eman ta zabal zazu

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Evaluación a nivel poblacional del beneficio en salud y costes del programa de detección precoz del cáncer de colon y recto en la CAPV

Tesis Doctoral

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“Ambicionad los carismas mejores. Y aún os voy a mostrar un camino excepcional”

(1 Co 12,31-13, 8a)

Para ti Inés, de tu hermana

Agradecimientos

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RESÚMENES

Resumen

Evaluación a nivel poblacional del beneficio en salud y costes del programa de detección precoz del cáncer de colon y recto en la CAPV

Introducción: El cáncer colorrectal (CCR) es un problema importante de salud pública por su incidencia y morbi-mortalidad. En la Comunidad Autónoma del País Vasco (CAPV) en 2009 se implantó un programa de cribado poblacional dirigido a las personas entre 50 y 69 años, mediante un test de sangre oculta en heces inmunoquímico (FIT), con colonoscopia con sedación en los casos positivos y posterior seguimiento de lesiones pre-malignas.

Objetivos: Conocer la efectividad del programa de cribado de CCR de la CAPV en términos de beneficio epidemiológico, supervivencia y costes.

Material y métodos: Se extrajeron y analizaron las bases de datos existentes en la CAPV para la realización de un estudio retrospectivo observacional de los CCR diagnosticados de los nacidos entre 01/01/1940 y 31/12/1964.

Aplicamos el modelo de análisis de simulación MISCAN-Colon (Microsimulation Screening Analysis) para predecir las tendencias en la incidencia y mortalidad del cáncer colorrectal y para cuantificar los efectos y los costes a corto y largo plazo (periodo de 30 años) del programa vasco de detección de cáncer colorrectal. El modelo fue estandarizado según la demografía vasca en 2008 y los datos de incidencia de cáncer colorrectal por edad en el Registro Vasco de Cáncer de 2005 a 2008, antes de que comenzara el cribado, y se calibró de acuerdo a la prevalencia de adenoma observada para la población vasca en un estudio publicado anteriormente. El modelo se ejecutó de manera diferenciada para hombres y mujeres.

Los CCR de la población susceptible de ser examinada fueron identificados y clasificados en cuatro grupos: a) nunca cribados (diagnosticados antes de la primera invitación y no participantes), b) detectados por el programa, c) cáncer de intervalo tras un FIT negativo y previos a la siguiente invitación y d) cánceres de intervalo tras colonoscopia (previos a la recomendación de una colonoscopia de seguimiento). Se compararon las características socio-demográficas, el estatus de salud, las características del tumor y la supervivencia entre los cuatro grupos.

Resultados: Los resultados del PCCR del País Vasco se ajustan a su estrategia y son comparables con otros programas de cribado en Europa.

De acuerdo con los parámetros de simulación de MISCAN-Colon y a través de los datos de los primeros años del programa, el cribado parece ser una estrategia efectiva para reducir la incidencia en un 17,2% y 14,7% en hombres y mujeres respectivamente, y la mortalidad 28,1% y 22,4% en hombres y mujeres en su proyección a 30 años desde su implantación. La evaluación económica mostró que con la intervención de cribado CCR se obtiene un importante beneficio en salud puesto que la esperanza de vida aumentó en 29,3 días por persona, y también produjo ahorros netos cuando se utilizó un seguimiento prolongado (30 años) para calcular el beneficio económico tardío.

Un total de 5.909 personas fueron diagnosticadas con un CRC en el periodo estudiado. La mediana de seguimiento de supervivencia fue de 4,6 años (rango 0-9 años). El estudio pone de relieve una diferencia significativa ($p < 0,0001$) en la supervivencia a 5 años en el grupo detectados por el cribado en comparación con los no cribados (90,1% frente a 66,0%). Aunque los cánceres de intervalo son eventos adversos, la tasa de supervivencia a 5 años es significativamente superior en este grupo con respecto a los no participantes ($p < 0,0001$) (76,3% frente a 60,5%), siendo éste el grupo con la tasa de supervivencia más baja.

Conclusión: La efectividad del programa queda evidenciada con las cifras tanto de reducción de incidencia como de mortalidad, así como en el aumento de la supervivencia en la población participante del programa de prevención de CCR del País Vasco. También según el modelo MISCAN-Colon de modelización económica fue la estrategia de cribado dominante en el análisis de coste efectividad en comparación con no hacer ningún cribado de CCR.

Laburpena

EAEn kolon-ondesteko minbizia goiz detektatzeko programaren osasun-onuraren eta kostuaren populazio mailako ebaluazioa

Sarrera: Kolon eta ondesteko minbizia (KOM) osasun publikoaren arazo garrantzitsu bat da bere intzidentziarengatik eta morbimortalitatearengatik. Euskal Autonomia Erkidegoan (EAE), 2009an, 50-69 urteko herritarrentzako baheketa-programa bat ezarri zen eginkarietan ezkutatutako odolaren test immunokimiko (FIT) baten bitartez, sedazio bidezko kolonoskopia eginez kasu positiboetan, eta, ondoren, lesio aurregaiztoei jarraipena eginez.

Helburuak: EAEko kolon eta ondesteko minbiziaren baheketa-programaren eraginkortasuna ezagutzea onura epidemiologikoari, biziraupenari eta kostuei dagokienez.

Materiala eta metodoak: EAEko datu-baseak atera eta aztertu ziren 1940/01/01etik 1964/12/31ra bitarteko aldian jaiotakoei diagnostikatutako KOMei buruzko behaketaren bidezko atzera begirako azterketa bat egiteko.

MISCAN-kolon (Microsimulation Screening Analysis) simulazioko azterketa-eredua aplikatu genuen kolon eta ondesteko minbiziaren intzidentzian eta hilkortasunean dauden joerak aurreikusteko eta kolon eta ondesteko minbizia detektatzeko euskal programak epe laburrean eta luzean (30 urteko aldia) dituen ondorioak eta kostuak kuantifikatzeko. Eredua estandarizatu egin zen, 2008ko euskal demografiaren arabera eta kolon eta ondesteko minbiziaren adinaren araberako 2005etik 2008ra (baheketarekin hasi aurretik) bitarteko Minbiziaren Euskal Erregistroko intzidentzia-datuen arabera, eta lehenago argitaratutako azterlan batean euskal populazioaren kasuan ikusitako adenomaren nagusitasunaren arabera kalibratu zen. Eredua bereiz aplikatu zitzaien gizon eta emakumeen datuei.

Azterketa egin zezakeen populazioaren KOMak lau multzotan identifikatu eta sailkatu ziren: a) baheketan inoiz neurtu ez zirenak (lehenengo gonbidapena baino lehen diagnostikatu zirenak eta programan parte hartu ez zutenak), b) programak detektatu zituenak, c) tarteko minbizia FIT negatibo baten ondoren eta hurrengo gonbidapena egin aurretik, eta d) tarteko minbiziak kolonoskopia egin ondoren (jarraipena egiteko kolonoskopia gomendatu aurrekoak). Ezaugarri soziodemografikoak, osasunaren estatusa, tumorearen ezaugarriak eta biziraupena alderatu ziren lau taldeen artean.

Emaitzak: Euskal Herriko KOMParen emaitzak programaren estrategiara egokitzen dira eta Europako beste baheketa-programa batzuekin aldera daitezke.

MISCAN-koloneko simulazio-parametroen arabera eta Programaren lehenengo urteetako datuen bitartez, badirudi baheketa estrategia eraginkorra dela intzidentzia % 17,2 eta % 14,7 jaisteko gizonen eta emakumeen kasuan, hurrenez hurren, eta hilkortasuna % 28,1 eta % 22,4 jaisteko gizonen eta emakumeen kasuan, ezarri zenetik 30 urteko proiekzioan. Ebaluazio ekonomikoak erakutsi zuen KOMaren baheketa eginez onura garrantzitsua lortzen dela osasunean; izan ere, bizi-itxaropena 29,3 egun igo zen pertsona bakoitzeko, eta, era berean, aurrezki garbiak izan ziren irabazi ekonomiko berantiarra kalkulatzeko jarraipen luzea (30 urtea) erabili zenean.

Aztertutako aldian, guztira, 5.909 pertsonari diagnostikatu zitzaien KOMa. Biziraupenaren jarraipen-mediana 4,6 urte izan zen (0-9 urteko tartea). Azterlanak agerian jartzen du alde esanguratsua dagoela (n <0,0001) 5 urterako biziraupenean baheketak detektatutako taldea eta baheketan parte hartu ez dutenak alderatzen baditugu (lehenak % 90,1; bigarrenak, aldiz, % 66,0). Tarteko minbiziak kontrako gertaerak diren arren, 5 urterako biziraupen-tasa askoz ere handiagoa da talde honetan programan parte hartu ez dutenen artean baino (n <0,0001) (lehenak % 76,3; bigarrenak, aldiz, % 60,5), eta azken talde horrek du biziraupen-tasa txikiena.

Ondorioa: Ikusten da programa eraginkorra dela intzidentziaren bahiz hilkortasunaren zifrak murrizten direlako, baita Euskadiko KOMa prebenitzeko programan parte hartu duen populazioaren biziraupenak gora egin duelako ere. Era berean, MISCAN-kolon ereduaren araberako modelizazioko kostu-eraginkortasunaren azterketan baheketa-estrategia nagusitu zen, KOMaren baheketarik ez egitearekin alderatuta.

Summary

Populational evaluation of the benefits in health and cost of the early detection programme for colon and rectal cancer in the Basque Country

Introduction: Colorectal cancer (CRC) is a major public health problem because of its high incidence rate, morbidity and mortality. In 2009, a population based screening programme was introduced in the Autonomous Community of the Basque Country, aimed at people between 50 and 69 years of age. This screening programme is carried out using a faecal immunochemical occult blood test (FIT) with a colonoscopy under sedation for positive cases and a follow-up of pre-malign lesions.

Objectives: To find out the effectiveness of the CRC screening Programme in the Basque Country in terms of epidemiological benefits, survival rates and cost.

Material and methods: The existing databases in the Basque Country were extracted and analyzed in order to carry out an observational, retrospective study of the CRCs diagnosed in people born between 01/01/1940 and 31/12/1964.

We applied the simulation analysis model MISCAN-colon (Microsimulation Screening Analysis) in order to predict the trends in incidence and mortality of colorectal cancer as well as to quantify the effects and costs in both the short and long term (a 30-year period) of the Basque colorectal cancer screening Programme. The model was standardized according to the Basque population in 2008 and the colorectal cancer incidence data by age in the Basque Cancer Registry from 2005 to 2008, before the screening began. It was calibrated in accordance with the prevalence of adenoma observed in the Basque population in a previously published study. The model was implemented differentially for men and women.

The CRCs in the population subject to examination were identified and classified into 4 groups: a) never screened (diagnosed before the first invitation or non-participants) b) detected through the programme c) interval cancers after a negative FIT but before the next invitation and d) interval cancers after a colonoscopy (before the recommended follow-up colonoscopy). The socio-demographic characteristics, state of health, characteristics of the tumour and survival rates of the four groups were compared.

Results: The results of the Basque Country's BCSP adjust comply with its strategy and are comparable to other European screening programmes.

In accordance with the parameters of simulation of the MISCAN-colon and through the data of the first few years of the Programme, screening seems to be an effective strategy to reduce the incidence rate of 17.2% and 14.7% in men and women respectively, and the mortality rate of 28.1% and 22.4% in men and women in its 30-year projection from its implementation. The economic evaluation showed important health benefits due to the intervention of CRC screening, as life expectancy was raised by 29.3 days per person, and net savings were produced when a prolonged surveillance (30 years) was carried out to calculate the delayed economic benefit.

A total of 5,909 people were diagnosed with a CRC during the period studied. The mean of the follow up was 4.6 years (ranging from 0 – 9 years). The study highlights a significant difference ($p<0.0001$) in the survival rate at 5 years in the group detected through screening compared with those who were not screened (90.1% compared to 66.0%). Although interval cancers are adverse events, the 5-year survival rate is significantly higher in this group with regard to non-participants ($p<0.0001$) (76.3% compared to 60.5%), this being the group with the lowest survival rate.

Conclusion: The effectiveness of the Programme is statistically evident, not only in the decrease in incidence and mortality, but also in the increase in the survival rate in the population who participate in the Basque Country's CRC detection programme. The dominant screening strategy was also clearly cost effective, as shown in the MISCAN-model modelling analysis in comparison with not doing any CRC screening.

