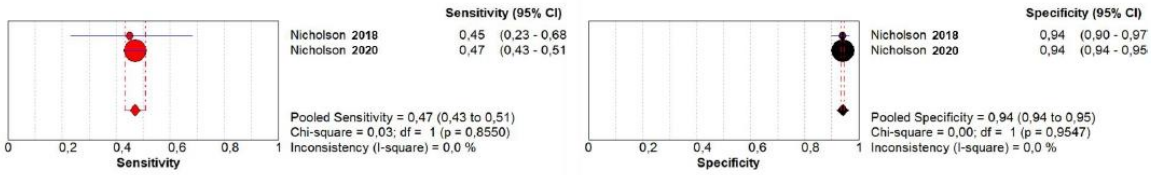
E) Cut-off value above the limit of detection (Significant colonic lesion)



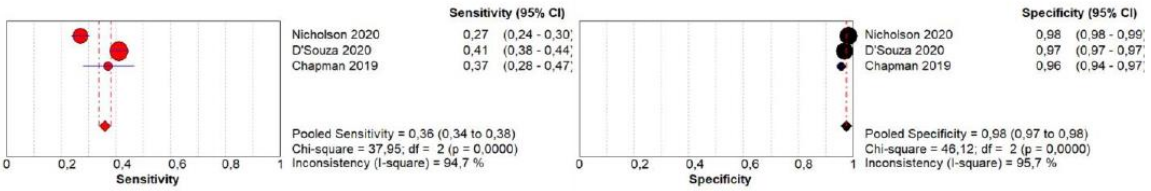
F) Cut-off value at 10 µg Hb/g faeces (significant colonic lesion)



G) Cut-off value at 20 µg Hb/g faeces (significant colonic lesion). DerSimonian method.



H) Cut-off value at 150 µg Hb/g faeces (significant colonic lesion). DerSimonian method.



Supplementary table 1: Characteristics of the studies included in the systematic review.

Author & Objective	Design & Setting	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Hogberg, 2010 **Aim**: to gain better knowledge about the use and outcome of an immunochemical faecal haemoglobin method in Swedish primary care, and how these tests contribute to the diagnosis of colorectal cancer.	Prospective cohort study. Setting: Primary care, Jämtland (Sweden). Period of recruitment: 1 December 2005 – 31 December 2007. The FIT was regarded positive when one or more of three samples showed a positive result.	All patients aged 18 years and over were eligible for the study when a a general practitioner ordered a FIT during the period of study.	Not reported. A total of 11 patients did not submit the tests, and 2 patients moved outside the county council during the observation period and were excluded.	Enrolled: 316 patients, of these 303 (95.9%) were included in the analysis. Three FIT samples were provided by 226 (75%) of the patients. 58 patients (19%) had positive samples. Symptoms: 250 (82.5%) abdominal pain, 70 (23.1%) change in bowel habit, 47 (15.5%) rectal bleeding, 51 (16.8%) anaemia. In 17 of the 58 who left a positive F-Hb test no examination of either the colon or rectum was performed. 1 (0.3%) CRC was found.	***Index test:*** Point of care qualitative FIT (Actim Faecal Blood; Oy Medix Biochemica Ab, Finland). 1 sample from each of 3 consecutive stools. Cut-off value for a positive result: 50 ng hb/ml of faecal solution (25–50 lg hb/g faeces according to the manufacturer). ***Reference standard:*** 54% performed bowel imaging. Medical records of the Care Administration System Development & Cancer Registry were reviewed. Follow up: 5–31 (mean 18) months.
Mowat, 2015 ***Aim:*** to study the diagnostic accuracies of faecal haemoglobin and faecal calprotectin, in a cohort of patients presenting to primary care with bowel symptoms. Other target: High risk adenoma; Significant colonic lesion;	Prospective cohort study. Setting: Primary care, NHS Tayside, Scotland (UK). Referrals are triaged by consultant gastroenterologists; 75% are brought straight to investigation and the remainder were seen in outpatient clinics. The percentage of referrals from GPs marked as 'urgent' or 'urgent suspected cancer' consistently runs at 35–40%.	All adult patients referred to secondary care for investigation of bowel symptoms from October 2013 to March 2014. (if patients had more than one symptom, they were attributed only one in order of decreasing importance: rectal bleeding, anaemia, diarrhea, altered bowel habit, abdominal pain and weight loss)	Not reported. 12 patients were excluded (seven in whom neither faecal sample was suitable for analysis, four who returned samples outside the study period and one patient with known inflammatory bowel disease.)	2189 patients were referred for investigation. 1032 (47.1%) referrals were either 'urgent' or 'urgent suspected cancer' and 1043 (34.5%) patients returned faecal samples; 1031 patients (47.1%) formed the study cohort. A total of 755 patients (54.7% women, median age 64 years) returned faecal samples and completed bowel investigations and were included in the analysis. Prevalence CRC: 3.7%. Prevalence SCL (CRC + HRA + IBD) 10.0%. 100% Symptomatic (Weight loss 7 (0.9%); Pain 83 (11.0%); rectal bleeding 258 (34.2%), anemia 67 (8.9%); change in bowel habit 323 (42.8%); diarrhea 127 (16.8%)).	***Index test:*** OC-Sensor (Eiken Chemical Co., Tokyo, Japan). Any faecal haemoglobin sample that was reported by the analytical system as a positive numerical result greater than zero mg/g was considered as a 'detectable faecal haemoglobin'. Cut-offs: detectable faecal haemoglobin and 10 µg hemoglobin/ g feces. ***Reference standard:*** colonoscopy up to the caecum or obstructing carcinoma plus histopathology.
Elias, 2016 ***Aim:*** to develop a diagnostic model for significant colonic disease (CRC + IBD + diverticulitis + advanced adenoma) with routine clinical information, extended with faecal calprotectin and/or FIT results. In 2012 (subgroup data) Kok's article aimed to quantify the diagnostic accuracy of 3 biomarker tests (Quantum Blue® calprotectin quantitative lateral flow assay, EK-CAL calprotectin ELISA and Clearview One Step immunochemical faecal occult blood test device) for the inclusion or exclusion of organic bowel disease in patients with persistent (i.e., ≥2 weeks) lower-abdomen complaints in primary care. Other analysis: accuracy of combined faecal calprotectin & FIT	This paper reports data from the CEDAR (Cost-effectiveness of a Decision Rule for Abdominal Complaints in Primary Care) study: A prospective cross-sectional diagnostic study in 266 general practices in 2 regions of the Netherlands: central (Gelderse Vallei) and south (Oostelijke Mijnstreek). Period of recruitment: from July 2009 through January 2012. When patient referral outpaced study resources, every nth case was screened to keep study participants representativeness.	Patients consulting their general prectitioners for persistent lower-abdomen complaints in the period of study. Patients were eligible if they were at high risk of organic bowel disease (lower-abdomen complaints present for ≥ 2 weeks plus ≥ 1 of the following: rectal bleeding, altered defecation pattern, abdominal pain, fever, diarrhea, weight loss, sudden onset in the elderly, or palpable abdominal or rectal mass). Recruitment was at the general practitioner's office (19.9%) or after scheduling at the endoscopy department (80.1%).	Patients < 18 years, unable to give informed consent, previously diagnosed with organic bowel disease or positive on the triple faeces test, used for the detection of intestinal parasites, not requiring endoscopy. In some patients, endoscopy was scheduled in <1 week so they could not become part of the study. Patients not reached or who refused participation also were not included.	Eligible patients: 1495. Of these, 843 were enrolled and 810 (54.2%) were included in the analysis. The median age of participants was 61 years 54.9% were female. Organic bowel disease was present in 141 patients (17.4%), the majority of whom had neoplastic disease (37 carcinoma and 49 adenomas), followed by IBD (37) and diverticulitis (18). Sixteen patients had advanced adenomas. Symptoms: 80.7% abdominal pain; 43.6% rectal bleeding; 65.5% change in bowel habit; 29.1% Diarrhoea; 57.9% constipation; 19.2% weight loss; 5.5% anaemia.	***Index test:*** A qualitative point of care test: Clearview One Step Fecal Occult Blood Test Device, (Inverness Medical Innovations). The lower detection limit as stated by the manufacturer was 6 µg hemoglobin/ g feces. ***Reference standard:*** endoscopy (i.e., colonoscopy or sigmoidoscopy). Furthermore, all patients for whom there was an inconclusive diagnostic reference procedure were followed for 3 months to establish a definite diagnosis.
Hogberg, 2016 ***Aim:*** to assess the value of a point of care FIT and a quantitative faecal calprotectin test in detecting CRC, HRAs and IBD in primary care. *Secondary aim:* to assess the value of combining these tests with tests for haemoglobin concentration, iron saturation and serum ferritin. Another target: significant colonic lesion (CRC + HRA + IBD)	Prospective cohort study. Setting: Primary care, four health care centres which provide care for approximately 29.000 (23%) inhabitants of the Jämtland Härjedalen region of Sweden. There is no CRC screening program.	All patients aged 20 years and over were eligible for the study when a physician ordered a FIT and/or a faecal calprotectin test during the period of 30 January 2013–31 May 2014. Nurses invited consecutive patients to participate in the study. The sample size was calculated, based on the hypothesis that there would be a significant difference in sensitivity between the faecal calprotectin test and the FIT for detecting CRC and high-risk adenomas.	Not reported.	In total, 510 patients were eligible for the study, 391 agreed to participate and 384 returned both tests. Of these, five died of other conditions before endoscopy, and six moved away from the area during the 2-year follow-up, thus, 373 (73.1%) patients (median age 63.0 years, 64.6% women) were included in the final analysis. All patients were symptomatic. 92 (25.3%) of patients consulted with rectal bleeding, 207 (58%) abdominal pain, 161 (45.7%) change in bowel habit,156 (44.7%) diarrhoea, 98 (28.2%) constipation, 46 (13.5%) weight loss, 62 (21.0%) anaemia. CRC, HRA and SCL were diagnosed in 8 (2.1%), 8 (2.1%) and 26 (6.8%) patients respectively.	***Index test:*** Point of care qualitative FIT (Actim Faecal Blood; Oy Medix Biochemica Ab, Finland). One sample from each of three consecutive stools. The cut-off value for a positive result was set at 50 ng haemoglobin/ml of faecal solution, which corresponded to 25–50 lg haemoglobin/g faeces according to the manufacturer. The FIT was regarded positive when one or more of three samples showed a positive result. ***Reference standard:*** colonoscopy and/or follow up (2 years) through medical records.
Juul, 2018 ***Aim:*** to investigate in a large-scale study the value of using FIT in general practice on patients presenting with non-alarm symptoms of CRC. Another target: significant bowel disease (CRC + IBD + HRA)	Prospective cohort study based on the establishment of access to the FIT for general practitioners in the Central Denmark Region. The study took place from 1 September 2015 to 30 August 2016.	All individuals aged ≥30 years who presented in general practice with non-alarm symptoms of CRC (change in bowel habits, abdominal pain, unexplained anaemia, and unspecific symptoms e.g., fatigue or weight loss). Furthermore, FIT was recommended as part of the diagnostic work up of irritable bowel syndrome.	Individuals aged ≥40 years with alarm symptoms: rectal bleeding, change in bowel habits >4 weeks, abdominal pain and iron deficiency anaemia. Or symptoms which could be eligible for urgent referral in the cancer patient pathway for CRC. Invalid FIT (2.4%) and duplicated (5.1%) were also excluded.	During the study period, 3745 FITs were requested, and 3462 (92.5%) FITs were included in the analyses. Of these, 540 (15.6%) were positive. Diagnostic investigation was performed in 416 (77.0%) of individuals with a positive FIT and 418 (14.3%) with a negative FIT. Among all individuals with a positive FIT, 51 (9.4%) were diagnosed with CRC, 11 with IBD and 62 with HRA. Less than three (<0.1%) CRCs and 26 (0.9%) cases of SBD (20 IBDs and 6 HRAs) were found among individuals with a negative test. Symptoms: 1579 (45.6%) abdominal pain, 1867 (53.9%) change in bowel habit, 424 (12.3%) anaemia.	***Index test:*** OC Sensor DIANA (Eiken Chemical Company, Ltd, Japan). The measuring range was 7–200 µg Hb/g faeces (stated as <7 µg Hb/g faeces for faecal haemoglobin concentrations below the detection limit). Only one FIT per individual was included (Defined either the latest performed FIT or the FIT requested immediately before the referral to diagnostic investigation). Cut-off: 10 µg hemoglobin/ g faeces. ***Reference standard:*** follow up during 3 months from the day of FIT request through Danish registers.