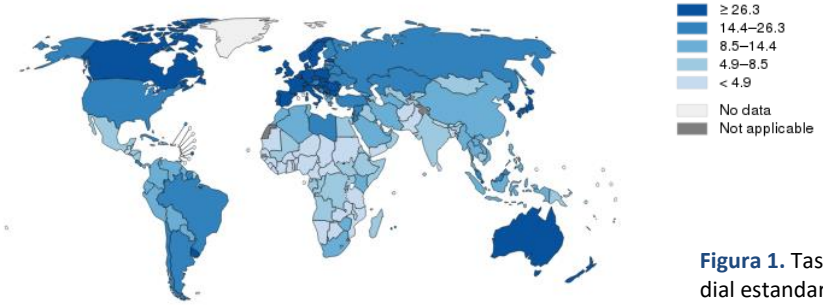
INTRODUCCIÓN

I.- INTRODUCCIÓN

1. CÁNCER COLORRECTAL

1.1. Epidemiología: incidencia, mortalidad, supervivencia

El cáncer colorrectal (CCR) es un importante problema de salud pública a nivel mundial. De hecho, según Ferlay *et al.* en 2015, es el tercero más incidente en hombres (746.500 casos, 10% del total) y el segundo en mujeres (614.000 casos, 9,2% del total). Alrededor del 55% de los casos ocurre en las regiones más desarrolladas del mundo, presentando una gran variación geográfica tanto en incidencia como en prevalencia (ver figuras 1 y 2). Aunque los patrones geográficos son muy similares en hombres y mujeres, sin embargo, las tasas de incidencia varían hasta diez veces entre regiones. Si tenemos en cuenta ambos sexos, las tasas más altas se han descrito en Australia y Nueva Zelanda (Tasa Ajustada por Edad (TAE) 44,8 y 32,2 por 100.000 en hombres y mujeres respectivamente), y las más bajas en África occidental (4,5 y 3,8 por 100.000 en hombres y mujeres respectivamente). La mortalidad es baja, 694.000 muertes, 8,5% del total, con más muertes (52%) en las regiones menos desarrolladas, destacando la baja supervivencia en dichas regiones (ver figura 3). Las tasas de supervivencia varían entre 20,3 por 100.000 en hombres y 11,7 por 100.000 en mujeres en Europa Central y Oriental y las más bajas en África Occidental (3,5 y 3,0 por 100.000 en hombres y mujeres respectivamente) [http://globocan.iarc.fr; Ferlay, *et al.* 2015]. Los niveles más altos de supervivencia a 5 años se han visto en el Sudeste Asiático, concretamente Corea del Sur, colon (71,8%), y recto (71,1%) [Allemani, *et al.* 2018].



Tomada de http://globocan.iarc.fr (2012)

Figura 1. Tasas de incidencia mundial estandarizada de CCR para ambos sexos en 2012.

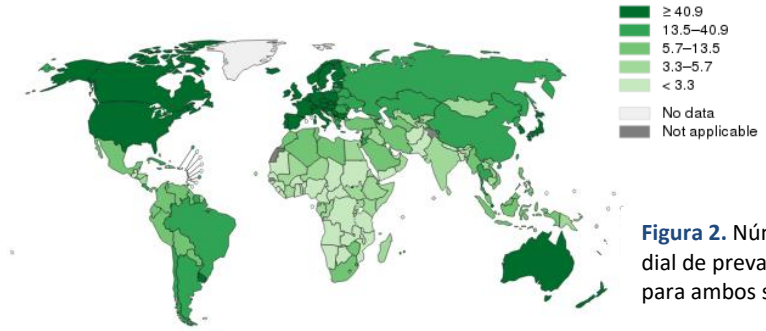


Figura 2. Número de casos mundial de prevalencia (1 año) de CCR para ambos sexos en 2012.

Tomada de http://globocan.iarc.fr (2012)

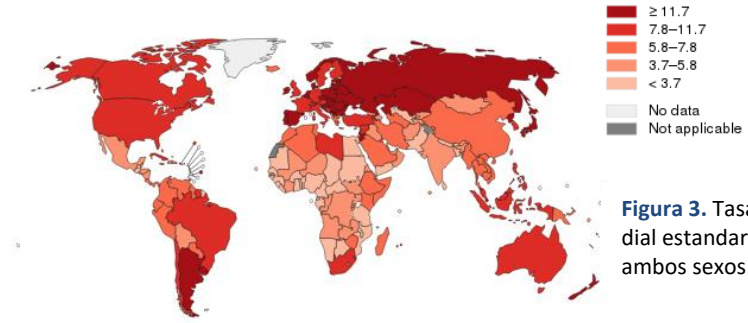


Figura 3. Tasa de mortalidad mundial estandarizada de CCR para ambos sexos en 2012.

Tomada de http://globocan.iarc.fr (2012)

En Europa, el CCR es uno de los tumores malignos más frecuentes, siendo el primero en incidencia y el segundo en mortalidad para ambos sexos, con 471.000 casos nuevos y 228.000 muertes en 2012 (ver figura 4). La incidencia media en los países de la Unión Europea es de 39,9 por 100.000 para hombres y 25,2 por 100.000 para mujeres y el número de muertes es de 31,7 por 100.000 para hombres y 26,5 por 100.000 para mujeres [Ferlay, *et al.* 2015]. Ambas, incidencia y mortalidad han ido aumentando en las últimas décadas en paralelo al envejecimiento de la población. De hecho, se prevé que para el 2020 se incremente en Europa en más de un 23% [Ferlay, *et al.* 2010]. De acuerdo con el estudio de Holleczek, *et al.* 2015, la supervivencia relativa a 5 años en pacientes con cáncer de colon, fue en el periodo 2000-2007 muy similar para hombres y mujeres y fue para ambos sexos del 57,0%, en hombres 56,4%, en mujeres 57,8% y ligeramente inferior la supervivencia del cáncer de recto, 54,9% en hombres y 57,3% en mujeres. Comparando diferentes regiones europeas observamos gran variabilidad, con un 60,5% en Europa Central, un 51,8% en Irlanda y Reino Unido y un 49,4% en la Europa del Este. La supervivencia a 1 año fue en global del 78%. Ligeramente más baja fue la supervivencia relativa a los 5 años para los diagnosticados de cáncer de recto 56% sin existir diferencias estadísticamente significativas [Holleczek, *et al.* 2015].

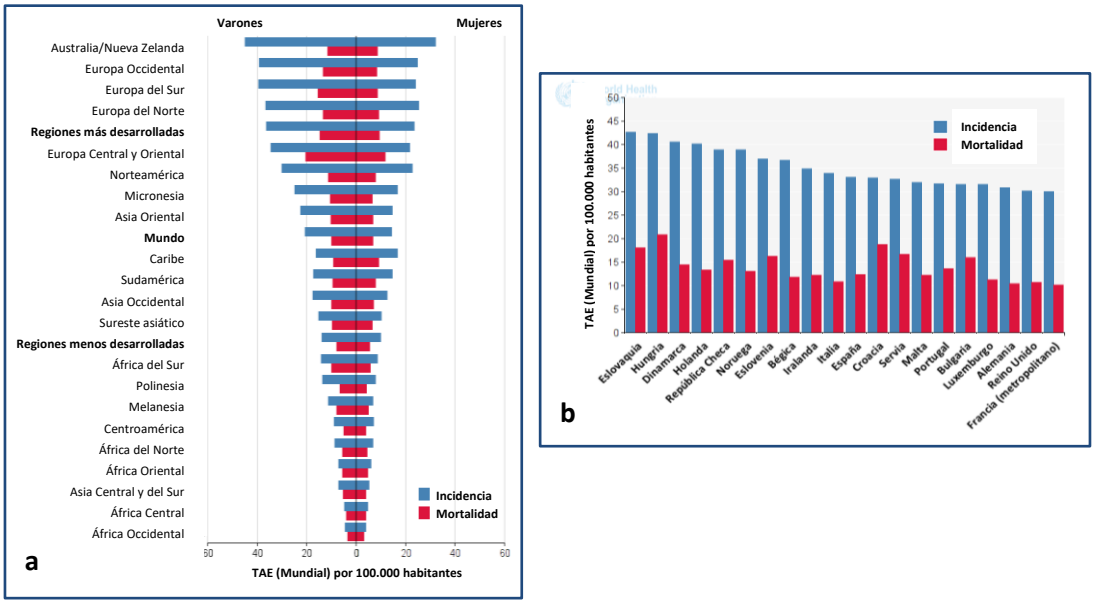


Figura 4. a) Incidencia y mortalidad estandarizadas de CCR en diferentes regiones del mundo. b) En los 20 países europeos con tasas más elevadas. *Tomada de http://globocan.iarc.fr (2012).*

En España según la última estimación realizada en 2015 para el conjunto de la población [Galceran, *et al.* 2017], el número total de casos nuevos diagnosticados estimado de CCR fue de 41.441 (ver figura 5). En hombres fue el segundo más incidente tras el de próstata con 24.764 casos y en mujeres con 16.677 justo tras el de mama. Las tasas de incidencia han ido incrementando progresivamente desde 1993 (48 por 100.000) hasta 2007 (68 por 100.000), y en 2015 la proyección de la incidencia alcanzó 78 por 100.000 habitantes. Comparada con los países de la Europa de los 28, España tiene una incidencia observada muy superior (73,0 vs 59,0 por 100.000 en hombres y 39,9 vs 36.1 por 100.000 en mujeres).

	CASOS	%
Próstata	33.370	22
Colon y recto	24.764	17
Pulmón	22.430	15
Vejiga	17.439	12
Estómago	5.150	3
Oro-faríngeo	4.980	3
Hígado	4.252	3
Linfoma No Hodgkin	4.190	3
Leucemia	3.782	3
Riñón	3.590	2
Todos (salvo melanoma)	148.827	100

	CASOS	%
Mama	27.747	28
Colon y recto	16.667	17
Útero	6.160	6
Pulmón	5.917	62
Vejiga	3.654	4
Linfoma No Hodgkin	3.480	4
Páncreas	3.401	3
Estómago	3.306	3
Ovario	3.228	3
Leucemia	2.736	3
Todos (salvo melanoma)	98.944	100

Figura 5. Los diez tipos principales de cáncer incidental por género en España, 2015. *Tomada de Galceran, et al. (2017).*

En el periodo 1975-2004 la tendencia mostró un incremento anual de 2,5% (2,8 en hombres y 2,1 en mujeres en dicho periodo) [Lopez-Abente, *et al.* 2010]. Es además la segunda causa más frecuente de mortalidad tanto en hombres como en mujeres, siendo para todas las edades del 14,3 y TAE 12,3 por 100.000 (hombres 13,7 y TAE 17,1, y mujeres 15,2 TAE 15,2) para el 2012 [Ferlay, *et al.* 2015]. La supervivencia fue 56,6% en hombres y de 58,1% en mujeres. Por otro lado, el CCR se encuentra entre los cánceres que han mostrado mejoría en la supervivencia. Si se comparan los periodos 1995-1999 y 2000-2007 en ambos sexos, hay un aumento de la supervivencia para cáncer de colon de 2,7 puntos en hombres y de 1,8 puntos en mujeres y para cáncer de recto 4,8 puntos en hombres y 4,6 puntos en mujeres [Chirlaque, *et al.* 2017].

En la Comunidad Autónoma del País Vasco (CAPV) según los últimos datos publicados en el periodo 2000-2015 [López de Munain, *et al.* 2017], fue también el tumor más frecuente cuando se consideran ambos sexos, con 6.916 casos nuevos (Tasa Bruta (TB) 130,0 por 100.000 en hombres) y 4.030 en mujeres, (TB del 72,2 por 100.000). En el periodo 2000-2013 la incidencia en hombres aumentó significativamente, un 2,6 anual (IC 95% 2,1-3,0) y en mujeres se mantuvo estable en el periodo 2000-2007, aumentando posteriormente de forma significativa entre 2007-2013, un 5,7 anual (IC95% 2,8-8,6). En lo que respecta a la mortalidad entre 2011-2015 fallecieron por CCR 2.547 hombres (TB 47,4 y TAE 29,2) y 1.672 mujeres (TB 29,6 y TAE 13,6). En el periodo 2000-2012, en los hombres la tasa de mortalidad se mantuvo estable y posteriormente en el periodo 2012-2015 descendió sin alcanzar significación estadística. En mujeres entre 2000-2009 la tasa de mortalidad disminuyó significativamente un 1,9 anual (IC 95% -3,6 a -0,1) y posteriormente entre 2009 y 2015 la tendencia se estabilizó 3,0 (IC 95% -0,2 a -6,2) (ver figura 6).

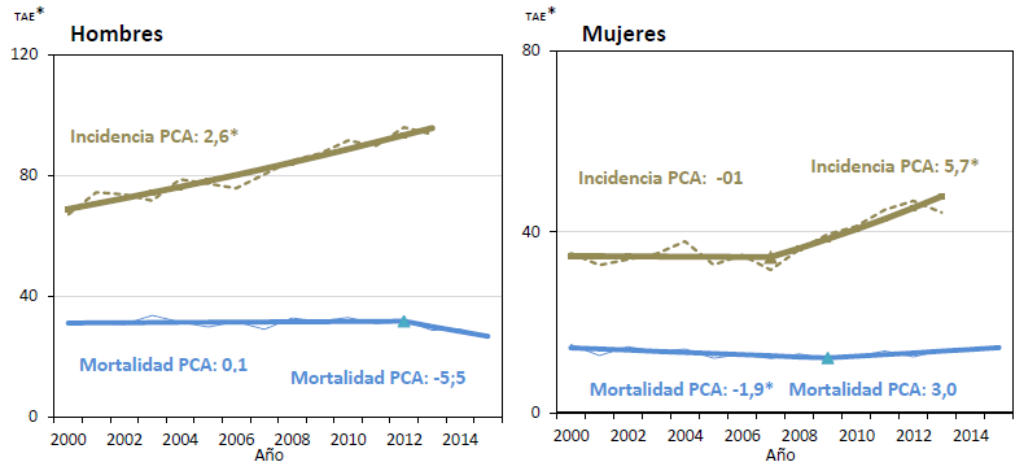


Figura 6. Evolución de las tasas de incidencia (2000-2013) y mortalidad (2000-2015) de tumor maligno de colon-recto. (CIE-O: C18-C21) según sexo en CAPV. *Tomada de López de Munain, et al. (2017).*

En cuanto a la supervivencia, desde la década de los 90, se ha registrado una mejora en la supervivencia relativa del CCR a los 5 años en ambos sexos que puede explicarse por un diagnóstico precoz en estadios iniciales, también por el avance en los tratamientos oncológicos y por la disminución de la mortalidad peri-operatoria. Son varias las teorías que intentan dar una explicación a la diferencia en la tasa de mortalidad por CCR entre ambos sexos, una de las cuales es que el uso de terapia hormonal sustitutiva por las mujeres puede ser un factor de protección [Fernández, *et al.* 2001]. Otros factores que podrían explicar los diferentes patrones de mortalidad son un mayor acceso a la atención médica y la adopción de estilos de vida más saludables por parte de las mujeres [Binefa, *et al.* 2014]. En un estudio publicado en 2010, se observó un aumento de supervivencia relativa a los 5 años del diagnóstico, entre 1986–1989 y 2000-2004 de 14 puntos en hombres (43,3% vs 57,2%) y de 10 puntos en las mujeres (44,2% vs 54.3%) [Izarzugaza, *et al.* 2010]. En el análisis de supervivencia para el periodo 2000-2012, la supervivencia neta estandarizada por edad a los 5 años del diagnóstico fue de 52,2% (IC 95%: 51,8-52,6) en hombres y 59,9% (IC 95%: 59,5-60,4) en mujeres [López de Munain, *et al.* 2017] (ver tabla 1). En el caso concreto de la población susceptible de cribado, la Supervivencia Neta estandarizada por edad (SNst) al año en hombres fue del 87,5% (86,7-88,4); a los 3 años, 74,8% (73,6-76,0) y a los 5 años 67,2% (65,8-68,5). Para las mujeres fue al año del 88,7% (87,5-89,9), a los 3 años del 74,8% (73,2-76,4) y a los 5 años del 68,3% (66,4-70,1). Por el contrario, para todas las edades fue 78,2% en hombres y

77,7% en mujeres al año de diagnóstico, y a los 5 años, disminuyó hasta 56,8% en los hombres y 57,3% en las mujeres [Gil, *et al.* 2018] (ver tabla 1). La supervivencia fue similar en ambos sexos y disminuyó al aumentar la edad. Por localización, la SNst al año del diagnóstico fue significativamente superior cuando el cáncer se localizaba en recto, pero dicha diferencia no se mantuvo a los 5 años. Por sexo y localización, a los 5 años del diagnóstico, la SNst del cáncer de colon, fue 57,3% en hombres y 58,1% en mujeres y la SNst del cáncer de recto fue del 55,8% en hombres y del 55,4% en mujeres, no encontrándose diferencias estadísticamente significativas (ver figura 7).

La supervivencia global por período diagnóstico (2000-2004, 2005-2009 y 2010-2012) aumentó significativamente entre el primer y tercer periodo, en ambos sexos, al año y a los 5 años del diagnóstico. A los 5 años, en hombres aumentó 8 puntos (56,4% vs. 64,4%) y en mujeres 9 puntos (56,8% vs. 65,8%). La supervivencia aumentó en todos los grupos de edad y en ambos sexos. A los 5 años del diagnóstico, la mejora fue estadísticamente significativa en los hombres de 50 a 69 años y en las mujeres de 50 a 79 años [Gil, *et al.* 2018] (ver figura 8).

Tabla 1. Supervivencia neta a uno, tres y cinco años por sexo y grupo de edad. CAPV 2000-2012. *Tomada de Gil, et al. (2018).*

	HOMBRES			MUJERES		
EDAD	CASOS	SN %	IC95%	CASOS	SN %	IC95%
<50 años	651			539		
1		87,9	85,4-90,4		89,4	86,8-92,1
3		75,1	71,7-78,5		77,4	73,8-81,0
5		68,3	64,5-72,1		66,8	62,5-71,0
50-69 años	6161			2936		
1		87,5	86,7-88,4		88,7	87,5-89,9
3		74,8	73,6-76,0		74,8	73,2-76,4
5		67,2	65,8-68,5		68,3	66,4-70,1
70-79 años	5106			2574		
1		78,6	77,3-79,8		78,2	76,5-79,8
3		64,0	62,5-65,6		64,4	62,4-66,4
5		56,9	55,1-58,7		59,3	57,0-61,5
>=80 años	2483			2337		
1		64,0	61,8-66,1		60,7	58,6-62,9
3		47,8	45,2-50,5		46,0	43,4-48,5
5		40,9	37,6-44,1		40,4	37,3-43,5
Total*	**14401**			**8386**		
1		**78,2**	**77,6-78,8**		**77,7**	**76,9-78,4**
3		**63,9**	**63,1-64,7**		**63,9**	**63,0-64,9**
5		**56,8**	**55,9-57,7**		**57,3**	**56,2-58,4**

*Ajustada por edad

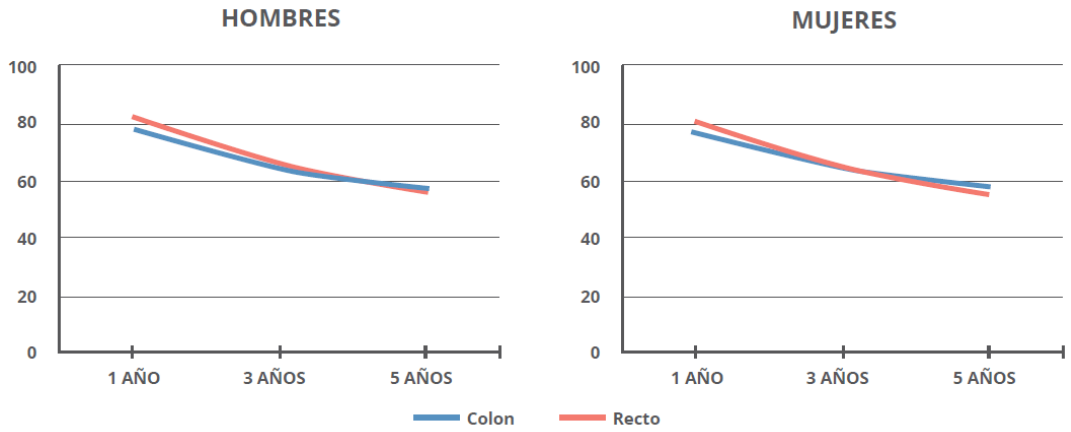


Figura 7. Supervivencia neta estandarizada por localización anatómica de CCR. CAPV 2000-2012. *Tomada de Gil, et al. (2018).*

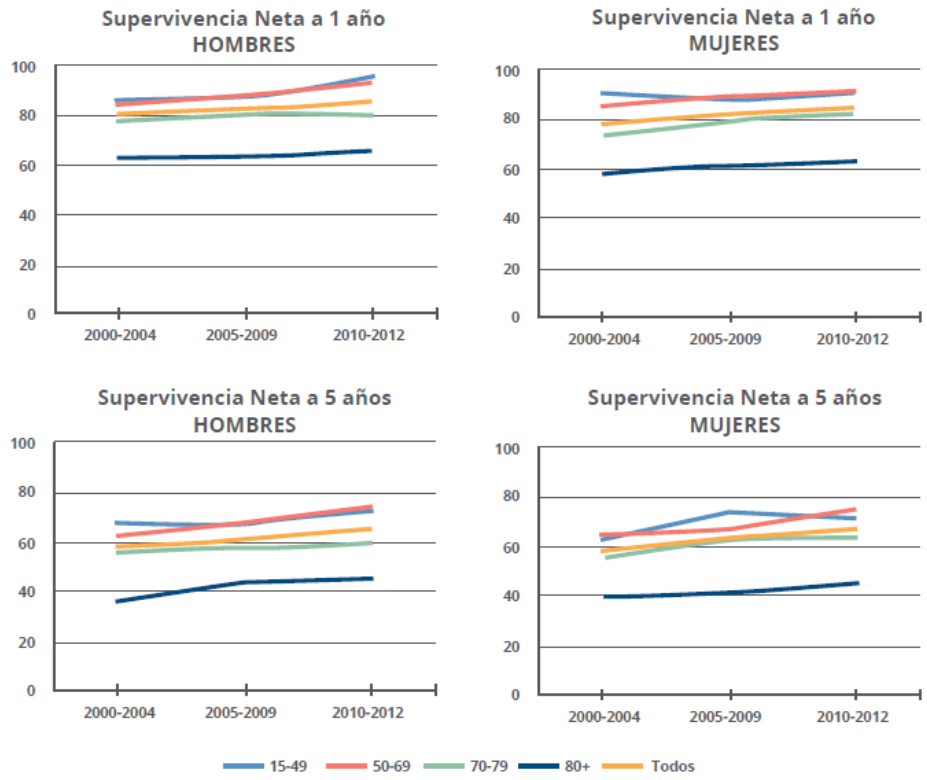


Figura 8. Evolución de la supervivencia de CCR (%) por periodo diagnóstico y grupo de edad. CAPV 2000-2012. *Tomada de Gil, et al. (2018).*

En la figura 9 se muestra el exceso de riesgo relativo (ERR) de muerte por diferentes factores analizados. Los hombres y mujeres mayores de 69 años tuvieron un riesgo de muerte significativamente superior al de los pacientes menores de 50 años; en ambos sexos el riesgo aumentó con la edad. El riesgo disminuyó significativamente en el segundo y tercer periodo analizado, en ambos sexos. En cuanto al análisis por áreas sanitarias, los hombres residentes en la Comarca Sanitaria de Uribe (Bizkaia) presentaron un riesgo superior al de los residentes en Donostialdea y las mujeres de Goierri-Urola Garaia (Gipuzkoa) un riesgo significativamente inferior al de las mujeres de Donostialdea. El riesgo de muerte asociado al cáncer de recto fue similar al presentado por el cáncer de colon [Gil, *et al.* 2018].