Author & Objective	Design & Setting	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Widlak, 2018 ***Aim:*** to assess the diagnostic accuracy of FIT, faecal calprotectin and urinary volatile organic compounds in patients with lower GI symptoms. Other results: Diagnostic performance of FIT in combination with faecal calprotectin and urinary volatile compounds for CRC, high-risk adenoma and all adenomas.	Single-centre, prospective, blinded study. Patients referred from primary care to tertiary care with suspected CRC. Unknown recruitment period.	Patients with lower GI symptoms with suspected CRC.	Under the age of 18, pregnant, did not meet the referral criteria for urgent review for lower gastrointestinal symptoms or had incomplete colonic examinations were excluded. 834 patients were excluded for a combination of reasons including "physical frailty, illness, language barriers, etc."	Invited: 1850 patients. Of these, 562 (30.4%) patients with matching urine and stool samples were included for statistical analysis. 49% female; Median age 68 (range 29-89). Symptoms: Altered bowel habit 369 (66%), Weight loss 87 (15%), Rectal bleeding 232 (41%), Anaemia 121 (22%), Iron-deficiency anaemia 91 (16%), Abdominal pain 164 (29%). Of these, 35 were diagnosed with CRC (6.2%)	***Index test:*** HM-JACKarc (Kyowa Medex). The lowest detection limit of this assay for FIT is 3 µg /g faeces. EIA Calprotectin iluoroimmunoassay -automated Thermo Fisher Immuno-Cap 250 analyser (Thermo Fisher Scientific, Waltham, Massachusetts, USA). A commercial gas analysis instrument [Lonestar (FAIMS), Owlstone, Cambridge, UK] was used to analyse VOCs emanating from the urine samples. ***Reference standard:*** endoscopic or radiological colonic cross-sectional imaging.
Turvill, 2018 ***Aim:*** To assess the diagnostic accuracy of FIT and faecal calprotectin for CRC, significant adenomatous polyps (10 mm or multiple 5 sub-centimetre polyps or with high-grade dysplasia) and organic enteric disease (which required secondary care management: IBD, microscopic colitis, radiation proctopathy and significant diverticular disease). To determine whether repeat or combined biomarker testing improves diagnostic accuracy for CRC or clinically significant disease. Other analysis: Diagnostic accuracy of a single FIT for CRC in subgroups of NICE NG12 symptom complexes and demographics.	Prospective Cohort study. Patients referred from primary care. Period of recruitment: February 2016 to March 2017. UK; England (York)	Patients who were referred through the 'two-week wait' pathway, fulfilling alarm criteria for suspected CRC (NICE NG12 Sections 1.3.1–1.3.3).	Patients under the age of 18, unbeing able to give informed consent to participate in the research study or who did not return one or both faecal samples before investigation.	Invited: 1491; Enrolled 700; Analysed: 515 (34.5%). 50% Female. Median age 69 years (IQR 61–76). 18% had a family history of CRC and 30% were taking NSAID, antiplatelet therapy or anticoagulants. 93% of the referrals were judged to strictly fulfil criteria for a 'two-week wait' suspected CRC referral. 79% of the patients had a change in bowel habit, 36% rectal bleeding, 26% abdominal pain, 18% iron-deficiency anaemia, 14% weight loss, 4% abdominal mass and 1% rectal mass.	***Index test:*** HM-JACKarc (Kyowa-Medex Co., Ltd, supplied by Alpha Laboratories Ltd, Eastleigh SO50 4NU, UK). The manufacturer's quoted limit of quantitation of 7 µg Hb/g faeces was used in this study; Limit of detection was determined as 2 µg Hb/g faeces. Cut-off: 12 µg hemoglobin/ g faeces. Monoclonal Enzyme-Linked Immuno-Sorbent Assay (EK-CAL Calprotectin ELISA, Buhlmann) ***Reference standard:*** full colonoscopy or CT colonography or a lesser investigation (such as CT abdomen/pelvis with contrast plus flexible sigmoidoscopy)
Ayling, 2019 **Aim:** to study FIT in patients with anaemia attending a gastroenterology clinic in Plymouth and to look at an artificial intelligence learning algorithm (ColonFlagTM) in these patients, together with a cohort who had undergone colonoscopy for iron deficiency anaemia in London.	One of this cohort of the study is used. Retrospective cohort analysis. Patients recruited in a Gastroenterology Clinic at Plymouth, between March 2014 and March 2017, who had been referred from Primary Care.	Patients seen in the Gastroenterology Clinic, referred from Primary Care with a low haemoglobin concentration, ostensibly secondary to iron deficiency, on a 2-week wait cancer pathway	Not reported	Plymouth cohort was compound by 428 patients. The median age was 71 and 51.2% were female. Of these, FIT was performed in 178 patients (41.6%). Seven (3.9%) and 13 (7.3%) were diagnosed with CRC and HRA respectively.	***Index test:*** OC Sensor (Eiken Chemical Co, Tokyo, Japan). Cut-off: 10 µg hemoglobin/ g faeces. ***Reference standard:*** colonoscopy.
Nicholson, 2018 ***Aim:*** To compare the diagnostic performance of guaiac faecal occult blood testing with FIT. Another target: significant colonic lesion (CRC+IBD+polyp > 10 mm)	Retrospective cohort study. Data & Setting: Consecutive samples sent to the laboratory from primary care in the period January to March 2016 for investigation of faecal occult blood in Oxfordshire, UK (population of approximately 660,000)	Patients with lower gastrointestinal symptoms. Where more than one sample result was available for any individual patient, any positive result within those samples tested was considered a positive outcome on the basis that a single positive would trigger referral. Where multiple samples on a single patient were collected, these were on sequential days, which precluded assessment of changes in FOB test results with disease progression.	Not reported	Faecal occult blood testing by both FIT and guaiac faecal occult blood was undertaken on 332 samples from 238 patients, (median age 58 years (range 19–93); 57% women). Symptoms: change in bowel habit 59 (24.8%), abdominal pain /discomfort 45 (18.9%), blood in stools 23 (9.7%), rectal bleeding 9 (3.5%) and weight loss 4 (1.7%), anaemia 62 (26.1%) absent / uninterpretable clinical info (n=46). Significant colorectal disease was detected in 20 patients, 7 of which had CRC.	***Index test:*** HM-KACKarc (Kyowa Medex, Tokyo, Japan). The method had a calibration range of 7 to 450 µg Hb/g faeces. Various cut-off used: 7; 10; 20 and 50 µg haemoglobin /g faeces. ***Reference standard:*** clinical and diagnostic databases were searched for between 21 and 23 months following the faecal occult blood testing for all patients.