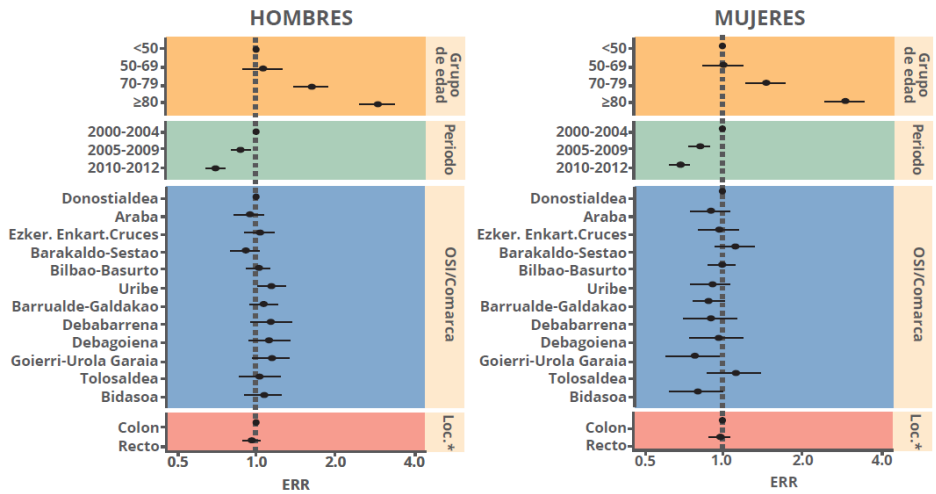


Figura 9. Exceso de riesgo relativo (ERR) de muerte por edad, periodo diagnóstico CCR y lugar de residencia. CAPV 2000-2012. *Tomada de Gil, et al. (2018).*

1.2. Historia natural

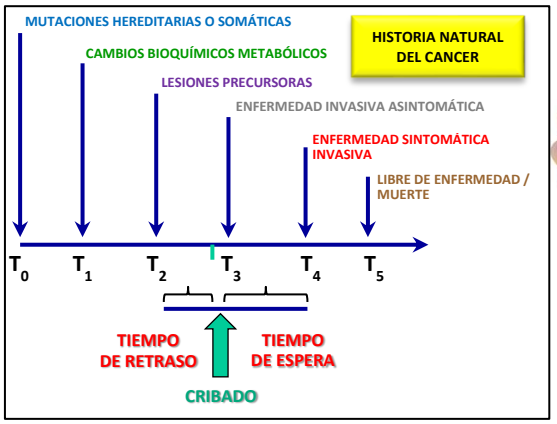
Es conocido que son necesarios al menos 10 años para que los cambios genéticos y epigenéticos, así como moleculares, que provocan el CCR, progresen y llegue a formarse un tumor con potencial de invadir la submucosa y convertirse en un CCR, a partir de un adenoma benigno. Resulta, por tanto, un proceso secuencial de alteraciones genéticas, que se acumulan a lo largo del tiempo, dando lugar tanto a la activación de oncogenes como a la inactivación de genes supresores de tumores, que generan cambios en la replicación de ADN y en el ciclo celular (ver figura 10). El CCR es una enfermedad heterogénea donde cada

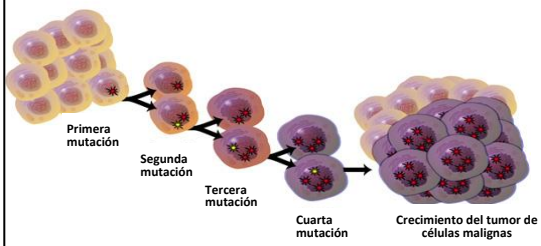
cáncer posee un único perfil molecular tumoral [IJspeert, *et al.* 2015].

Este cáncer posee la peculiaridad de desarrollarse a partir de una lesión premaligna, denominada pólipo, susceptible de ser diagnosticada y tratada por medio de su extirpación mediante la colonoscopia terapéutica.

Ha habido grandes avances en el conocimiento de la oncogénesis del CCR en los últimos años, que nos han permitido distinguir estas lesiones precursoras y sus características moleculares.

Figura 10. Fases de la historia natural del CCR.





Adaptada por Segnan de Walter y Day (1983)

En tiempos pasados la etiopatogenia del CCR se creía que era sencilla, pero es mucho más compleja de lo que se ha considerado clásicamente. Anteriormente, únicamente se distinguían 2 tipos de pólipos: por un lado los pólipos hiperplásicos, considerando a estas lesiones inocuas, con muy escaso potencial degenerativo y, por otro los adenomas, con potencial carcinogénico mediante la vía de progresión adenoma-carcinoma ya descrita hace dos décadas [Vogelstein, *et al.* 1988]. Dicha progresión es el resultado de un proceso secuencial de alteraciones genéticas que se acumulan a lo largo del tiempo, dando lugar tanto a la activación de oncogenes como a la inactivación de genes supresores de tumores, los cuales generan cambios en la replicación de ADN y en el ciclo celular. Esta secuencia adenoma - carcinoma ha sido el paradigma de la tumorogénesis del CCR y no ha sido hasta hace unos años cuando se han descrito otras vías carcinogénicas tales como: la vía de la inestabilidad cromosómica (CIN), la vía de la inestabilidad de micro satélites (IMS) y la vía serrada (vía de las islas CpG metiladoras o CIMP) todas ellas determinantes del CCR, pudiendo entremezclarse las mismas (ver figura 11).

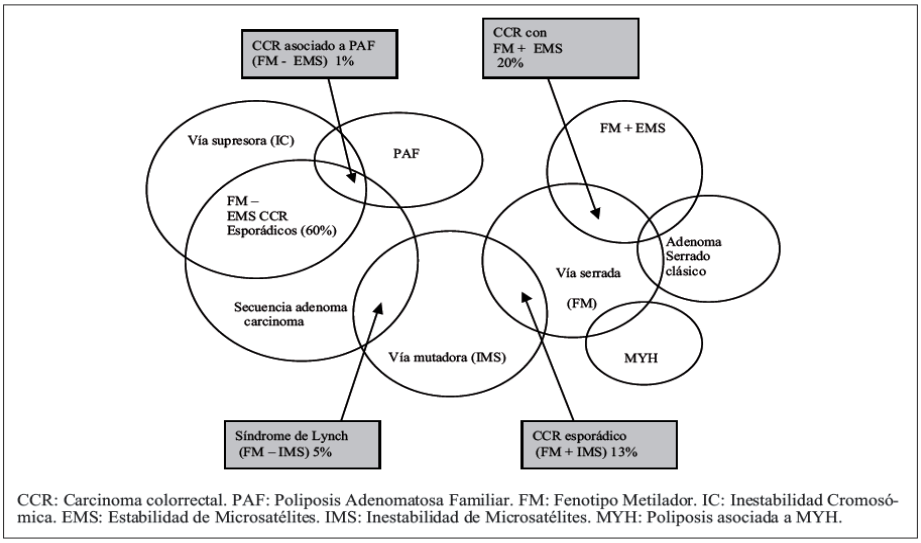


Figura 11. Esquema de las diferentes vías de carcinogénesis y sus solapamientos. *Tomado de Snover (2011).*

1.2.1. Vía de la inestabilidad cromosómica

La lesión precursora de esta vía es el adenoma [WHO, 2016], siendo los adenomas etiquetados con displasia de alto grado (> 25% de componente velloso) y/o tamaño ≥10mm los que se encuentran en una fase más avanzada de malignización en la secuencia adenoma-carcinoma, puesto que dichas características se asocian a un mayor riesgo [Eide, *et al.* 1986]. Esta vía se basa en el acúmulo de alteraciones cromosómicas produciendo finalmente el cambio del cariotipo de células individuales. Se considera que la mutación del gen supresor de tumores APC (Adenomatous Polyposis Coli) es un evento inicial en esta vía oncogénica, aumentando la proliferación de colonocitos. Asimismo, la mutación del proto-oncogén K-RAS puede producirse en fases tempranas, permitiendo a la célula evadir la apoptosis. Otros eventos más tardíos en la malignización de los adenomas son la mutación en el gen supresor de tumores p53 del cromosoma p17 y la alteración del cromosoma q18 [Noshirwani, *et al.* 2000] (ver figura 12).

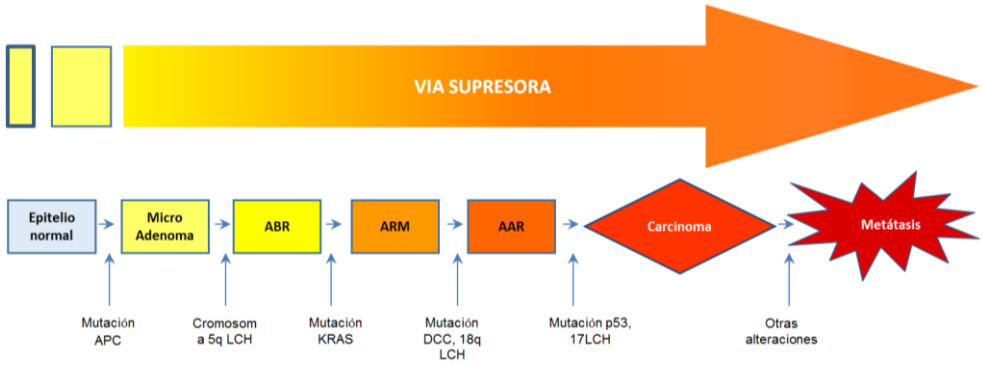
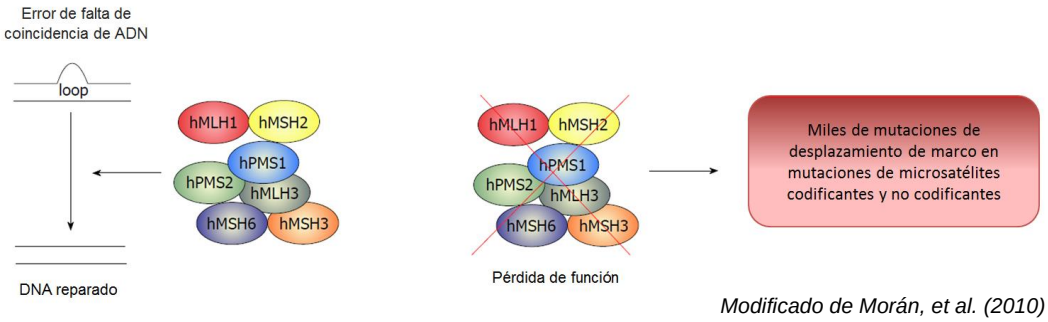


Figura 12. Esquema de la secuencia adenoma-carcinoma y alteraciones moleculares en la vía supresora. *Modificado de Moran, et al. 2010.*

1.2.2. Vía de la inestabilidad de microsatélites

Los tumores con IMS representan el 10-15% de todos los CCR, y es habitual en las formas hereditarias como el Síndrome de Lynch, que suponen el 3-5% del total del CCR y cuya base molecular son mutaciones a nivel germinal en los genes que codifican para la IMS (ver figura 13). El tiempo de desarrollo tumoral mediante esta vía es muy inferior y se estima en 3-5 años, mientras que en los casos esporádicos, el mecanismo de IMS es debido a la hipermetilación en la región promotora de cualquiera de los genes relacionados con el sistema de reparación del ADN, siendo estas secuencias cortas de ADN de entre 1 y 6 bases repetidas en parejas y dispersadas a lo largo del genoma humano [Grady, 2004]. La IMS se debe a una alteración del sistema de reparación del ADN. Éste se encarga de corregir los errores que se producen durante la replicación del ADN, y es controlado por varios genes (MLH1, MSH2, MSH6, PMS2, entre otros). La alteración del sistema conduce a la acumulación de alteraciones en los microsatélites, que están distribuidos por todo el genoma [Peltomäki, 2003]. Si existe una mutación en el sistema IMS, estos errores no son corregidos y puede llegar a modificar la longitud de los microsatélites mediante deleciones o repeticiones, con la consiguiente mala transcripción y traducción de los genes asociados a los mismos. Cuando este cúmulo de errores en la reparación del ADN se da en genes que regulan la proliferación celular o la apoptosis, se produce un aumento en la formación de tumores y un desarrollo mucho más rápido de los mismos (pudiendo multiplicarse el potencial oncogénico por 100). El otro 80% de los CCR derivados de esta vía se cree que son

secundarios a la hipermetilación del promotor de MLH1 (uno de los IMS). No sólo los adenomas sufren malignización por este mecanismo, sino que dicho mecanismo también es importante en el desarrollo de la vía serrada [IJspeert, *et al.* 2015].



Modificado de Morán, et al. (2010)

Figura 13. Origen del fenotipo de la IMS.