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Mowat, 2019 ***Aim:*** to determine the impact of introducing quantitative FIT into routine practice within primary care on the outcome of patients presenting with new bowel symptoms. Another target: significant colonic lesion (CRC+IBD+polyp > 10 mm) collected from Digby's study. *Other results:* Cases of colorectal cancer presenting in patients with f-Hb <10 µg/g but who had been referred from primary care on clinical judgement.	Single-centre prospective cohort study. Period of study: the first calendar year beginning December 2015. NHS Tayside, Scotland (UK). (population of around 400,000 with approximately 4000 referrals from primary care to secondary care for assessment of bowel symptoms per year).	Patients who consulted primary care with lower GI symptoms. This population has no access to guaiac faecal occult blood tests (out with the National Bowel Cancer Screening Programme). These patients may be referred to either the direct-to-test colorectal service or to gastroenterology.	Not reported but 152 samples (2.7%) were unsuitable for analysis (most commonly due to faecal contamination) in whom 40 patients did not complete a repeat test. Ten patients had known IBD. In total, 50 patients were excluded from further analysis.	A total of 5422 patients submitted a total of 5660 FIT samples to the laboratory. 5372 (99.1%) were included in the final analysis. The median age of patients was 65 years (range: 2–99, IQR: 51–75) and 56.4% were female.	***Index test:*** HM-JACKarc (Kyowa Medex) with an analytical working range of 7–400 µg Hb/g faeces. Results with f-Hb ≥10 µg/g were defined as positive. ***Reference standard:*** 2848 patients were referred to secondary care and colonoscopy was performed in 2141 (39.9%) patients and was complete in 1447 (26.9%) patients. Other patients were assessed with CT colonography, sigmoidum endoscopy or barium enema) & All patients were followed through post hoc anonymised record linkage with the Scottish Cancer Registry to identify all incident cases of CRC.
Keenan, 2019 ***Aim:*** to compare the accuracy of faecal M2-PK and FIT in detecting pre-cancerous bowel lesions and CRC in patients who present in primary care with bowel symptoms. Another target: significant colonic lesion (CRC+Adenoma > 9 mm)	Prospective cohort study. Setting: Primary care. New Zealand. Unknown period of recruitment.	One of the cohorts of the study was used: this included patients who presented to their general practitioners with bowel problems and were subsequently referred for a faecal immunochemical test to detect the presence of faecal haemoglobin.	Not reported Four patients were subsequently excluded from the general practitioner derived cohort, because bacterial pathogens were detected in their samples.	Enrolled: 189. Analyzed: 185 (97.9%). 50.8% female; Median age (interquartile range): 59 (51–70). 7 were found to have evidence of Significant colonic lesions that included CRC (n=2), adenomas greater than 1 cm in size (n=5).	***Index test:*** A qualitative (one-step membrane cassette) immunoassay (Ngaio Diagnostics Ltd, Nelson, New Zealand). This assay detects human haemoglobin above 50µg of f-Hb per gram of faeces. ***Reference standard:*** Clinical follow-up on the patients in the GP cohort was monitored for a minimum of 12 months after stool collection.
Chapman, 2019 ***Aim:*** to evaluate anaemia and faecal haemoglobin levels as risk stratification tools in a '2 week wait' pathway, and to assess FIT within an operational urgent colorectal cancer pathway in England. Anaemia was defined as a haemoglobin level below 120 g/l in women and 130 g/l in men. Data about FIT as "Rule in" tool. Another target: significant colonic lesion (CRC+IBD+HRA + complicated diverticular disease)	Prospective cohort study. Recruitment of patients in primary care setting between 6 September 2016 and 31 August 2017. (Nottingham, England, UK)	All patients referred under the 2 week-wait pathway from primary care for suspected colorectal cancer in the period of study were included.	Patients referred with rectal bleeding were excluded from FIT stratification. Patients who should be evaluated through other pathways (not 2ww).	During the study period, 1891 referrals were vetted by the straight-to-test team and 1106 referrals were deemed suitable for FIT and were sent kits, 895 OC-Sensor™ kits were returned (80.9%), three patients had incomplete data and one kit was unanalysable. Finally, 810 (73.2%) were analysed. The median age of those referred was 71.7 (62.6–79.3) years. 55.7% were female. 40 CCR were diagnosed (4.9%). Symptoms: 58.2% change in bowel habit, 288 (37.8%) anaemia.	***Index test:*** OC-Sensor™; Eiken Chemical Company, Tokyo, Japan. Various cut-off used: LoD; 10; and 150 µg haemoglobin /g faeces. 4 µgHb/g faeces was the limit of reliable detectability on the analyser platform. ***Reference standard:*** all outcomes were censored on 22 September 2017. Patient data including clinical outcomes for all 2WW referrals were recorded on a NUhCLEUS software system.
D'Souza, 2019 ***Aim:*** to determine the diagnostic accuracy of FIT to rule out colorectal cancer in symptomatic patients, including low risk patients meeting the NICE criteria (DG30). Another target: significant colonic lesion (CRC+IBD+HRA)	Prospective cohort study. Setting: Patients from primary care referred for colonoscopy at Croydon University Hospital between November 2016 and October 2017.	All symptomatic patients undergoing colonoscopy who were referred through a 2WW pathway.	Colonoscopy was performed for surveillance in 86 patients who were excluded.	800 patients accepted and 384 completed colonoscopy and FIT (48%). 298 were analyzed. Mean age 60.6 years (range 20–90); 198 (51.4%) women. 160 NG12 & 138 DG30 criteria. 33% Iron deficiency anaemia or change in bowel habit > 60y; 18% change in bowel habit < 60 y; 16% rectal bleeding > 50y.	***Index test:*** HM-JACKarc (Kyowa Medex/Alpha Labs). Various cut-off used: LoD; and 10 µg haemoglobin /g faeces. The analytical working range was 2–8000 µg Hb/g faeces (µg/g). The limit of detection of the assay is 2 µg/g and the limit of quantification was 10 µg/g. ***Reference standard:*** colonoscopy.
Pin-Vieito, 2020 ***Aim:*** To assess the diagnostic accuracy of FIT in daily clinical practice in primary health care for CRC diagnosis. To evaluate the performance of FIT when threshold is increased from 10 µg Hb/g faeces to 20 µg Hb/g faeces	Population-based retrospective cohort study. Setting: Primary care (real life data). Two areas of northern Spain between 2012 and 2016.	Asymptomatic and Symptomatic patients aged ≥18 years who consulted their general practitioners who requested a FIT as part of their medical treatment	Hospitalization; Secondary care patients; Regional screening program; < 18 years old; Patients with a history of CRC in the 2 years prior to FIT determination.	Included: n=38,675; Age: (median) 65.2 years; Sex: 54.0% women. Prevalence CRC: 1.7%; Information regarding FIT indication and CRC location was only available for San Sebastián (5623 symptomatic patients).	***Index test:*** OC-Sensor (Eiken Chemical, Tokyo, Japan). cut-off of 10 and 20 µg haemoglobin /g faeces. ***Reference standard:*** Spanish Health System's Hospital Discharge Records Database (CRC diagnosis)
Hogberg, 2020 ***Aim:*** to evaluate the usefulness of FITs requested by primary care physicians for patients with and without histories of rectal bleeding, in the diagnosis of CRC.	Retrospective cohort study. Setting: patients recruited in primary care from 1 January to 31 December 2015 in the region of Örebro in Sweden (population 290,890 on 1 November 2015).	Patients aged ≥ 18 with FIT results requested by primary care physicians in the period of study. Samples registered within 14 days of each other were considered as belonging to the same FIT. The date of the FIT was set as the date of the first faecal sample. If more than one FIT had been provided during the year, the first FIT was registered only. The FIT was considered as positive if one or more of the samples tested positive.	Not reported	5683 patients (Median age 64 years, 59.9% women, 107 (1.9%) CRC) provided FITs with 1-8 samples. Three sample FITs were provided by 4232 patients (60.7% women, median age 62 years, 79 (1.9%) CRC). Information about rectal bleeding was available for 2404 patients, of which 2027 (84.3%; 62.0% women, median age 58 years, 59 (2.9%) CRC) provided three-sample FITs. In total, rectal bleeding was registered for 606 (29.9%) of the 2027 patients with three-sample FITs who had 26 (4.3%) CRCs.	***Index test:*** Actim Fecal Blood (Oy Medix Biochemica AB, Finland). Cutoff: 50 ng haemoglobin/ml of faecal solution corresponding to 25–50 µg haemoglobin/g faeces. ***Reference standard:*** patients with CRC within 2 years after their FIT date were identified from the Swedish Cancer Register.
Ayling, 2020 ***Aim:*** to audit a new FIT service for primary care for use in symptomatic patients at low risk of CRC, focusing on the indication for request and referral for diagnostic tests as recommended in NICE guidance.	Prospective cohort study. Setting: Primary care. Period: between 1 April and 30 September 2019. Newham, Tower Hamlets and Waltham Forest (combined population of about 950,000 years and 128 Primary Care practices).	All patients with samples that were analysed between 1 April and 30 September 2019 were included.	Not recorded 309 samples (25.7%) were not able to be analysed; 17 samples were unlabelled, 37 were grossly overfilled with contamination of the collection device, 227 were in screw top pots rather than specimen collection devices and 13 requests had no accompanying sample.	Enrolled: 1203, of these, FIT analysis was performed in 894 (74.3%) patients (median age 60 years, range 23-98; 55.7% women), 209 (23.4%) patients were younger than 50 years of age. Eight (0.9%) CRC were diagnosed.	***Index test:*** OC-Sensor (Eiken Chemical, Tokyo, Japan) cut-off of 10 µg haemoglobin /g faeces. The lower limit of quantification was 4 µg/g. The upper analytical limit was 200 µg/g and samples with a concentration above this were reported as >200 µg/g. ***Reference standard:*** CRC and other diagnoses were determined by reviewing clinical notes and endoscopy, histology and radiology report.

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Nicholson, 2020 ***Aim:*** to assess the diagnostic performance of FIT to detect serious bowel disease based on age-group, gender and FIT threshold. Another info: to describe FIT negative cases of colorectal cancer and the effect of adjusting the period of follow-up on diagnostic accuracy measures for colorectal cancer using FIT ≥10 µg Hb/g faeces	Retrospective cohort study. Setting: primary care. Oxfordshire (population of approximately 660 000), England,UK. Period of study from March 2017 to March 2020.	Consecutive FIT samples sent to Oxford University Hospitals Trust clinical biochemistry laboratory from primary care for adults (≥18 years old) during the period study. *Where more than one sample result was available for any individual patient, any positive result within those samples tested was considered a positive outcome on the basis that a single positive would trigger referral.*	Not described. *"Although 'high-risk' symptoms qualifying for urgent colonoscopy were noted in the clinical details, such as weight loss or anaemia, it can be assumed that GPs assessed these cases to be lower risk and not to qualify for fast-track referral and that GPs required additional information to guide their management."*	A total of 14,487 consecutive FITs were conducted for 12,509 patients, of these 9896 (79.1%) patients had at least 6 months of follow-up. The median age was 60 years and 58.6% were women. Patients commonly presented with combinations of clinical features: change in bowel habit (50.6%), anaemia (28.2%), abdominal pain (25.2%), blood in stools (19.7%) and iron deficiency (12.2%). CRC and Significant colorectal disease was detected in 105 (1.1%) and 682 (6.9%) of patients, 373 (3.8%) large >10 mm or high-grade dysplastic polyps and 204 (2.1%) had bowel inflammation.	***Index test:*** HM-JACKarc (Hitachi Chemical Diagnostics Systems Co., Ltd). The method had a calibration range of 7-450 µg Hb/g faeces and immunoassay reproducibility, assessed across 12 months was between 4.5% and 8.7% when expressed as a percentage coefficient of variation. Multiple cut-offs used (7, 10, 20, 50, 100, 120 and 150 µg haemoglobin / g faeces ***Reference standard:*** clinical and diagnostic databases were searched for evidence of cellular pathology for up to 36 months following the FIT test for all patients.
D'Souza, 2020 ***Aim:*** To assess whether FIT could be used to select patients with suspected colorectal cancer symptoms for urgent investigation. The primary outcome measure was to identify a suitable faecal haemoglobin cut-off that would maximise sensitivity for CRC. The secondary outcome measures were to establish the diagnostic accuracy of FIT for CRC and other serious bowel disease at different faecal haemoglobin cut-offs, and investigate the impact of other variables, such as age, sex, ethnicity and deprivation.	Multicentre, double-blinded diagnostic accuracy study using patients referred from primary care to 50 National Health Service (NHS) hospitals across England between October 2017 and December 2019.	Patients referred from primary care with symptoms of suspected CRC meeting NICE referral criteria under the 2WW pathway and who were triaged by secondary care clinicians to investigation by colonoscopy. Patients referred urgently on a 2WW pathway without meeting NICE criteria due to clinical concerns were classified as 'others' and included in the analysis.	Patients were not included if they did not return a suitable for analysis FIT sample or did not have a complete colonoscopy unless due to CRC or withdrew consent. Patients due to undergo colonoscopy within 3 days of identification were not invited to participate in the study, as there would not have been sufficient time to return a sample. FIT samples that were performed after the colonoscopy were not included in the study.	Invited: 21,126 patients; Complete FIT and colonoscopy outcomes were available for 9,822 (46.5%) patients (median age 65.0 years, 54.9% women). Ethnic groups: white (75.9%), other (11.2%) and Asian (6.3%). The median deprivation index score was 6.0. High-risk symptoms meeting NG12 criteria (73.2%), low-risk symptoms meeting DG30 criteria (21.4%) or other symptoms warranting urgent referral (6.4%). CRC and SBD (CRC, HRA or IBD) was detected in 3.3% and 11.9% of patients.	***Index test:*** HM-JACKarc (Hitachi Chemical Diagnostics Systems, Tokyo, Japan, supplied by Alpha Labs, Eastleigh, Hants, UK). The analytical working range is 7–400 µg/g. The limit of detection (LoD) of the assay is 2 µg/g and the limit of quantitation is 7 µg/g. Cut-off LoD, 10 and 150 µg Hb/g faeces. ***Reference standard:*** colonoscopy.
Mc Sorley, 2020 ***Aim:*** to examine the yield of CRC in patients who 1) underwent colonoscopy across three Scottish NHS Boards after referral from primary care with lower gastrointestinal symptoms and 2) had submitted a FIT at the time of referral.	Retrospective audit of data from three cohorts. Some data were prospectively collected as part of Mowat´s study published in 2019. Primary care setting. Three Scottish NHS Boards: The period of data collection was between December 2015 and December 2016 (12 months) in Tayside, June 2018 and December 2019 (18 months) in Fife and September 2018 and January 2019 (5 months) in Greater Glasgow and Clyde.	Patients who had undergone colonoscopy because of a primary care referral with lower GI symptoms (including rectal bleeding) and had an associated FIT result were included. All categories of urgency of referral were included.	Patients without a FIT result, who had undergone colonoscopy without submitting a previous FIT, had not undergone colonoscopy following a FIT, or had been investigated by other methods such as CT colonography were not included in the analysis.	A total of 4841 patients were included. Of these, 266 (5.5%) were diagnosed with CRC. NHS Tayside included 1447 patients (with a median age of 66, 52.7% women, of whom 92 (6.4%) were diagnosed with CRC). NHS Fife included 2082 patients (median age 65; 54.0% women, of whom 125 (6.0%) were diagnosed with CRC). NHS Greater Glasgow and Clyde included 1312 patients (median age 60, 56.4% women, of whom 49 (3.7%) were diagnosed with CRC).	***Index test:*** HM-JACKarc (HM-JACKarc, Hitachi Chemical Diagnostics Systems Co., Ltd, Tokyo, Japan). Limit of detection (LoD) of 2 µg/g, a limit of quantification (LoQ) of 7 µg/g and an upper measurement limit of 400 µg/g. Multiple cut-offs used (10, 20, 50, 100, 150, 200, 250, 300, 350 and 400 µg haemoglobin / g faeces ***Reference standard:*** colonoscopy
Khan, 2020 ***Aim:*** to assess the diagnostic accuracy of FIT for CRC in symptomatic patients referred by local primary care physicians via the 2-week-wait pathway. Secondary aims were to assess the diagnostic accuracy of FIT in detecting high-risk polyps and to evaluate the impact on FIT results of using digital rectal examination to obtain stool samples. Other results: Cases of colorectal cancer presenting in patients with f-Hb <10 µg/g reported on Cunin´s study.	Single-centre prospective and blinded study undertaken at East Sussex Healthcare NHS Trust, England, UK. The period of study was from August 2017 to August 2018.	Patients with bowel symptoms, referred via the 2-week-wait CCR pathway.	72 patients were excluded. 45 (63%) were deemed unfit for further investigation, 17 (24%) declined further investigation, nine (13%) had not completed investigation at the time of analysis, and one (1%) had no stool for analysis on digital rectal examination.	Enrolled 1000 patients, of these, 928 (92.8%) patients (59.5% female; median age 72) were included in the final analysis. Change in bowel habit 609 (65.6%), Anaemia 189 (20.4%), Intermittent rectal bleeding 94 (10.1%), Weight loss 70 (7.5%), Abdominal pain 69 (7.4%), Abdominal mass 29 (3.1%), Rectal mass 21 (2.3%), FOB test-positive 2 (0.2%).	***Index test:*** HM-JACKarc (Kyowa Medex and Alpha Laboratories, Eastleigh, UK). Minimum and maximum reported values were 0-0 and > 450 µg Hb/g faeces respectively. Cut-off 10 µg Hb/g faeces. ***Reference standard:*** Definitive diagnostic investigations performed depending on the patient's fitness status and willingness. Colonoscopy (68.4%); Colon TC (16.9%); Sigmoidoscopy + Plain CT (14.7%)
Bailey, 2020 ***Aim:*** to evaluate the impact of general practitioner access to FIT and Rapid Colorectal Cancer Diagnosis. Retrospective audit of FIT results, CRC outcomes and resource utilization before and after introduction of FIT in Primary Care. Another info: objective criteria to define different cut-offs based on clinical data. Rule in criteria.	Retrospective Cohort study. Setting: primary care, Nottingham, England, UK. Period of study from November 2017 – December 2018	All patients that were subject of a FIT request between 7th November 2017 and 31st December 2018.	Requests mentioning rectal bleeding were rejected (4.0%). Duplicate requests (1.4%) and patient who did not return their kit within 14 days (9.6%) and kits not suitable for analysis (0.5%).	6747 general practitioner FIT test requests yielded 5733 (89.8%) FIT results, (56% female, mean age 67.4 years) of which 4082 (71.2%) were <4.0 mg Hb/g faeces, 579 (10.1%) were 4.0-9.9 mg Hb/g faeces, 836 (14.6%) were 10.0-149.9 mg Hb/g faeces, and 236 (4.1%) were >150.0 mg Hb/g faeces.	***Index test:*** OC-Sensor™; Eiken Chemical Company, Tokyo, Japan. Multiple cut-offs used (4, 10 and 150 µg haemoglobin / g faeces ***Reference standard:*** Various datasets were used to evaluate diagnoses of CRC previously recorded with a censor date of 31st December 2018. NUH Trust data, electronic patient records and NUhCLEUS data were used for cross-checking and data validation.

Author & Objective	Design & Setting	Inclusion criteria	Exclusion criteria	Study population	Index and reference test
Hogberg, Nov 2020 ***Aim:*** To evaluate the usefulness of qualitative FITs requested for symptomatic patients in primary care, alone and combined with findings of anaemia and thrombocytosis, in the diagnosis of CRC. Another information: calculated the accuracy of FIT using one and two years as follow up period	Population-based cohort study using electronic health records and data from the Swedish Cancer Register. Five Swedish regions (Jämtland Härjedalen, Kronoberg, Västerbotten, Västernorrland and Örebro; Period of study from 1 January 2015 to 31 December 2015.	Patients aged ≥18 years, for whom FITs had been requested and test results had been registered in primary care in the study period.	Not reported	15789 patients with three FIT samples (60.9% female; median age 65 years); 304 (1.9%) were diagnosed with CRC within 2 years.	***Index test:*** Actim Fecal Blood (Oy Medix Biochemica AB, Finland) in Örebro; cut-off: 25–50 µg/g faeces. Analyz FOB (LumiraDx AB, Sweden) in Kronoberg, Västerbotten, and Västernorrland; cut-off level: 2 µg/g faeces. Chemtrue FOB Test (Chemtron Biotech Co Ltd, China) in Jämtland Härjedalen; 40 ng/ml faecal solution (µg/g not available). Diaquick FOB (Dialab GmbH, Austria) in Kronoberg; cut-off 5 µg/g faeces. ***Reference standard:*** Swedish Cancer Register
Laszlo, 2020 ***Aim:*** To evaluate the ability of quantitative FIT to rule out colorectal cancer for patients who present to primary care with 'high risk' symptoms defined by national guidelines for urgent referral for suspected cancer (NICE NG12). Another reported data: clinical features and location of tumour in the 15 patients diagnosed with colorectal adenocarcinoma who had f-Hb <10 µg/g.	Prospective multi-centre observational study (24 hospitals in England and 59 general practices in London) between April 2017 and March 2019.	Adult patients with abdominal symptoms that merited an urgent referral to the NG12 CRC pathway referred from primary care.	Patients < 16 years and people were unable to understand instructions. Patient characteristics were similar between the 3596 patients who were included in the analyses and the 1055 who were excluded because their cancer outcome was unknown by the study team.	Recruited: 4676 patients; Included: 3596 (76.9%) patients (Median age 67 years; 53% were female) Of these, 78% had colonoscopy. CRC: 90 (2.5%), 7 (0.2%) had other cancers; 99% were recruited in secondary care. Symptoms: Change of bowel habit 1835 (51%), rectal bleeding 970 (27%), anaemia 684 (19%), abdominal pain 427 (11.9%) and weight loss 312 (8.7%).	***Index test:*** OC-Sensor™; Eiken Chemical Company, Tokyo, Japan. LoD 4 µg/g. Upper analytical limit 200 µg/g. Multiple cut-offs used (4, 6, 10, 20, 50, 80, 100, 120, 150 and 200 µg haemoglobin / g faeces ***Reference standard:*** patient examination reports (colonoscopy 77.7%, colono TC 18.3%, sigmoidoscopy 7.5%, CT 0.1%, other/missing 0.4%) were verified by researchers.

Supplementary Table 2. Results of bivariate meta-regression with covariates.

Covariate	Studies (n)	Sensitivity (95% CI)	*P* Value	Specificity (95% CI)	*P* Value
FIT Brand					
• **OC-Sensor**	8	0.88 (0.81 – 0.95)	0.07	0.84 (0.78 – 0.90)	0.00
• **HM-JACKarc**	7	0.86 (0.78 – 0.94)		0.84 (0.78 – 0.91)	
CRC prevalence					
• **< 3% CRC**	8	0.86 (0.78 – 0.93)	0.01	0.87 (0.82 – 0.92)	0.01
• **≥ 3% CRC**	7	0.89 (0.82 – 0.96)		0.81 (0.74 – 0.88)	
Recruitment					
• **PCF**	9	0.87 (0.80 – 0.94)	0.03	0.85 (0.80 – 0.91)	0.01
• **CU**	6	0.88 (0.80 – 0.95)		0.83 (0.75 – 0.90)	
Reference Standard					
• **Follow-up**	8	0.86 (0.79 – 0.94)	0.02	0.86 (0.81 – 0.91)	0.01
• **Colonoscopy**	7	0.88 (0.81 – 0.95)		0.82 (0.75 – 0.89)	

CRC, colorectal cancer; CU, colonoscopy unit; PCF, primary care facility

SUPPLEMENTARY FIGURE LEGENDS AND FOOTNOTES

Supplementary Figure 1. Hierarchical summary receiver-operating characteristic curves for colorectal cancer detection by cut-off value using all available studies (*top*) and after removing outliers (*bottom*).

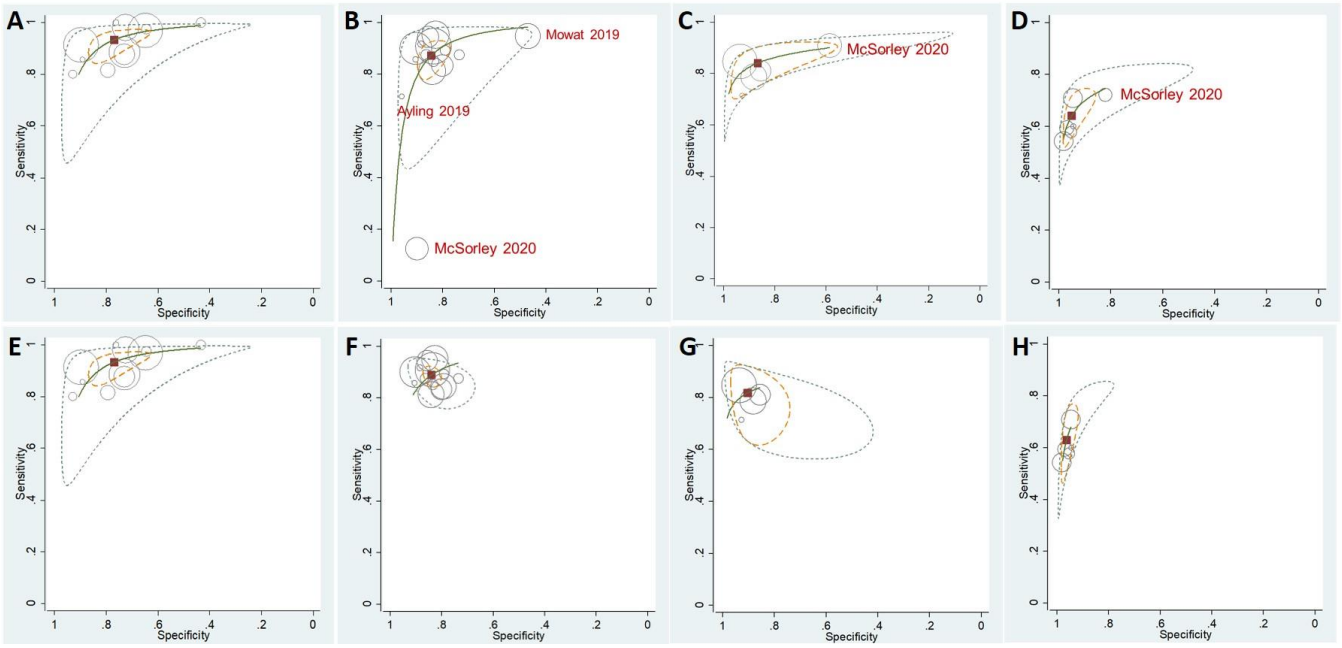
(A & E) cut-off value at limit of detection; (B & F) cut-off value at 10 µg Hb/g faeces; (C & G) cut-off value at 20 µg Hb/g faeces; (D & H) cut-off value at 150 µg Hb/g faeces.

Supplementary Figure 2. Fagan nomograms used to calculate post-test probabilities based on different scenarios defined by colorectal cancer prevalence and faecal immunochemical test cut-off value.

A-E: These scenarios are defined by colorectal cancer prevalence of 1%,2%,3%,4% and 5% respectively and faecal immunochemical test for haemoglobin accuracy at 10 µg Hb/g faeces; H-J: These scenarios are defined by colorectal cancer prevalence of 1%,2%,3%,4% and 5% respectively and faecal immunochemical test for haemoglobin accuracy at 20 µg Hb/g faeces; K-O These scenarios are defined by colorectal cancer prevalence of 1%,2%,3%,4% and 5% respectively and faecal immunochemical test for haemoglobin accuracy at 150 µg Hb/g faeces

Supplementary Figure 3. Funnel scatterplot to evaluate publication bias for studies using different cut-off values to detect colorectal cancer.

Symmetry suggests absence of publication bias. OR diagnostic odds ratio. (A) cut-off value at limit of detection; (B) cut-off value at 10 µg Hb/g faeces; (C) cut-off value at 20 µg Hb/g faeces; (D) cut-off value at 150 µg Hb/g faeces.