1.2.3. Vía serrada o de fenotipo metilador

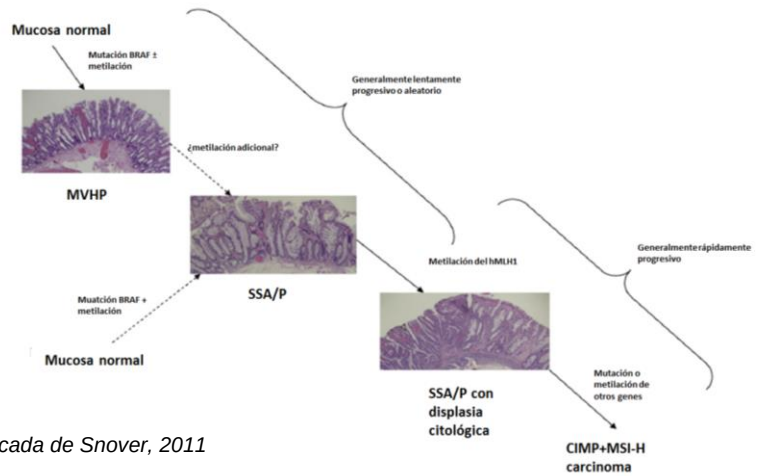
Es la vía de carcinogénesis la última en ser identificada. Los tumores que surgen de esta vía representan aproximadamente el 35% y surgirían de una lesión precursora serrada. Se caracterizan por la metilación de islas CpG en la región promotora de genes supresores de tumores (ver tabla 2). Estas alteraciones consisten en la transferencia de grupos metilos sobre algunas de las bases citosinas del ADN situadas previa y contiguamente a una guanina, lo que se conoce como "islas CpG". Esta metilación en zonas promotoras de genes conlleva a su silenciamiento, es decir, anulan la expresión a nivel del ARN del gen, sin necesidad de que se produzca una alteración en la secuencia del ADN. Esta situación de metilación aberrante de islas CpG promotoras de genes supresores se conoce como CIMP (CpG island methylation phenotype). La mayoría de los CCR que se desarrollan por la vía serrada parece que comienzan con la mutación del gen BRAF, un gen que al estar mutado inhibe la apoptosis normal de las células epiteliales del colon. Estas lesiones con mutación BRAF progresan a pólipos hiperplásicos microvesiculares (MVHP) o P/ASS. Posteriormente se produce una metilación de las islas CpG promotoras de genes supresores lo que provoca el silenciamiento epigenético de varios genes. Uno de los más frecuentes es el silenciamiento del gen MLH1, el cual está silenciado en los CCR con IMS. El MLH1 es uno de los genes de reparación del ADN y la hipermetilación de su promotor conduce a su silenciamiento y por tanto, a una mayor predisposición a desarrollar nuevas mutaciones que favo-

recerán la progresión rápida a displasia y posteriormente a carcinoma. Estas alteraciones genéticas y moleculares favorecerán el desarrollo de CCR con CIMP+ e IMS [Snover, 2011] (ver figura 14).

Tabla 2. Clasificación de los tumores según su estado de Inestabilidad de microsatélites y fenotipo metilador. *Tomado de Ogino y Goel (2008).*

Grupo	*BRAF*	*IC*	*TP53*	*KRAS*	*Histopatología*
IMS Alta FM Alto	*Mutado*	*Negativa*	*Normal*	*Normal*	*CCR pobremente diferenciados, con reacción linfocitaria y presencia de células en "anillo de sello" y tumores muncinosos*
IMS Alta FM Bajo/0	*Normal*	*Negativa*	*Normal*	*Mutado*	*Reacción linfocitaria, características mucinosas*
IMS Baja/ EMS FM Alto	*Mutado*	*Negativa*	*Normal*	*Normal*	*Presencia de CCR pobremente diferenciados, con Células en "anillo de sello"*
IMS Baja FM Bajo	*Normal*	*Negativa*	*Normal*	*Mutado*	
EMS FM Bajo	*Normal*	*Negativa*	*Normal*	*Mutado*	
IMS Baja/ EMS FM Cero	*Normal*	*Positiva*	*Normal*	*Normal*	

IMS: Inestabilidad de Microsatélites. EMS: Estabilidad de Microsatélites. IC: Inestabilidad Cromosómica. FM: Fenotipo Metilador. CCR: Cáncer Colorrectal.



Modificada de Snover, 2011

Figura 14. Representación de la vía serrada o de fenotipo metilador en el desarrollo de CCR con IMS.

De esta forma, las diferentes lesiones precursoras del CCR pueden progresar a través de las distintas vías de carcinogénesis, desarrollándose un amplio abanico de expresiones fenotípicas moleculares diferentes, que en algunos casos se asociarán a una respuesta al tratamiento diferente y a un pronóstico diferenciado (ver tabla 3). Todo se complica puesto que se sabe que las distintas vías de carcinogénesis no son excluyentes y en algunas ocasiones, las alteraciones moleculares de diferentes vías pueden coexistir en la misma lesión neoplásica.

Tabla 3. Variantes genéticas identificadas usando estudios de asociaciones de genes candidatos, significativamente asociadas con el riesgo de CCR en meta-análisis y mostrando una evidencia de acumulación de moderada a fuerte de acuerdo a los criterios de Venecia y los análisis de probabilidad de falsos positivos.

Gen	Variante	Frecuencia en controles	OR (IC 95%)	Evidencia acumulada de asociación	Grupo étnico
MUTYH	Biallelic mutation	0,01%	10,19 (5,0-22,0)	Fuerte	Caucásica
MUTYH	G382D (rs36053993)	0,00%	6,49 (2,6-10,4)	Fuerte	Caucásica
MUTYH	Y165C (rs34612342)	0,01%	3,32 (1,1-9,8)	Fuerte	Caucásica
APC	I1307K (rs1801155)	6,80%	1,96 (1,4-2,8)	Fuerte	Askenazi
CHEK2	1100delC	0,71%	1,88 (1,3-2,7)	Fuerte	Caucásica
CHEK2	I157T (rs17879961)	3,91%	1,56 (1,3-1,8)	Fuerte	Caucásica
MLH1	rs1800734 (promoter)	21,11%	1,51 (1,3-1,7)	Fuerte	Caucásica
DNMT3B	rs1569686 (promoter)	16,99%	0,57 (0,5-0,7)	Fuerte	Todas
GSTM1	Present/null	50,64%	1,10 (1,0-1,2)	Moderada	Todas
TERT	rs2736100 (intron 2)	49,34%	1,07 (1,0-1,1)	Moderada	Caucásica

Modificado de Ma, et al. (2014)

1.3. Clasificación histopatológica

Las neoplasias más frecuentes en esta región C18-21 son los adenomas y los carcinomas. Otros tumores malignos más raros son los linfomas, los sarcomas, los melanomas y los carcinomas de células pequeñas.

Los pólipos colónicos (lesiones premalignas, susceptibles de ser extirpadas en la colonoscopia terapéutica) se clasifican en hiperplásicos (con muy escaso poder de malignización) y pólipos adenomatosos. Pueden distinguirse entre

estos diferentes tipos histológicos: tubular, velloso (> 50% de componente velloso) y túbulo-velloso (20-25% al 50% de componente velloso).

Para determinar el nivel de infiltración de un carcinoma en un adenoma se utilizan los niveles de invasión y se basan en la morfología macroscópica del adenoma (pediculado, sesil, plano o deprimido) y en el nivel de invasión profunda del carcinoma. En un adenoma pediculado se distinguen niveles del "0 al 4", pero en los adenomas sesil, plano o deprimido, sólo son posibles los niveles "0" y "4" (ver tabla 4 y figura 15).

Tabla 4. Grados de invasión en lesiones polipoideas según Haggitt *et al.* (1985).

Grado 0	Invasión mucosa por encima de la muscularis mucosae (carcinoma in situ)
Grado 1	Invasión de la submucosa, pero limitado a la cabeza del pólipo
Grado 2	Invasión de la submucosa del cuello
Grado 3	Invasión de la submucosa de cualquier parte del tallo
Grado 4	Invasión de la submucosa por debajo del tallo sin alcanzar la muscular propia

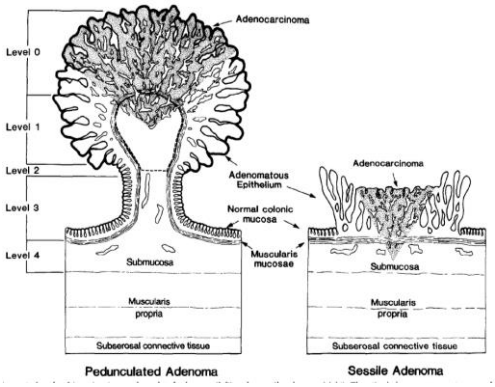


Figura 15. Grados de invasión en lesiones polipoideas según Haggitt, *et al*. (1985).

Más del 95% de las neoplasias malignas colorrectales son adenocarcinomas y dependiendo de sus características histológicas, los carcinomas colorrectales se clasifican en [Sobin, *et al.* 2009]:

a) Adenocarcinoma, siendo la forma más habitual de neoplasia del epitelio glandular colónico.

b) Adenocarcinoma mucinoso o coloide, cuando > del 50% de la lesión está formada por lagos de mucina extracelular que contienen epitelio maligno formando acinos, tiras epiteliales o células sueltas. Se asocia con frecuencia a inestabilidad de microsatélites.

c) Adenocarcinoma de células en anillo de sello, cuando > del 50% de las células neoplásicas muestran abundante mucina intracelular ("células en anillo de sello") independientemente de que pueda también haber lagos de mucina extracelular. Sólo

algunos muestran inestabilidad de microsatélites.

d) Carcinoma adenoescamoso, posee características de carcinoma epidermoide y de adenocarcinoma, bien en áreas separadas del mismo tumor o entremezcladas.

e) Carcinoma medular, característico por una sábana de células malignas.

f) Carcinoma con núcleo vesicular, nucleolo prominente y citoplasma eosinófilo abundante rodeadas por un infiltrado linfocitario intenso. Es una variante rara que se asocia invariablemente a inestabilidad de microsatélites y con mejor pronóstico que el carcinoma pobremente diferenciado e indiferenciado.

g) Carcinoma indiferenciado sin evidencia de diferenciación. Son genéticamente distintos y se asocian típicamente con inestabilidad de microsatélites.

Los grados de diferenciación histológica del adenocarcinoma son:

- bien diferenciado (G1; > 95% del tumor forma glándulas);
- moderadamente diferenciado (G2; 50-95% del tumor forma glándulas);
- pobremente diferenciado (G3; <50% del tumor forma glándulas).

Los cánceres colorrectales se clasifican con la pieza histológica de acuerdo a:

- La profundidad de la invasión del tumor primario (T): T1 es la afectación de la lámina propia ó de la submucosa < 2cm (T1a <1 cm; T1b 1 a 2 cm); T2 cuando infiltra la muscularis propia ó > 2cm; T3 invasión de la subserosa, o tejidos pericolorrectales y, T4 cuando penetra en la serosa o en otro órgano contiguo.
- La presencia de metástasis ganglionares o nódulos linfáticos invadidos (enfermedad regional) (N): N1 cuando hay de 1-3 ganglios linfáticos regionales invadidos y, N2 cuando la metástasis está presente en 4 o más ganglios linfáticos regionales.
- La presencia de metástasis a distancia (enfermedad diseminada) (M): M1a si la metástasis está localizada en un órgano y, M1b si la metástasis está presente en más de un órgano o peritoneo.

La combinación de estos tres parámetros (T, N, M) marcan el estadio global que proporciona las bases para la decisión terapéutica [Sobin et al, 2009] (ver figuras 16 y 17).