A
B
Mowat 2019
Ayling 2019
McSorley 2020
C
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D
McSorley 2020
E
F
G
H
Sensitivity
Specificity
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.2
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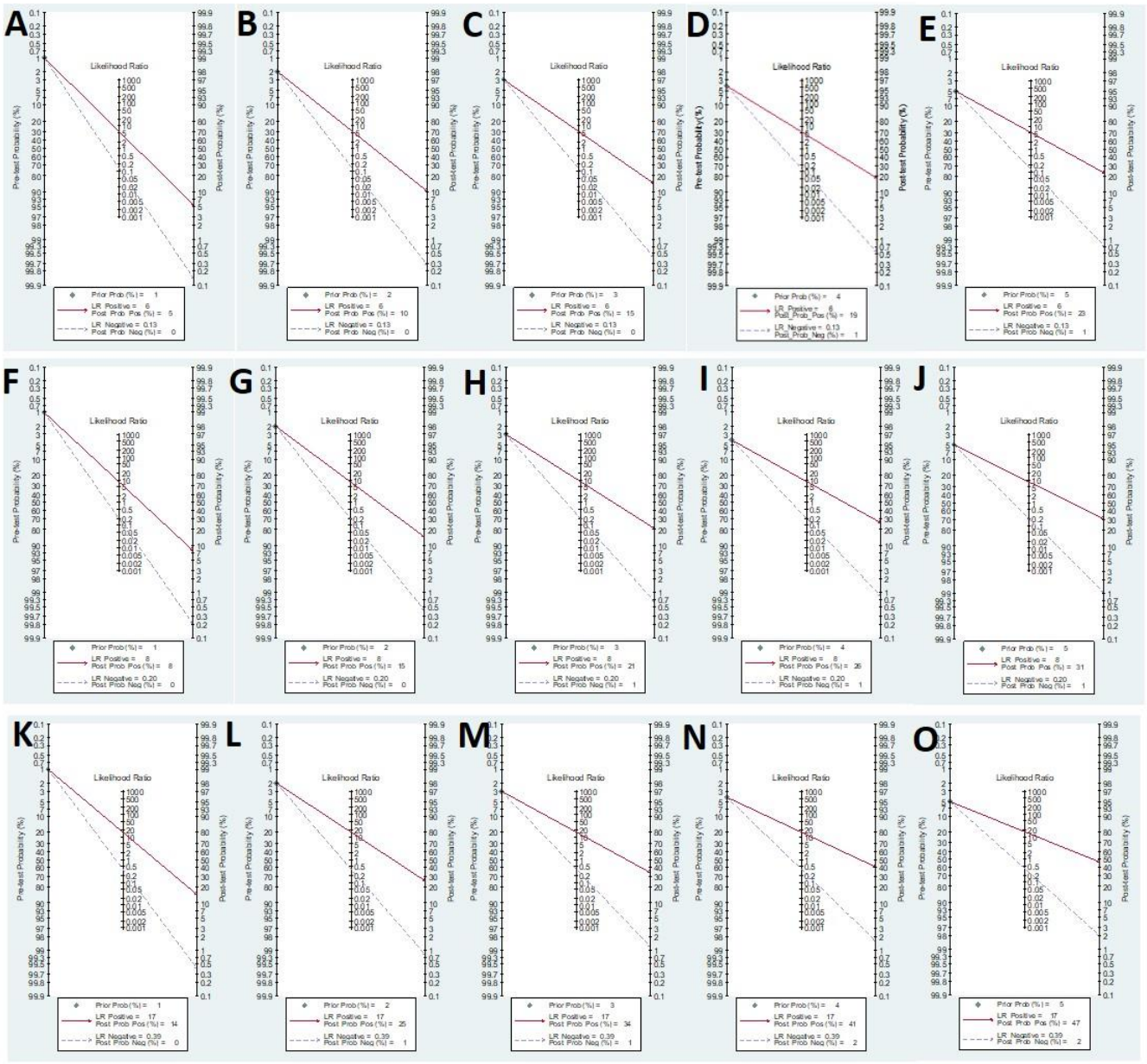
.8
1


A
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I
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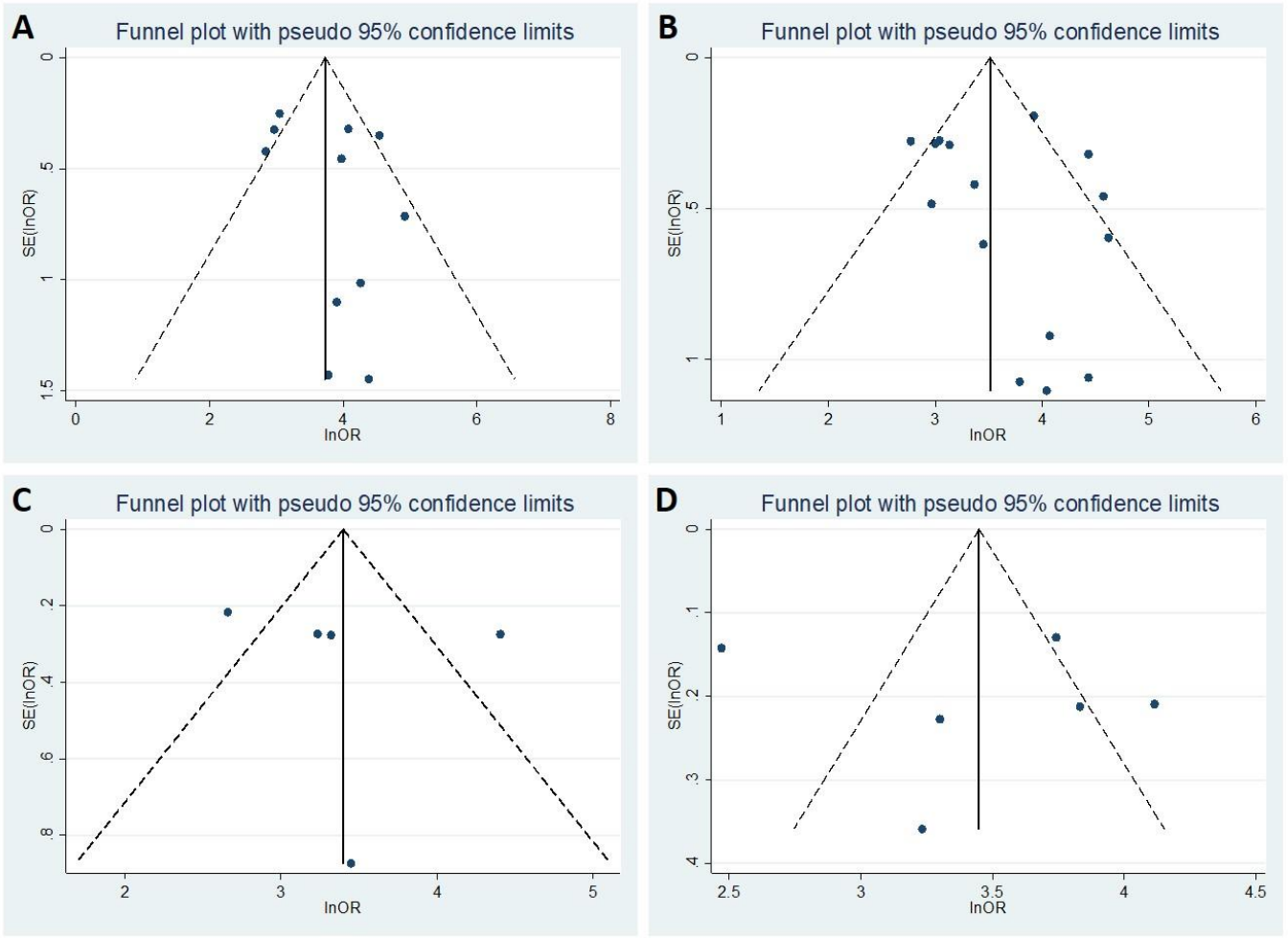
K
L
M
N
O
Likelihood Ratio
Pre-test Probability (%)
Post-test Probability (%)


A
Funnel plot with pseudo 95% confidence limits
SE(lnOR)
lnOR
B
Funnel plot with pseudo 95% confidence limits
SE(lnOR)
lnOR
C
Funnel plot with pseudo 95% confidence limits
SE(lnOR)
lnOR
D
Funnel plot with pseudo 95% confidence limits
SE(lnOR)
lnOR

Text S1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 & Appendix1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 Figure 1 Appendix 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 Appendix 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 -10 & Table 1 & Supplementary table 1-2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	10 & Figure 2 &
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 & Appendix 3 & Supplementary Table 2 & Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2 & Supplementary Table 2 & Figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

DISCUSIÓN

Resumen de hallazgos principales

Este trabajo confirma que el test de SOH-i cuantitativo posee una sensibilidad elevada y una especificidad moderada para la detección de CCR en pacientes con síntomas digestivos, al igual que sucede en sujetos asintomáticos. Esta precisión se mantiene también en el entorno específico de atención primaria independientemente de la sintomatología o las características demográficas de cada paciente, si bien algunos resultados orientan a que la presencia de determinadas formas de presentación podría estar asociada a una mayor sensibilidad de SOH-i para detectar CCR.

Por otra parte, los pacientes con síntomas digestivos con una colonoscopia sin CCR, que presentan una concentración de Hb-f por encima del umbral de 20 μg Hb/g de heces o niveles séricos de CEA superiores a 3 ng/dl, no mostraron un mayor riesgo de ser diagnosticados o fallecer por tumores localizados en el tracto gastrointestinal proximal al colon. Sin embargo, presentan tasas más elevadas de CCR de intervalo en comparación con aquellos sujetos sin alteraciones en cualquiera de estos biomarcadores.

Precisión de SOH-i en pacientes con síntomas en el entorno de atención primaria

El primer metaanálisis confirma que el test de SOH-i cuantitativo posee una elevada precisión para detectar el CCR, y que por lo tanto puede ser útil para identificar aquellos pacientes con síntomas digestivos a los que se debería priorizar la realización de pruebas complementarias adicionales debido a su mayor riesgo de presentar esta neoplasia. Además, el análisis por subgrupos realizado tras la revisión sistemática de la literatura existente sugiere que la sensibilidad de SOH-i para detectar CCR puede ser incluso mayor en la población de pacientes con síntomas digestivos que en el entorno de cribado, independientemente de la prevalencia de CCR.

La mayor parte de estudios incluidos en nuestra revisión utilizaron la marca comercial OC-Sensor®. Con esta marca, el comportamiento óptimo de SOH-i definido a partir del cálculo del área bajo la curva (maximizando la relación entre sensibilidad y especificidad de esta prueba) se obtuvo con el umbral de 20 μg Hb/g de heces.

Por otra parte, tras analizar retrospectivamente la precisión de SOH-i para detectar CCR en datos de práctica clínica real en el entorno de atención primaria, hemos obtenido resultados similares a los de nuestro metaanálisis previo.

Este segundo estudio, confirma la elevada sensibilidad de SOH-i para descartar CCR utilizando un umbral incluso más elevado que el recomendado por NICE (10 μg Hb/g de heces) en el entorno de atención primaria. Así, el uso del punto de corte de 20 μg Hb/g de heces, solamente condicionaría la pérdida de un único CCR adicional por cada 1000 pacientes evaluados independientemente de características demográficas como la edad o el sexo, mientras que con este umbral sería necesario realizar aproximadamente un 30% menos de colonoscopias de las que serían precisas utilizando el umbral recomendado por NICE, debido al menor porcentaje de falsos positivos resultante de elevar el umbral escogido.

Finalmente, nuestros resultados del segundo metaanálisis confirman que el test de SOH-i es la prueba de elección para evaluar pacientes que consultan a su médico de atención primaria en relación con la aparición reciente de síntomas gastrointestinales sugestivos de patología en el tracto GI bajo. La elevada sensibilidad de esta prueba para detectar CCR utilizando el umbral de 10 μg Hb / g de heces, implica que cualquier resultado por debajo de ese umbral descarta la presencia de CCR con una probabilidad de 99.6%-99.9%, para el rango de prevalencia de CCR más comúnmente notificado en atención primaria (1-5%) e iguala el riesgo de presentar un falso negativo al riesgo de sufrir un efecto secundario grave durante la realización de la colonoscopia.

Al igual que en el análisis retrospectivo de los datos en práctica real de nuestro entorno, este metaanálisis de estudios que analizan la precisión de SOH-i en el entorno específico de atención primaria también refleja la pequeña diferencia de sensibilidad existente cuando usamos los umbrales de 10 μg Hb y 20 μg Hb por g de heces. Para terminar, la elevada sensibilidad de SOH-i permite que más del 60% de CCR sean identificados utilizando una f-Hb umbral de 150 μg Hb / g de heces.

Pronóstico de los pacientes con SOH-i positivo y una colonoscopia sin CCR

El seguimiento de aquellos pacientes con síntomas digestivos que no fueron diagnosticados de CCR tras realizar una colonoscopia completa de calidad, nos permitió comprobar que independientemente del resultado de SOH-i, estos sujetos poseen un riesgo elevado de ser diagnosticados de diferentes tipos de cáncer a lo largo de los siguientes años.

La presencia de una concentración de Hb-f por encima del umbral de 20 μg Hb/g de heces únicamente estuvo asociada al diagnóstico de CCR, sin que existiesen diferencias significativas en la incidencia o mortalidad por otro tipo de neoplasias del tracto gastrointestinal. Las únicas variables asociadas al diagnóstico de una neoplasia en el tracto gastrointestinal alto fueron la edad avanzada y la presencia de anemia, por lo que sólo en este contexto podría recomendarse continuar el estudio mediante la realización de una esófago-gastroscopia.

En cambio, la elevación de los niveles séricos de CEA en los pacientes con síntomas si estuvo asociada a un incremento significativo del riesgo de detección y muerte por neoplasias localizadas fuera del tracto gastrointestinal y por CCR, independientemente del resultado de SOH-i, sin que existiesen diferencias en el caso de la incidencia o mortalidad por tumores del tracto gastrointestinal alto.

A pesar de ello, la baja sensibilidad y especificidad para detectar neoplasias de cualquier tipo que ha mostrado este biomarcador en nuestra cohorte, unido a la baja incidencia de este tipo de patología en la población de pacientes con síntomas, desaconsejan la determinación sistemática del CEA no sólo en los pacientes sin síntomas como análisis rutinario "de salud", sino también en el contexto de la evaluación de síntomas de nueva aparición.

Fortalezas y debilidades de nuestro trabajo

Precisión de SOH-i en pacientes con síntomas en el entorno de atención primaria

Nuestra revisión sistemática inicial tuvo como resultado un escaso número de estudios con diferencias metodológicas relevantes. La diversidad en el espectro clínico de los pacientes estudiados y las diferentes marcas comerciales de SOH-i empleadas en estos trabajos pueden explicar la elevada heterogeneidad detectada durante la realización de nuestro primer metaanálisis.

Tampoco podemos asegurar a partir de esta primera revisión cual será el comportamiento de SOH-i en el entorno de atención primaria, ya que excepto un trabajo [86], todos los estudios incluidos utilizaban pacientes reclutados en unidades de endoscopia, donde el espectro clínico de los pacientes es diferente.

Este escaso número de trabajos ha impedido el control de todas esas variables mediante procedimientos como la meta-regresión o la realización de análisis por subgrupos, lo que constituye la principal debilidad de este primer metaanálisis. Sin embargo, el número de estudios que utilizaban OC-Sensor® permitió valorar la influencia de la presencia de síntomas de alto riesgo y la prevalencia de CCR sobre la precisión de SOH-i al menos en esa marca comercial, lo cual era nuestro principal objetivo.

Este limitado número de estudios también ha comprometido la posibilidad de usar el modelo bivariante para calcular los estimadores de sensibilidad y especificidad de SOH-i. Se ha descrito que el uso de otros modelos de efectos aleatorios como el de DerSimonian no ofrece resultados tan robustos [192]. A pesar de ello, cuando ha sido posible hemos aplicado ambos modelos para estimar la precisión de SOH-i sin que existiesen diferencias significativas entre ambos resultados.

Algunas de estas limitaciones han sido solventadas tras la realización de una segunda revisión sistemática, centrada en el entorno específico de atención primaria. En este nuevo trabajo, se ha identificado un elevado número de estudios que permite realizar un análisis menos sesgado de la precisión de SOH-i para detectar CCR en aquellos sujetos que consultan por la aparición de síntomas digestivos en su centro de salud, donde el uso de SOH-i como herramienta de priorización tendría mayor impacto en la optimización del uso de recursos [85], especialmente en aquellas regiones con una capacidad limitada para realizar colonoscopias o en circunstancias como la actual, en el contexto de la pandemia por COVID-19 [193].

Sin embargo, no es sencillo obtener información fiable en este entorno debido a las limitaciones metodológicas que supone la investigación en ese tipo de pacientes. Aunque la precisión de SOH-i se ha evaluado en un gran número de cohortes formadas por pacientes de atención primaria desde la publicación de nuestra revisión sistemática inicial, algunos estudios son retrospectivos y/o carecen de un estándar de oro fiable como la colonoscopia [86,170-174,177,179-181,183-185,187,187,189,190].

Muchas de estas cohortes carecen de un periodo de monitorización prolongado que permita confirmar la ausencia de un CCR en aquellos sujetos con un resultado de SOH-i por debajo del umbral escogido, por lo que poseen un riesgo elevado de presentar un sesgo de verificación diagnóstica. Diversos metaanálisis han usado la colonoscopia y el seguimiento de un mínimo de dos años como único "estándar de oro" fiable para valorar la presencia de CCR. La elección de este periodo de tiempo mínimamente aceptable es coherente con la definición de cáncer post-colonoscopia en Reino Unido [194].

Por otra parte, hay que destacar que esta definición se ha empleado en el entorno de cribado. En cambio, un trabajo que evaluó la precisión de SOH-i en entorno de la

evaluación de síntomas de nueva aparición en atención primaria comparó diferentes periodos de seguimiento (3, 6 y 12 meses) sin encontrar diferencias significativas en la precisión calculada de SOH-i para cada uno de los mismos. Los autores explican que cualquier CCR que provoque síntomas debería ser diagnosticado en los siguientes tres meses independientemente de que exista un resultado negativo de SOH-i, ya que en ese tiempo la progresión tumoral, la persistencia de síntomas o el desarrollo de complicaciones provocarían la realización de estudios que posibilitarían el diagnóstico [170].

Un segundo tipo de estudios en esta revisión sistemática, utilizan la colonoscopia como estándar de oro [175,176,178,182,186,188,191]. El problema de estos trabajos es que, a pesar de disponer de una prueba de referencia adecuada, han reclutado sus pacientes en unidades de colonoscopia. Así, aunque todos los pacientes que integran la cohorte estudiada hayan sido derivados por médicos de atención primaria, está claro que sólo aquellos pacientes que más preocupan al médico de cabecera serán explorados por medio de una prueba molesta e invasiva como la colonoscopia. Por ese motivo, estas cohortes poseen un elevado riesgo de sesgo de selección ya que tendrán un menor porcentaje de síntomas vagos e inespecíficos [119], mientras que aquellas molestias más relacionadas con estadios avanzados de CCR estarán sobrerrepresentadas.

A pesar de estos problemas, la principal fortaleza de nuestros resultados se encuentra en su consistencia. Tanto las estimaciones de la precisión de SOH-i para detectar CCR estimadas en los dos metaanálisis comentados previamente, como nuestro estudio retrospectivo de los datos de práctica real en el entorno de atención primaria de dos provincias españolas sugieren que SOH-i posee una precisión suficiente para estratificar el riesgo de pacientes con síntomas digestivos de nueva aparición en el entorno de atención primaria.

En este estudio retrospectivo, se analiza la precisión de SOH-i en una enorme muestra de pacientes, obtenida a partir de datos reales de práctica clínica en el centro de salud, que es donde surge la sospecha inicial de un CCR subyacente.

La principal debilidad de este análisis, además de su carácter retrospectivo, es la ausencia de colonoscopia como estándar oro de referencia, como se ha comentado previamente. Se ha descrito que la sensibilidad en los trabajos que realizan el seguimiento de los pacientes con un resultado negativo de SOH-i por medio de los registros clínicos puede estar sobreestimada. Sin embargo, este sesgo afecta principalmente a los estudios que limitan su seguimiento a sólo un año [195], y un reciente metaanálisis ha estimado que la precisión de SOH-i no es distinta en los trabajos que usan seguimientos de dos años por medio de registros clínicos, con respecto a los que utilizan la colonoscopia como prueba de referencia [196].

Otra limitación de este análisis retrospectivo es que sólo incluye como objetivo aquellos casos de CCR que requieren hospitalización. Este dato no es equivalente a la incidencia de CCR en la población, ya que determinadas lesiones “in situ” no estarían recogidas en el CMBD. El efecto de este sesgo es impredecible ya que, por una parte, podría conducir hacia la sobreestimación de la sensibilidad de SOH-i debido a que un número indeterminado de supuestos “verdaderos negativos” podrían constituir en realidad falsos negativos, al existir en realidad un CCR resecable endoscópicamente que no requiere ingreso posterior. Sin embargo, el efecto podría ser el contrario. La sensibilidad podría estar infraestimada, ya que se ha descrito que la concentración de Hb-f se correlaciona con la severidad de las lesiones subyacentes [120], por lo que un número indeterminado de “falsos positivos” podrían ser en realidad verdaderos positivos por estar en relación también con este tipo de lesiones resecables endoscópicamente.

Nuestros datos ofrecen información contradictoria sobre la influencia de la forma de presentación sobre la precisión de SOH-i. El primer metaanálisis refleja que la sensibilidad de SOH-i para detectar CCR es mayor en las cohortes con un mayor porcentaje de síntomas independientemente de la prevalencia, mientras que nuestro análisis retrospectivo de datos de práctica real no ha mostrado diferencias en función del motivo de solicitud de SOH-i (seguimiento de patología conocida, estudio de síntomas o cribado oportunista). Hay que resaltar que la información de las bases de datos analizadas en nuestro estudio retrospectivo no aporta detalles sobre el espectro clínico de los pacientes. Así, la presencia de síntomas inespecíficos gastrointestinales, comunes en la población y que podrían estar asociados a CCR no se comunica muchas veces al médico [122], y está incluso peor detallada en los registros clínicos por lo que basarse en el motivo de solicitud de SOH-i para categorizar a un paciente como asintomático implica un elevado riesgo de sesgo de información.

Un objetivo secundario de nuestra primera revisión sistemática fue conocer si todas las marcas comerciales podrían ofrecer la misma precisión en la detección de CCR. Aunque no hemos podido comparar en ninguno de los dos metaanálisis realizados el comportamiento de las principales marcas comerciales de SOH-i, muchos de los trabajos llevados a cabo en atención primaria han utilizado OC-Sensor® y HM-JACKarc® con el mismo punto de corte (10 μg Hb/g de heces) sin que se aprecien diferencias relevantes entre ambas. Esto puede explicarse porque, aunque estas marcas tienen diferentes límites de detección de Hb-f (2 μg Hb/g de heces y 4 μg Hb/g de heces en el caso de HM-JACKarc® y OC-Sensor® respectivamente), la correlación entre las medidas llevadas a cabo por ambas aumenta a medida que usamos un punto de corte más elevado, alcanzando el 91.7% en el umbral de 10 μg Hb/g de heces en el único

estudio que las ha comparado directamente en el entorno de pacientes con síntomas [197].

Además, aproximadamente el 90% de los CCR estarán asociados a concentraciones de Hb-f superiores a ese umbral, por lo que pequeñas diferencias de precisión entre dispositivos no se traducen en cambios clínicamente relevantes. Más aún, nuestra segunda revisión sistemática muestra que más del 60% de los CCR están asociados a concentraciones de Hb-f por encima de 150 μg Hb/g de heces. Esto explica que en un estudio que compara varias marcas de SOH-i cualitativas que usan puntos de corte entre 2 μg Hb/g de heces y 50 μg Hb/g de heces no mostrara tampoco diferencias de precisión relevantes entre ellas [190].