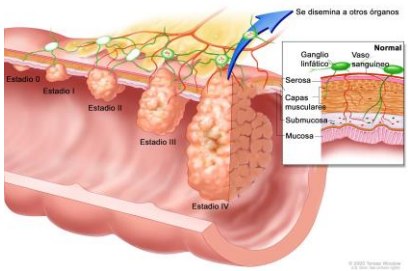


Figura 16. Diferentes estadios del CCR. *Tomado de Edge, et al. (2010).*

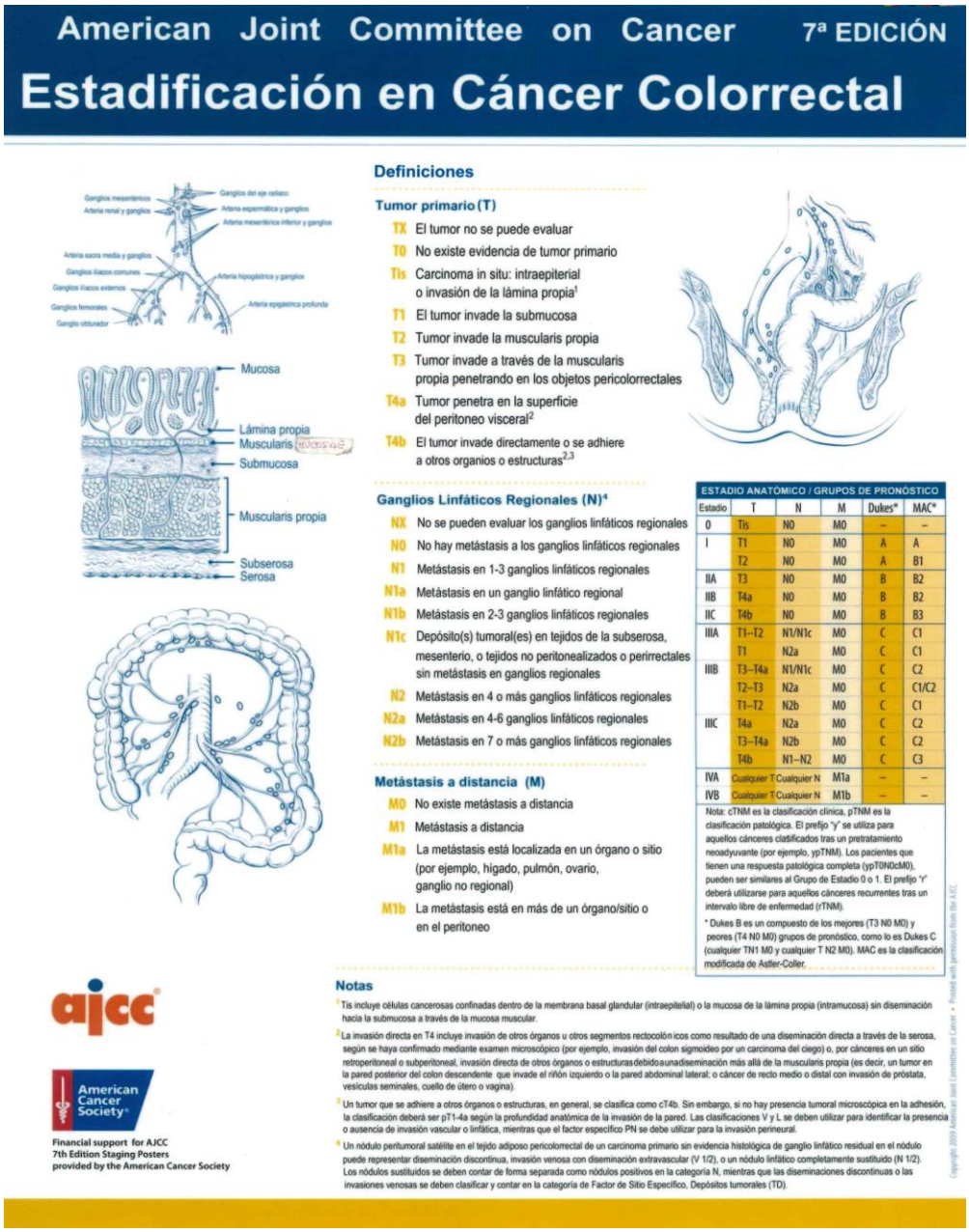


Figura 17. Agrupación por estadios del American Joint Committee on Cancer y definiciones TNM. *Tomado de Edge, et al. (2010).*

2. ETIOLOGÍA: RIESGO Y FACTORES PREVENTIVOS

2.1. Prevención primaria

Más del 90% de los cánceres colorrectales son esporádicos y diagnosticados en personas mayores de 50 años [Winawer, *et al.* 1999]. Como en la mayor parte de las patologías tumorales, la edad es el principal factor de riesgo no modificable. En las personas con predisposición genética o con enfermedad inflamatoria intestinal (enfermedad de Crohn y Colitis ulcerosa) también se observa un riesgo aumentado, así como en las personas con determinadas patologías de carácter hereditario conocido, como la Poliposis familiar o el Síndrome de Lynch [Lukas, *et al.* 2010]. Respecto a los factores de riesgo modificables, uno de los más importantes es la disminución en el consumo de **carnes rojas**, carne muy cocinada o hecha directamente al fuego y carnes procesadas (curada, ahumada, salada o con conservantes químicos añadidos) [Domingo JL, *et al.* 2010]. Por el contrario, el aumento en el consumo de alimentos ricos en fibra vegetal como las legumbres, frutas y hortalizas, así como el consumo de productos lácteos o micronutrientes ricos en folatos, calcio y vitamina D, son protectores para este tipo de cáncer [World Cancer Research Fund/ American Institute for Cancer Research, 2011]. Parece por tanto haber una relación directa entre la ingesta de carne roja y procesada, así como un bajo consumo de alimentos protectores, además del aumento de peso, con el riesgo de aparición de las lesiones precursoras del cáncer [Schwingshackl, *et al.* 2018]. Se estima que un 70% de los CCR pudieran ser evitables sólo con medidas dietéticas [Platz, *et al.* 2000; Torres Stone, *et al.* 2000]. La obesidad es otro factor de riesgo en ambos sexos, sobre todo la obesidad abdominal. En cambio, el ejercicio y la actividad física actúan como factores protectores. Tanto la hiperinsulinemia como el consumo elevado de almidón juegan un papel importante, y su presencia comporta un aumento de riesgo de aparición de adenomas colorrectales [World Cancer Research Fund/ American Institute for Cancer Research, 2017]**.** En los últimos años se ha evidenciado el papel que juega también el consumo excesivo de **alcohol** (superior a 100 gramos a la semana) [Fedirko, *et al.* 2011]. Esta relación ha sido demostrada posteriormente en un estudio prospectivo, con un consumo de 30 gramos/día [Vogel, *et al.* 2007]. Hay también estudios que señalan el papel negativo del consumo de **tabaco**, sobretodo en el cáncer de recto, con un aumento de riesgo de hasta dos veces respecto de las personas no fumadoras [Hooker, *et al.* 2008]. A pesar de que se ha demostrado que el consumo de **ácido acetilsalicílico** es protector del CCR en personas mayores de 50 años y en dosis

superiores a 300mg/día, la aparición de efectos adversos en la mucosa gastrointestinal hace que no se recomiende de forma sistemática como medida de quimio-prevención [Flossmann, *et al*. 2007]. Algo parecido sucede con la **capsaicina** (presente en guindillas, pimienta de Jamaica) cuyo factor protector es bien conocido, pero aún no hay estudios lo suficientemente potentes que avalen su uso [Yang, *et al*. 2013].

2.2. Prevención secundaria

La prevención secundaria es crucial, pero su implementación está siendo lenta e incompleta, incluso en los países de altos ingresos. Esta es una estrategia a largo plazo para reducir la incidencia y mortalidad y mejorar la supervivencia. En 2016, el Consejo Ejecutivo de la OMS recomendó fortalecer los sistemas de salud para asegurar el diagnóstico temprano y una atención accesible, asequible y de alta calidad para todos los pacientes con cáncer [WHO, 2016]. La Asamblea Mundial de la Salud (WHA) promulgó una resolución sobre el control del cáncer en mayo, 2017. Incluía recomendaciones tales como qué estrategias de control deberían tratar de reducir los estadios avanzados y garantizar el tratamiento y cuidado apropiados para posibles neoplasias curables como el CCR [WHO, 2017].

Si bien de manera histórica desde las consultas médicas y de enfermería se han puesto en marcha medidas de prevención primaria, tales como consejos de vida saludable, potenciando la alimentación y vida equilibradas, parece que a la población le resulta realmente difícil asumirlo en su rutina, puesto que la tendencia creciente de la incidencia de CCR así lo demuestra, aunque pudiera ser también debida a otros factores como el aumento de la esperanza de vida. Por tanto, la prevención secundaria se priorizó como estrategia para disminuir de forma efectiva la carga de enfermedad a propuesta del Consejo Asesor del Cáncer de Euskadi, por ser el CCR una enfermedad prevenible, tratable y con una elevada carga de enfermedad y ser, además, susceptible de cribado poblacional como habían demostrado experiencias en otros países.

La detección precoz mediante el análisis de sangre oculta en heces a personas entre 50-74 años, fue una recomendación del Consejo Europeo a todos los Estados miembros desde el año 2003 [European Council, 2003], basándose en la evidencia científica disponible y en el cumplimiento del CCR de los principios marcados por Wilson y Jungner en 1968, de ser una patología susceptible de mejora mediante el empleo del cribado poblacional. Aunque el valor de los criterios de estos científicos sigue siendo

indiscutible a día de hoy, 40 años después hay nuevas directrices políticas en el campo de la salud que han visto la necesidad de revisarlos con el fin de tomar de manera más acertada las decisiones políticas a este respecto, tal y como describen Andermann, *et al.* en 2008 (tabla 5).

Tabla 5. Criterios de selección para el cribado.

CRITERIOS CLÁSICOS DE CRIBADO DE WILSON Y JUNGER	SÍNTESIS DE LOS NUEVOS CRITERIOS DE SELECCIÓN PROPUESTOS EN LOS ÚLTIMOS 40 AÑOS
La enfermedad debe ser un problema de salud importante	El programa de detección debe responder a una necesidad reconocida
Debe entenderse bien la historia natural de la enfermedad	Los objetivos del cribado deben definirse desde el principio
Debe existir un estadio inicial detectable	Debería haber una población diana definida.
El tratamiento en su estadio inicial debería ser más beneficioso que en su etapa avanzada	Debe haber evidencia científica de la efectividad del programa de cribado
Debe existir un test adecuado para detectarlo en el estadio inicial	El programa debe integrar educación, pruebas, servicios clínicos y gestión de programas
El test debe ser bien aceptado	Debe haber garantía de calidad, con mecanismos para minimizar los riesgos potenciales de detección
Los intervalos para repetir la prueba deben estar determinados	El programa debe garantizar la decisión informada, la confidencialidad y el respeto de la autonomía
Debe hacerse una provisión adecuada de servicios de salud para la carga de trabajo clínica adicional resultante de la detección	El programa debe promover la equidad y el acceso a la detección para toda la población diana
Los riesgos, tanto físicos como psicológicos, deberían ser menores que los beneficios	La evaluación del programa debe planificarse desde el principio
Los costes deben equilibrarse con los beneficios	Los beneficios generales del cribado deberían superar el daño

Modificado de Wilson y Junger (1968) y de Andermann, et al. (2008)

Es la Comisión Europea en el año 2008 la que alerta del incumplimiento de la recomendación hecha en 2003, puesto que se registran programas poblacionales de cribado en tan sólo 12 de los 28 Estados miembros [von Karsa, *et al.* 2008]. Posteriormente, el Parlamento Europeo, el 6 de mayo de 2010, edita una resolución donde insta a los Países de la Unión a promocionar la prevención invirtiendo principalmente en medidas de prevención primaria, secundaria y diagnósticos tempranos de cáncer [Committee on the Enviroment, Public Health and Food Safety, 2014].

El Código europeo contra el cáncer es un conjunto de recomendaciones que brindan asesoramiento sobre la prevención del cáncer. Su tercera edición, publicada en 2003 [Boyle, *et al.* 2003] (originalmente el Código fue desarrollado en 1987 y revisado en 1994), enumera siete recomendaciones sobre la adopción de estilos de vida más saludables para mejorar muchos aspectos de la salud general y la prevención de muchas muertes por cáncer; cuatro recomendaciones se enumeraron como intervenciones exitosas (detección y vacunación).