Llegados a este punto, merece la pena reconsiderar la necesidad de utilizar puntos de corte diferentes en función de las características demográficas de los pacientes o el tipo de síntomas. Nuestro análisis retrospectivo de datos en práctica real apoya el uso de un único umbral independientemente del sexo o la edad al igual que un metaanálisis reciente [196], y probablemente las elevadas concentraciones de Hb-f asociadas a la mayor parte de CCR contribuyan a justificar esta postura.

Existe menos información respecto a la necesidad de utilizar más de una muestra fecal en la evaluación de estos pacientes. Sólo dos trabajos incluidos en el primer metaanálisis examinaron la utilidad de estudiar la concentración de Hb-f en una o dos muestras fecales para detectar neoplasia avanzada (CCR & adenoma avanzado) mediante test de SOH-i cuantitativos en cohortes formadas por pacientes a los que se realiza una colonoscopia para estudio de síntomas digestivos o como seguimiento tras la realización de una polipectomía previa [111,133]. Aunque estos dos trabajos utilizan dos marcas comerciales diferentes (HM-JACKarc® y FOB-Gold®) demostraron que la precisión diagnóstica de analizar dos muestras fecales con el umbral de 20 μg Hb/g de

heces era equivalente a la del análisis de una única muestra usando un punto de corte de 10 μg Hb/g de heces. Esta información puede ser útil para valorar el mejor modo de utilizar el test de SOH-i cuando el objetivo es detectar cualquier LCS y no sólo CCR.

En el entorno de atención primaria, es relevante no sólo conocer la precisión de esta prueba para identificar CCR sino cualquier LCS. A pesar de que varios trabajos de los incluidos en esta revisión ofrecieron información sobre este punto, existieron importantes diferencias en la definición de LCS, lo que impide obtener conclusiones precisas. Para algunos autores, la definición de LCS está limitada a la presencia de CCR, adenoma de alto riesgo o enfermedad inflamatoria intestinal, mientras que otros incluyen cualquier tipo de colitis en la definición. El concepto más amplio de LCS fue el usado por Cubiella et al [104], incluyendo en el mismo CCR, adenoma avanzado, poliposis, colitis, pólipos mayores de 9 mm, enfermedad diverticular complicada, úlcera de colon y angiodisplasia sangrante. En cualquier caso, la sensibilidad de SOH-i para detectar LCS disminuyó considerablemente con respecto a la que tiene como objetivo el CCR sin que se apreciasen cambios relevantes en la especificidad de esta prueba.

Pronóstico de los pacientes con SOH-i positivo y una colonoscopia sin CCR

Nuestro trabajo es el primero que ofrece información sobre la utilidad de determinar la concentración de Hb-f y el nivel sérico de CEA para valorar el pronóstico de aquellos pacientes con síntomas de nueva aparición en quienes se ha descartado la presencia de CCR de manera fiable (por medio de una colonoscopia hasta ciego, preparada correctamente).

Una limitación de este trabajo es la ausencia de un protocolo de seguimiento. Los pacientes fueron seguidos por sus respectivos médicos que programaron la realización de revisiones clínicas o pruebas complementarias en función de su propio criterio. Esto podría dar lugar a que la incidencia acumulada de cualquier tipo de neoplasia fuese

mayor a la estimada en este estudio, sin embargo, es poco probable que un cáncer de cualquier tipo que origine síntomas no produzca complicaciones que lleven al diagnóstico dentro del periodo de monitorización descrito, que es tan prolongado que permite que podamos ofrecer una perspectiva fiable del futuro de estos pacientes.

En segundo lugar, a pesar del respetable tamaño muestral de este estudio longitudinal y el carácter consecutivo del muestreo, el número de pacientes evaluados podría limitar nuestras conclusiones. La baja incidencia en la población general de neoplasias de esófago y estómago dificultan poder obtener en esta cohorte, una potencia estadística que permita encontrar diferencias significativas en la incidencia de tumores gastrointestinales del tracto superior entre los subgrupos definidos por la concentración de Hb-f (</≥20 μg Hb/g de heces) o el CEA (≤/> 3 ng/dL).

Sin embargo, la incidencia y la mortalidad por cáncer en la población de pacientes con síntomas que muestran una concentración de Hb-f por debajo del umbral recomendado por NICE y un nivel sérico de CEA dentro del rango considerado normal, ha sido muy elevada en esta muestra. Esto implicaría que, aunque la presencia de un nivel de CEA elevado suponga un mayor riesgo de neoplasia, no pueda utilizarse como criterio de limitar la realización de pruebas adicionales para la evaluación de síntomas de nueva aparición. Esto hace poco probable que un hipotético estudio de tamaño muestral superior modificara nuestra percepción sobre el uso limitado que tienen estos biomarcadores en el seguimiento de pacientes con síntomas a los que se descarta un CCR mediante colonoscopia.

C**omparación con la literatura existente**

Precisión de SOH-i en pacientes con síntomas en el entorno de atención primaria

Las revisiones sistemáticas realizadas confirman la elevada precisión de SOH-i para detectar CCR mostrada en metaanálisis previos [67,106].

Además, nuestro trabajo presenta datos inconsistentes sobre la influencia del espectro clínico de los pacientes en la precisión de SOH-i. Esta hipótesis está apoyada por un estudio donde se estratificó una cohorte de pacientes a los que se solicita una colonoscopia para estudio de síntomas en función del espectro clínico (alto o bajo riesgo de CCR) [198]. Este trabajo también mostraría que la sensibilidad de SOH-i para detectar CCR es diferente en ambos grupos de pacientes.

A pesar de ello, la revisión sistemática de los estudios realizados específicamente en pacientes del entorno de atención primaria, con un perfil más variado de síntomas que el apreciado en unidades de endoscopia digestiva donde sería esperable un mayor porcentaje de pacientes con estadios avanzados de la enfermedad asociados a concentraciones de Hb-f más elevadas, también muestra una precisión diagnóstica de SOH-i equiparable a la descrita en estudios previos confirmando que es el test de elección en atención primaria.

Estos valores son similares también a los descritos en el entorno de cribado en un metaanálisis realizado por Lee et al (sensibilidad de 89%; IC95% 80-95%) [57]. Sin embargo, en ese trabajo se calcula un estimador común para nueve trabajos que estudian puntos de corte variables, aunque siempre menores de 20 μg Hb/g de heces.

Toda esta información es consistente con la utilidad de SOH-i para la estratificación de pacientes con síntomas digestivos. La importancia de la necesidad de transmitir de esta idea queda demostrada por la información aportada por una reciente

revisión sistemática, que mostró cómo pocos países recomiendan el uso de SOH-i en el entorno de atención primaria como ayuda a la valoración clínica de los pacientes con síntomas de nueva aparición, probablemente porque todos los trabajos valoran esta prueba en un entorno diferente que la atención especializada se han llevado a cabo en los últimos tres años, habiendo sido incluidos en nuestra segunda revisión sistemática, publicada pocos meses antes de la redacción de este manuscrito [199].

Pronóstico de los pacientes con SOH-i positivo y una colonoscopia sin CCR

Como se ha comentado previamente, la información sobre el pronóstico de pacientes con Hb-f detectable a los que se realiza una colonoscopia que descarta CCR únicamente está disponible dentro del entorno de cribado [138,200]. Sin embargo, la falta de especificidad de los síntomas y la existencia de literatura donde se muestra que lesiones proximales al colon pueden dar lugar a la presencia de Hb-f detectable [139,140,141,201-203], hace que sea razonable monitorizar este tipo de pacientes para descartar que otro tipo de patología en el tracto gastrointestinal pueda estar en relación con un porcentaje de falsos positivos además de otras causas localizadas en el colon [204,205].

A pesar de ello, nuestros resultados no han mostrado que existan diferencias en la incidencia o en la mortalidad por TTGI distintos al propio CCR en función de la concentración de Hb-f a lo largo de un seguimiento prolongado. En este sentido es necesario resaltar que la incidencia de CCR en el periodo de seguimiento de nuestro estudio entra dentro de lo esperado si tenemos en cuenta la información disponible en la literatura de la incidencia de cáncer post-colonoscopia [206].

Sin embargo, la presencia de una concentración de Hb-f detectable se ha relacionado con un aumento de mortalidad por causas no relacionadas con CRC o incluso con TTGI de cualquier tipo [207]. En ese estudio los autores argumentan que

esto podría estar en relación con la presencia de inflamación subclínica en el colon relacionada con estado inflamatorio generalizado. Aunque nosotros no encontramos esa asociación, el umbral utilizado en nuestro trabajo es mucho menor al de 80 μg Hb/g de heces empleado por Libby et al.

Es interesante resaltar que un estudio reciente concluyó que la realización de un cribado de cáncer gástrico mediante esófago-gastroscopia podría ser coste-efectivo en caso de combinarse con las colonoscopias de cribado en aquellas poblaciones con un riesgo de cáncer gástrico mayor de 1/10,000 [208]. Dada la elevada incidencia de cáncer gástrico, independientemente de la concentración de Hb-f en nuestro estudio, podría valorarse la utilidad de realizar un estudio del tracto gastrointestinal alto en todos los pacientes a los que se realice una colonoscopia para el estudio de síntomas digestivos.

Con respecto a la utilidad del CEA en estos pacientes, nuestro trabajo constata que este biomarcador está principalmente asociado al CCR. Incluso seleccionando aquellos sujetos con síntomas y una colonoscopia que descarta inicialmente la presencia de CCR, el único riesgo que aumenta de forma significativa en aquellos sujetos con niveles de CEA elevados es precisamente el de presentar un CCR post-colonoscopia (cáncer de intervalo).

Este biomarcador mostró una baja precisión para detectar CCR en sujetos asintomáticos [146]. Sin embargo en un estudio se demostró que pacientes con riesgo medio y niveles de CEA elevados deberían ser investigados con pruebas complementarias adicionales, ya que el 9% presentan algún tipo de neoplasia en ese momento y un 7% adicional es diagnosticado de algún tipo de patología maligna durante el seguimiento [145]. Los resultados de este trabajo pueden estar en relación con un sesgo de selección ya que, a pesar de ser un trabajo en pacientes asintomáticos, el motivo por el que se solicita el CEA en estos pacientes puede estar en relación con la

elevada incidencia de cáncer en esta cohorte. A pesar de ello, estos resultados pueden ser consistentes con nuestro trabajo: el 13% de los pacientes con síntomas digestivos y niveles de CEA elevados presentaría algún tipo de cáncer durante el seguimiento, y aproximadamente la mitad de los pacientes serían diagnosticados el primer año de monitorización.

El punto de corte de CEA más frecuentemente utilizado es el de 5 ng/mL, aunque se ha recomendado utilizar un umbral de 10 ng/mL en el seguimiento de pacientes diagnosticados de CCR tras la realización de cirugía [209]. En nuestro estudio utilizamos un umbral menor, ya que nuestra intención fue evaluar el CEA como herramienta de triaje de un grupo de patologías que se beneficiarían de un diagnóstico precoz.

A pesar de que un trabajo previo ha diseñado un protocolo diagnostico para saber qué pruebas complementarias llevar a cabo en un paciente con niveles elevados de CEA [142], nuestros datos revelan que sólo un tercio de los pacientes con anemia y la mitad de los pacientes sin anemia de nuestra cohorte que serían posteriormente diagnosticados de algún tipo de cáncer, presentan niveles de CEA > 3 ng/mL. Por este motivo, la determinación de este marcador tumoral en un paciente con síntomas debe abandonarse ya que un resultado negativo puede dar lugar a una falsa sensación de seguridad que no se corresponde con la elevada incidencia de cáncer en el grupo de pacientes con síntomas y niveles de CEA por debajo de este punto de corte.

PERSPECTIVAS DE FUTURO

Efecto en el uso de recursos sanitarios y el pronóstico del CCR

Es previsible que el uso de SOH-i en pacientes con síntomas digestivos traiga consigo el diagnóstico precoz de un subgrupo de pacientes, que a pesar de presentar síntomas inespecíficos que no justificarían la realización de una colonoscopia fuera del periodo ordinario de lista de espera, poseen un elevado riesgo de CCR. Por otra parte, también se espera la reducción del número de colonoscopias sin alteraciones [177,183].

Un reciente estudio retrospectivo llevado a cabo en Taiwan, ha mostrado como el riesgo de muerte de los pacientes diagnosticados de CCR aumenta significativamente cuando el tiempo entre el diagnóstico y el tratamiento es superior a 30 días (HR 1.51; IC 95% 1.43-1.59) [210]. Basándose en estos datos, el conocimiento de la precisión de SOH-i en pacientes sintomáticos [186], y tomando la información existente en Reino Unido sobre incidencia, supervivencia y tiempos de espera habituales en el manejo del CCR entre los años 2008 y 2017, se diseñó un modelo para estimar el impacto del uso de SOH-i en la reducción de la demora diagnóstica del CCR durante la pandemia COVID-19. Este modelo, que estimaba sobre 11,266 pacientes diagnosticados de CCR una mortalidad atribuible a retrasos de 2, 6 y 12 meses de 653, 1419 y 2250 pacientes respectivamente, mostró que el 89% de esas muertes podrían evitarse mediante la priorización de aquellos pacientes que presentaban una concentración de Hb-f mayor o igual a 10 μg Hb/g de heces, a la vez que se reducía el uso de colonoscopias de manera inmediata en más del 80% [193].

Desde el punto de vista de los costes, también se ha desarrollado un modelo que tiene en cuenta el balance de años ajustados por calidad de vida con tres estrategias: a) priorización con SOH-i, b) priorización con SOH basada en métodos químicos y c) realización de colonoscopia a todos los pacientes con síntomas concluyendo que el uso de SOH-i era más coste efectivo que el uso de SOH basado en métodos químicos y

similar al uso de colonoscopia.

A pesar de que el uso de SOH-i puede suponer un ahorro de costes, es preciso demostrar que también supone una mejora en el pronóstico de los pacientes. Hasta la fecha, un estudio retrospectivo realizado en nuestro entorno ha mostrado que los pacientes con CCR diagnosticados tras un resultado positivo en SOH-i tienen una supervivencia a los tres años significativamente mayor que aquellos que tuvieron un falso negativo o no habían sido diagnosticados a través del uso de SOH-i (HR 1.50; IC95% 1.22-1.84) [211].

Se presupone que la causa de esta mejoría del pronóstico está en relación con una menor demora en el diagnóstico. Sin embargo, un tercio de los pacientes no tenían registrado el motivo de solicitud de SOH-i por lo que podrían haber sido sometidos a cribado oportunista y otro estudio retrospectivo de 563 pacientes no mostró los mismos resultados [212]. En este trabajo, el uso de SOH-i no supuso un ahorro de tiempo invertido en el diagnóstico ni una mejora en la supervivencia. Por todo ello, son precisos más estudios con carácter prospectivo que permitan aclarar cuál es la influencia de SOH-i sobre el pronóstico de los pacientes que consultan por la aparición de síntomas digestivos en atención primaria.

Áreas de mejora

Una cuestión relevante es la planificación de una estrategia que permita rescatar los pacientes con un resultado falso negativo de SOH-i.

Existen motivos para pensar que esto no debería suponer un problema de elevada magnitud. Por una parte, es previsible que pocos sujetos, aproximadamente dos personas de cada 1000 evaluadas con SOH-i, presenten un falso negativo en un entorno de prevalencia de 3% de CCR. Además, estos pacientes han consultado por síntomas que en caso de estar relacionados con la existencia de un CCR no mejorarán, requiriendo nuevas consultas que harán posible el diagnóstico [213].

La estrategia más sencilla es disminuir el punto de corte escogido. Sin embargo, esto sólo es factible en países desarrollados con un gran número de recursos destinados a la salud y puede ser contraproducente ya que el desequilibrio entre la capacidad de realizar colonoscopias y el porcentaje de falsos positivos podría afectar a la mortalidad del CCR o en el mejor de los casos aumentar el gasto sin modificar el pronóstico de estos enfermos, como sucedió tras la implantación de las vías rápidas de diagnóstico en Reino Unido. Por otra parte, incluso si utilizásemos el valor equivalente al límite de detección de Hb de cada marca, todavía existiría un pequeño porcentaje de CCR que se perderían correspondiente a aquellas lesiones que sangran de manera intermitente, o incluso no sangran [214].

Como se comentó previamente, no hay demasiada información sobre el uso de más de una muestra fecal en pacientes con síntomas. Un estudio reciente, realizado en el entorno de cribado, ha demostrado que si se estratifican los pacientes con concentraciones de Hb-f detectables en una primera ronda, pero inferiores a 20 μg Hb/g de heces en tres categorías (0-3.8 μg Hb/g de heces, 3.9-9.9 μg Hb/g de heces y 10.0-19.9 μg Hb/g de heces) la probabilidad de obtener en rondas sucesivas un resultado

superior al umbral de 20 μg Hb/g de heces y ser posteriormente diagnosticado de un adenoma avanzado o un CCR aumenta cuanto mayor es la concentración de Hb-f medida inicialmente [215]. En el entorno de pacientes con síntomas, es difícil imaginar que no se vaya a realizar una colonoscopia a un paciente con síntomas persistentes independientemente del resultado de SOH-i, sin embargo una segunda determinación podría utilizarse para determinar el tiempo de espera en aquellas situaciones donde los recursos sean limitados. Por ejemplo, en otro estudio se propuso solicitar colonoscopia también a aquellos pacientes que acumulasen en la suma de dos muestras una concentración de Hb-f ≥ 20 μg Hb/g de heces [216].

Por todo ello podría ser útil la búsqueda de un biomarcador complementario. Para ello es importante conocer mejor las características de este tipo de lesiones y hasta hoy, la información disponible está limitada a la descripción de 47 lesiones realizada en 5 trabajos recientes [177,187,188,191,217]. Esta descripción es coherente con los trabajos que establecen que las lesiones localizadas en colon derecho justifican un gran porcentaje de falsos negativos [135]. Con respecto a esto se ha propuesto como hipótesis la degradación de la Hb durante el tránsito colónico [218]. Sin embargo, otros trabajos han demostrado que la detección de Hb-f puede estar relacionada con lesiones sangrantes localizadas en tramos proximales al colon.

Una hipótesis alternativa puede ser que las lesiones con sangrado intermitente (o nulo) sean diferentes en su histología. Aunque la mayor parte de CCR se desarrollan a partir de una lesión premaligna (pólipo adenomatoso) a lo largo de un proceso que puede durar una década, aproximadamente un 30% de los CCR se desarrollan por la vía serrada [219]. Este tipo de lesiones han mostrado una menor tendencia al sangrado y una mayor prevalencia en mujeres de edad avanzada, grupo demográfico donde hemos

apreciado un mayor descenso en la sensibilidad de SOH-i [220].

La identificación de un tipo concreto de lesiones cuyo comportamiento dificultase su identificación por medio de SOH-i facilitaría la elección racional de biomarcadores complementarios a esta prueba. Aunque muchos de ellos han sido evaluados en entornos de cribado [221], pocos han demostrado tener utilidad en práctica clínica y ésta ha sido limitada [222].

En el entorno concreto de la evaluación de pacientes con síntomas sólo se ha combinado el test de SOH-i con la determinación de calprotectina fecal y con la forma dimérica del piruvato quinasa (M2-PK), la primera es un producto de los neutrófilos que se ha estudiado como marcador de inflamación intestinal [223], mientras que la segunda puede detectarse en plasma de muchos tumores además de en las heces de varios tumores del tracto gastrointestinal [224].

Pocos estudios han evaluado la posibilidad de mejorar la precisión diagnóstica del test de SOH-i con otros biomarcadores en el entorno de pacientes con síntomas [40,225], y algunos lo han hecho recientemente, en pacientes de atención primaria [175,176,180]. Sin embargo, estos trabajos han mostrado resultados variados debido probablemente a la presencia de heterogeneidad en su diseño.

Por otra parte, el estudio de la microbiota del colon está ofreciendo información muy interesante al relacionar el establecimiento de determinados fenotipos con el desarrollo de CCR [226]. Conocer de forma detallada el papel de la microbiota en la historia natural del CCR podría ofrecernos un biomarcador que identificara los sujetos a riesgo de desarrollar CCR en un momento en el que todavía no existiesen lesiones en la colonoscopia. Además, la combinación con SOH-i podría diferenciar aquellos sujetos en los que existe Hb-f detectable por un CCR de otro tipo de lesiones, mejorando la especificidad del test y limitando todavía más la necesidad de exploraciones invasivas

como la colonoscopia. Más aún, en el seguimiento de nuestra cohorte con síntomas digestivos se ha demostrado una elevada prevalencia de cáncer localizado fuera del tracto gastrointestinal. Otros trabajos han mostrado cómo muchos tumores se presentan por medio de síntomas digestivos sin clara relación entre ambos [227]. Es posible que el estudio de la microbiota pueda aclarar también este aspecto.

Mientras tanto, el uso de modelos predictivos puede mejorar la capacidad de los clínicos para identificar aquellos sujetos con un mayor riesgo de CCR. En el entorno de pacientes con síntomas, el modelo COLONPREDICT [134]**¡Error! Marcador no definido.** o el COLONOFIT [228], han sido desarrollados no sólo para identificar aquellos sujetos de mayor riesgo, sino también para definir un subgrupo de pacientes cuyo riesgo es tan bajo que no estaría indicada la realización de una colonoscopia al ser mayores los riesgos [229]. Estos modelos han sido criticados por su complejidad, que los hace poco prácticos para el uso cotidiano. Otros modelos como el FAST score [105], o el score desarrollado por Rodriguez-Alonso et al [107], son más sencillos pero ambos modelos se basan en la combinación de variables demográficas con la determinación de Hb-f y recientemente se ha criticado que esas variables tuvieran algo que aportar al test de SOH-i [230]. Aunque el estudio que fundamenta las críticas tiene problemas metodológicos [231], nuestros hallazgos también avalan la búsqueda de modelos que no utilicen variables como el sexo o la edad.

CONCLUSIONES

El test de SOH-i posee una elevada precisión para detectar CCR en pacientes con síntomas digestivos, que se ve reducida significativamente cuando el objetivo incluye la detección de otras LCS. El estudio retrospectivo de datos en vida real y el metaanálisis de estudios realizados en el entorno específico de atención primaria confirman que SOH-i mantiene su precisión, y por lo tanto es la prueba de elección para evaluar los pacientes con síntomas de reciente aparición también en ese entorno.

El umbral más eficiente para la estratificación de riesgo es el punto de corte de 20 µg Hb/g de heces independientemente de factores demográficos como edad o sexo. Sin embargo, la forma de presentación del CCR podría influir en la probabilidad de detección por SOH-i independientemente de la prevalencia.

Los pacientes con una concentración de Hb-f ≥ 20 µg Hb/g de heces y una colonoscopia normal tienen un mayor riesgo de ser diagnosticados y fallecer por CCR post-colonoscopia. Aunque la incidencia de otros tumores localizados en el tracto gastrointestinal proximal al colon está aumentada en los pacientes con síntomas digestivos, es independiente de la concentración de Hb-f.

Los pacientes con un nivel sérico de CEA > 3 ng/mL y una colonoscopia normal tienen mayor incidencia y mortalidad de neoplasias localizadas fuera del tracto gastrointestinal y CCR post-colonoscopia. A pesar de ello, la limitada precisión del CEA para detectarlas desaconseja su uso.

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