La 4ª edición del Código europeo contra el cáncer describe "12 maneras de reducir el riesgo de cáncer" (ver tabla 6). Las recomendaciones se desarrollaron para permitir y alentar a las personas a modificar su propio riesgo de cáncer, abordar una carga relevante de cáncer y ser comprensibles para la población en general. Cubrieron las siguientes áreas: tabaquismo y uso de otras formas de tabaco; exposición pasiva al humo; peso corporal saludable; actividad física; dieta saludable; consumo de alcohol; exposición a la radiación ultravioleta; carcinógenos ocupacionales; altos niveles de radón; amamantamiento; terapia de reemplazo hormonal; vacunas del virus del papiloma humano y del virus de la hepatitis B; cribado del cáncer de colon; cribado de cáncer de mama; y detección de cáncer de cuello uterino.

Tabla 6. Código Europeo contra el Cáncer, 4ª edición 2014. *Modificado de Armaroli, et al. (2015).*

CÓDIGO EUROPEO CONTRA EL CÁNCER

12 formas de reducir el riesgo de cáncer:

1 No fume. No utilice ninguna forma de tabaco.
2 Haga que su hogar esté libre de humo. Apoye políticas libres de humo en su lugar de trabajo.
3 Tome medidas para tener un peso corporal saludable.
4 Sea físicamente activo en la vida cotidiana. Limite el tiempo que pasa sentado.
5 Tenga una dieta saludable:
- Coma muchos granos enteros, legumbres, vegetales y frutas.
- Limite los alimentos altos en calorías (alimentos con alto contenido de azúcar o grasa) y evite las bebidas azucaradas.
- Evite la carne procesada; limite la carne roja y los alimentos con alto contenido en sal.

6 Si bebe alcohol de cualquier tipo, limite su consumo. No beber alcohol es mejor para la prevención del cáncer.
7 Evite demasiado sol, especialmente para los niños. Tome sol con protección. No use camas solares.
8 En el lugar de trabajo, protéjase contra exposiciones cancerígenas.
9 Averigüe si está expuesto a radiación de forma natural con altos niveles de radón en su hogar. Tome medidas para reducir los altos niveles de radón.
10 Para mujeres:
- La lactancia materna reduce el riesgo de cáncer de mama. Si puedes amamanta a tu bebé.
- La terapia de reemplazo hormonal aumenta el riesgo de ciertos cánceres. Limitar el uso de hormonoterapia (HRT).

11 Asegúrese de que sus hijos participen en los programas de vacunación para:
- Hepatitis B (para recién nacidos).
- Virus del papiloma humano (para niñas).

12 Participe en programas organizados de detección de cáncer para:
- Cáncer de colon (hombres y mujeres).
- Cáncer de mama (mujeres).
- Cáncer de cuello uterino (mujeres).

El Código europeo contra el cáncer se centra en acciones que ciudadanos individuales pueden realizar para ayudar a prevenir el cáncer. Para que estas acciones individuales sean exitosas deben ser apoyadas por políticas y acciones gubernamentales.

El código europeo contra el cáncer en el 2015 [Armaroli, *et al.* 2015] incluyó entre sus recomendaciones que hombres y mujeres de 50 años de edad en adelante deberían participar en los cribados de CCR. Tanto en el plan integral de cáncer de la

Unión Europea como del Ministerio Español de Sanidad, Servicios Sociales e Igualdad [Ministerio de Sanidad y Política Social, 2010] incluyen la implementación de programas entre sus recomendaciones para la prevención del CCR.

2.2.1. Situación de cribado de CCR en Europa

En 2013 sólo 5 países más tenían cubierta a su población por programas de prevención [Altobelli, *et al.* 2014]. A enero 2017, todos los países de la UE, excepto Bulgaria, Rumanía y la República Eslovaca tienen una recomendación institucional oficial sobre implementación de programas de detección precoz de CCR (ver figura 18). Dichos programas son de financiación pública y los test de cribado se proporcionan de forma gratuita a todos los ciudadanos, excepto en Croacia, donde los costes se reembolsan a través de un seguro de salud. Se implementaron por tanto programas de cribado poblacionales en 20 Estados miembros (Austria, Bélgica, Croacia, Chipre, la República Checa, Dinamarca, Finlandia, Francia, Hungría, Irlanda, Italia, Lituania, Malta, los Países Bajos, Polonia, Portugal, Eslovenia, España, Suecia y el Reino Unido). En estos países, se envían cartas de invitación a todos los hombres y mujeres susceptibles de participar en el programa de detección precoz a través de registros específicos, excepto en Lituania. Hay países que llevan a cabo programas de cribado no poblacionales como en Alemania, Grecia, Letonia, Estonia y Luxemburgo. Estos países tenían previsto comenzar a implantar programas poblacionales en 2017.

El cribado poblacional de este cáncer se ha ido implantando en las distintas regiones europeas desde las últimas dos décadas y de manera muy diversa [von Karsa, *et al.* 2012]. La estrategia predominante en países europeos, anglosajones y asiáticos es la detección de test de sangre oculta en heces (SOH), seguida de la colonoscopia cada 10 años y de la sigmoidoscopia cada 5 o 10 años con o sin test de sangre oculta en heces inmunoquímico (SOHi) anual [Levin, *et al.* 2008; von Karsa, 2013; Sung, *et al.* 2015; Lin, *et al.* 2016] (ver figura 19).

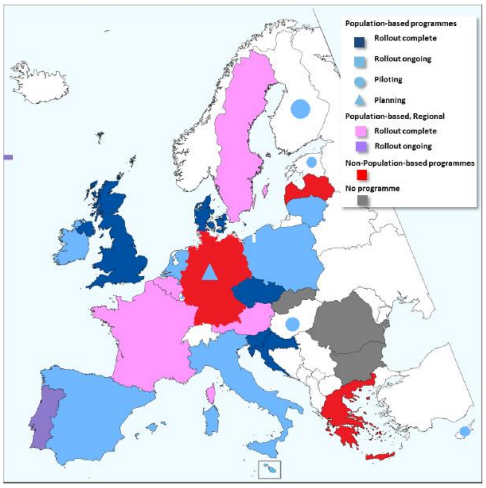
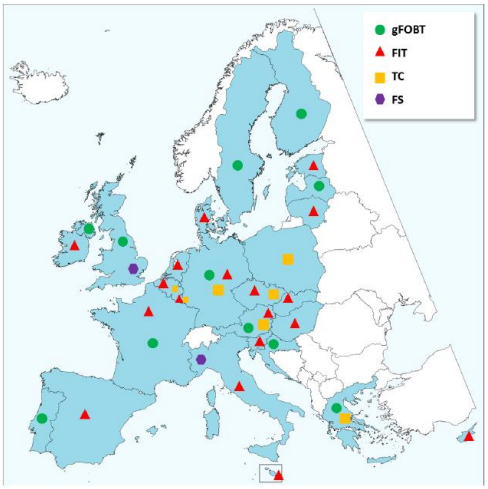


Figura 18. Situación en Europa de los programas de cribado de CCR. *Tomada de Ponti, et al. (2017).*

La mayoría de los países que comenzaron a realizar el cribado con la prueba de guayaco (SOHg) como prueba de cribado, posteriormente han cambiado al SOHi, como Inglaterra en el 2014 (además de mantener la sigmoidoscopia en una región amplia como método de cribado). Francia en el 2015, también cambió a SOHi en aras de mejorar las tasas de participación, ya que en la Guía Europea de calidad de colonoscopias de cribado y diagnósticas [von Karsa, *et al.* 2010] se establece como deseable llegar a un 65% de entrega de test válido, siendo pocos países los que lo logran incluso con el test inmunoquímico. Son primordialmente los países europeos con programas oportunistas los que continúan manteniendo la colonoscopia como prueba de cribado, así como en Estados Unidos de América [Schreuders, *et al.* 2015].

En España es en "La estrategia contra el Cáncer" del Sistema Nacional de Salud, donde se contempló en 2006 [Ministerio de Sanidad, 2006] esta recomendación, que fue ratificada en 2009, si bien en ese año se acordó el objetivo de cobertura de la población española entre 50-69 años del 50% para el 2015 [Ministerio de Sanidad, 2009], objetivo no alcanzado por la mayoría de las Comunidades Autonómicas (CCAA). En 2014 se incluyó en la cartera Básica de Servicios [Orden SSI/2065/2014, de 31 de octubre].



gFOBT: test de sangre oculta en heces guaico; FIT: test de sangre oculta en heces inmunohistoquímico; TC: tomografía computarizada; FS: sigmoidoscopia.

Figura 19. Distribución en Europa de los distintos métodos de cribado de CCR. *Tomada de Ponti, et al. (2017).*

2.2.2. Cribado de CCR en el País Vasco

En el País Vasco el control de esta enfermedad fue uno de los objetivos del Plan de Salud 2002-2010 del Gobierno Vasco [http://osakidetza.euskadi.eus, 2012], en el área de Cáncer, en cuanto al mantenimiento de las tasas ajustadas (estándar europea) de mortalidad registradas durante 1996-1998 (29,5/100.000 en hombres y 14,5/100.000 en mujeres), observándose en la evaluación realizada en 2011 un descenso en mujeres (15,86%), pero un incremento en hombres (9,15%).

En 2008 el Departamento de Sanidad del Gobierno Vasco aprobó la puesta en marcha de un programa poblacional organizado de cribado dirigido a hombres y mujeres de la CAPV de 50 a 69

años a través de la realización de un test de sangre oculta en heces inmunoquímico cuantitativo cada dos años, y confirmación diagnóstica en los casos positivos a través de la colonoscopia óptica, completa, terapéutica y con sedación, iniciando una primera fase (programa piloto) a la que fue invitada el 5,8% del total de la población vasca (ver figura 20).

El objetivo principal del programa es la detección temprana de lesiones precancerosas y malignas y de este modo conseguir la disminución de la incidencia y la mortalidad por dicha patología. Se cuenta con una aplicación web específica para la realización del programa de cribado y con la interconexión de distintas bases de datos clínicas (registro de altas hospitalarias, registro de procedimientos no quirúrgicos y registros de cáncer) para hacer una correcta selección de población elegible y excluida en el cribado a partir de la población diana.

Figura 20. Tríptico del programa de cribado de cáncer de colon y recto de la CAPV.

El programa se puso en marcha en 2009 logrando la extensión a prácticamente el 100% de la población diana (586.700 personas estimadas) a principios de 2014. Los resultados de primera invitación en 2009-2011 mostraron altas tasas de participación, muy por encima de las obtenidas en otras regiones europeas y también en otras CCAA (64,3%; IC95% 64,1-64,5), mayor en mujeres que en hombres, con una tasa de positividad media de 6,7% (IC95% 6,6-6,8) superior en hombres, una tasa media de aceptación de colonoscopias de 93,1% de los casos positivos, encontrándose diferencias significativas en la tasa de detección de Adenomas Avanzados entre mujeres y hombres (OR: 0,45; IC95% 0,41-0,49) y de CCR (OR: 0,80; IC 95%: 0,66-0,96), más frecuentes en hombres al igual que el Valor Predictivo Positivo (VPP) para cualquier adenoma que fue significativamente superior en hombres (72,4%; IC95% 71,2-73,5) que en mujeres (48,8%; IC 95% 47,2-50,5) con diferencias por grupo de edad y tipo de adenoma [https://www.osakidetza.euskadi.eus, 2017; Portillo, *et al.* 2013].

En lo que respecta a España, se utilizan en las distintas CCAA como prueba de cribado también el test SOHi con un intervalo de 24 meses a la invitación y siendo la población diana, hombres y mujeres de 50 a 69 años y habiendo cambiado algunas CCAA (Cataluña y Valencia) a test SOHi después de comenzar en el 2000 con SOHg. En 2016 la cobertura total de invitación a programas de cribado era del 37%, siendo la población objetivo de cribado informada por el Instituto Nacional de Estadística (INE) 11.430.747 y sólo 4.333.123 con invitación al cribado. El programa organizado y poblacional completó su invitación a toda la población diana exclusivamente en el País Vasco en 2014 y Valencia en 2016. El resto de las Comunidades están en proceso de extensión del programa a excepción de las de Madrid, Extremadura, Ceuta y Melilla, donde están aún planificándolo, según los últimos datos comunicados en 2016 en la Reunión Anual de la Red de Programas de Cribado de Cáncer de España [http://www.cribadocancer.es, 2016].

2.2.3. Test utilizados

La prevención secundaria se engloba en cuatro grandes categorías:

1. Pruebas en heces:
   a. Test de sangre oculta en heces
   b. Detección del ADN fecal
2. Biomarcadores en sangre periférica
3. Pruebas endoscópicas:
   a. Colonoscopia
   b. Sigmoidoscopia
4. Otras pruebas de imagen:
   a. Colonografía
   b. Cápsula endoscópica

2.2.3.1. Pruebas en heces

El test de SOH consiste en la detección de cantidades mínimas de hemoglobina en las heces no detectables por el ojo humano. Existen dos métodos: químico (test de guayaco) e inmunológico. La **prueba de guayaco,** se basa en la actividad pseudoperoxidasa del grupo hemo, que induce la oxidación del guayaco al añadirse peróxido de hidrógeno (ver figura 21). Para evitar falsos positivos o negativos, estas pruebas requieren de la toma de 3 muestras consecutivas, realizar una dieta previa durante 3 días (eliminando productos que interfieren con la determinación como las carnes rojas y embutidos cárnicos como la morcilla y cítricos), evitar el tratamiento con antiinflamatorios no esteroideos y los suplementos de vitamina C.

Figura 21. Prueba de sangre oculta en heces.

Los **métodos inmunológicos** se basan en anticuerpos monoclonales o policlonales anti-globina humana (ver figura 22). Estos métodos pueden ser cualitativos o cuantitativos, necesitan la toma de una sola muestra y no requieren restricciones dietéticas, ni de tratamientos médicos en los días previos a la realización de la determinación. Los test cuantitativos facilitan la lectura automatizada y dependiendo de los recursos para realización de colonoscopia existentes en las organizaciones sanitarias, permiten elegir el punto de corte para su positividad, siendo el consensuado en España ≥100 ngr/ml buffer equivalente a 20 µgr/gr heces [Chiang, *et al.* 2014].

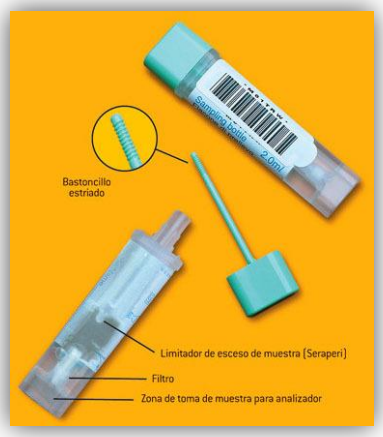


Figura 22. Test de sangre oculta en heces inmunoquímico.

Varios ensayos clínicos aleatorizados (ECA) han demostrado una reducción estadísticamente significativa tanto de la incidencia como de la mortalidad con cribado anual o bienal con SOHg comparado con no cribado [Hardcastle, *et al.* 1996; Mandel, *et al.* 2000; Shaukat, *et al.* 2013]. Incluso la revisión sistemática (RS) Cochrane

actualizada en 2008, atribuyó al cribado con SOH una reducción de la incidencia de 17% o 20% según el cribado fuera bienal (HR 0,83; IC 95% 0,73-0,94) o anual (HR 0,80; IC 95% 0,70-0,90), respectivamente [Hewitson, *et al.* 2008]. Existen también resultados de la revisión sistemática Cochrane actualizada en 2011 [van Roon, *et al.* 2011] que analizó 4 ECAs con SOHi y donde estimaron una reducción de la mortalidad por CCR en el grupo de cribado con SOHg del 13% (RR 0,87; IC 95% 0,82-0,92) tras 15 a 19 años de seguimiento.

La **detección de ADN fecal** (DNA stool) es el procedente de la exfoliación de células tumorales intestinales (ver figura 23). Permite identificar alteraciones moleculares presentes en los adenomas y en el CCR. Es un método no invasivo, se realiza por el individuo en su domicilio y sin necesidad de restricciones dietéticas o de medicamentos, ni preparación de limpieza colónica. Así como en el SOH el resultado positivo requiere de la realización de una colonoscopia como test de confirmación diagnóstica.

La capacidad de esta prueba para detectar lesiones pre-malignas y malignas colónicas ha sido evaluada en numerosos estudios, sin encontrar diferencias significativas en las curvas ROC pero sí en la sensibilidad y especificidad entre distintos tipos de test [Traverso, *et al.* 2002; Ahlquist, *et al*. 2008; Song, *et al.* 2016]. Sin embargo, no se dispone de ECAs que evalúen la eficacia del cribado con análisis del ADN fecal sobre la incidencia o mortalidad por CCR, ni evidencia de la periodicidad de la realización de la prueba. Su elevado coste, si lo comparamos con otras estrategias de cribado, hacen difícil la implantación de este método como test de cribado a nivel poblacional [Lin, *et al.* 2016].

Figura 23. Prueba rápida de cáncer de colon en heces por análisis DNA.

2.2.3.2. Biomarcadores en sangre periférica

Los biomarcadores son moléculas presentes en la mucosa del colon o en la sangre, saliva o cualquier otro fluido biológico de las personas que presentan un cáncer o una lesión precursora del mismo, que, de ser identificados, podrían establecer el diagnóstico y el tratamiento de forma más eficiente. Aunque el análisis de los biomarcadores

sanguíneos no se contempla aún entre las estrategias recomendadas para el CCR, los avances recientes en proteómica y genómica sugieren que estas tecnologías pueden ser, en un futuro no muy lejano, alternativas, o incluso análisis complementarios a los actuales métodos de cribado [Ye, *et al.* 2017]. En la actualidad se están investigando diferentes tipos de moléculas (metilación del ADN, miRNAs, proteínas,…). El único estudio existente, realizado en población de riesgo medio, evaluó la precisión diagnóstica del ADN metilado de la septina 9 (mSEPT9) en sangre periférica. En una muestra de 7.941 personas asintomáticas, con edad media de 60 años, se analizó la precisión diagnóstica de la mSEPT9 circulante para detectar CCR. La sensibilidad y especificidad para detectar CCR fue de 48,2% (IC 95% 32,4-63,6%) y 91,5% (IC 95% 89,7%-93,1%), respectivamente [Church, *et al.* 2014].

La prueba de metilación del gen SEPT9 en plasma Epi proColon (Epigenomics AG, Berlín, Alemania) es actualmente la única prueba de sangre disponible comercialmente para la detección y cribado temprano de CCR, y fue aprobada recientemente por la FDA de los Estados Unidos como prueba de CCR para población de riesgo medio.

Antígeno Carcinógeno-embrionario (CEA) y antígeno de carbohidratos 199 (CA199) son los dos marcadores de CCR de glucoproteína en suero más comunes, sin embargo, no son apropiados para el cribado de CCR debido a su baja sensibilidad y la falta de especificidad, especialmente para CCR en estadio inicial.

Según las conclusiones del estudio de Song *et al.* en 2016, en personas asintomáticas de riesgo medio de padecer CCR, el test ADN fecal detectó significativamente más cánceres que SOHi pero también tuvo mayor número de falsos positivos (ver tablas 7 y 8).

Tabla 7. Estudio comparativo de Tasa de Sensibilidad y especificidad para CCR Y Adenoma Avanzado (AA) de 3 tipos distintos de test. *Modificado de Song, et al. (2016).*

	SOHi	DNA FECAL	SEPTINA9
Sensibilidad CCR	79%	92%	68%
Especificidad	94%	87%	80%
Sensibilidad AA	24%	42%	18%

Tabla 8. Tasa de detección positiva de SETP9, FIT y test CEA y varias combinaciones entre ellos. *Modificado de Song, et al. (2016).*

SEPT9 SÓLO	FIT SÓLO	CEA SÓLO	SEPT9+FIT	SEPT9+CEA	FIT+CEA	SEPT9+FIT+CEA
77,0%	74,6%	41,3%	94,4%	86,4%	84,5%	97,2%
(181/235)	(53/71)	(97/235)	(67/71)	(203/235)	(60/71)	(69/71)

2.2.3.3. Pruebas endoscópicas

La **colonoscopia**, considerada el Gold estándar como método para reducir la incidencia y la mortalidad, permite la visualización directa de la mucosa colónica mediante la introducción por el ano de un tubo flexible de 12mm. Debe de ser [Jover, *et al.* 2012]:

- completa (exploración hasta alcanzar válvula ileo cecal en ciego) (ver figura 24)
- precisa de una preparación colónica adecuada (en la escala de calidad de limpieza colónica Boston ≥ 6 en figura 25) [Calderwood, *et al.* 2010; Lai, *et al.* 2012].
- se realiza bajo sedación profunda
- se debe efectuar una exploración minuciosa con tiempo de retirada superior a 6 minutos y por profesionales de probada experiencia

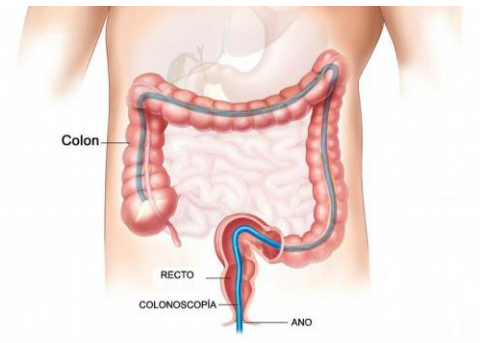


Figura 24. Colonoscopia completa.

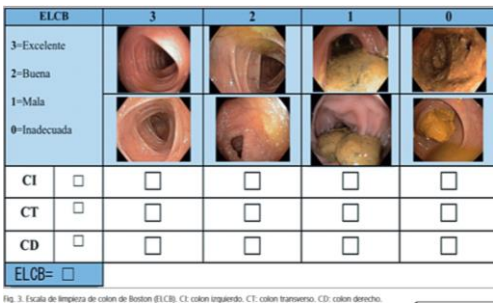


Figura 25. Escala de Boston.

La evidencia de los efectos de la colonoscopia de cribado sobre la incidencia y mortalidad del CCR, comparado con no cribado, proceden de estudios observacionales. En la cohorte del National Polyp Study, la resección de pólipos adenomatosos mediante colonoscopia disminuyó un 53% la mortalidad por CCR

(HR 0,47; IC 95% 0,26-0,80) [Zauber, *et al.* 2012] y la incidencia entre el 76% y el 90% [Winawer, *et al.* 1993]. No disponemos actualmente de ningún ECA sobre la eficacia de la colonoscopia para reducir la incidencia y la mortalidad del CCR en la población de riesgo medio, aunque están en marcha varios estudios como NordICC [Kaminski, *et al.* 2012], COLONPREV [Quintero, *et al.* 2012] y SCREESCO [https://clinicaltrials.gov] entre otros. Estos estudios comparan la colonoscopia versus SOHi bienal o anual y en un futuro próximo arrojarán datos comparativos muy relevantes a este respecto. En un reciente meta-análisis con 11 estudios observacionales incluyendo a prácticamente millón y medio de personas con riesgo medio de CCR, se estimó una mayor magnitud del beneficio para el cribado con colonoscopia, tanto sobre la mortalidad (RR 0,39; IC 95% 0,35-0,43) como sobre la incidencia de CCR (RR 0,39; IC 95% 0,26-0,60), con heterogeneidad importante en la combinación de los estudios sobre incidencia [Pan, *et al.* 2016].

La **sigmoidoscopia** también se realiza mediante la introducción por el ano de un endoscopio que permite examinar y tratar hasta 60 cm desde el margen anal (recto, sigma y escasos 10 cm aprox. del colon descendente) (ver figura 26). Esta exploración se realiza previa limpieza del colon con enemas, sin necesidad de sedación. Cuando en la sigmoidoscopia se detecta un pólipo ≥10 mm o un carcinoma es obligado realizar una colonoscopia completa dada la mayor incidencia de lesiones sincrónicas proximales al trayecto explorado [Senore, *et al.* 2004; Castells, *et al.* 2013].

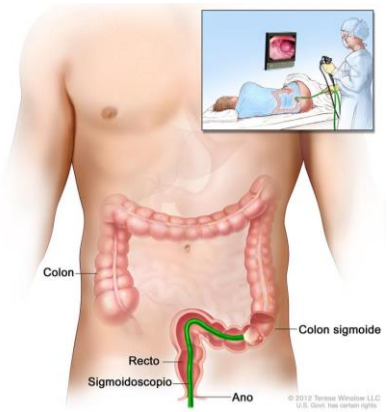


Figura 26. Sigmoidoscopia.

La disminución de la sigmoidoscopia sobre la incidencia y mortalidad de CCR ha sido demostrada de forma consistente en cuatro ECAs, uno de ellos en Reino Unido "Sigmoidoscopy Screening Trial" [Atkin, *et al.* 2010], otro en Italia "SCORE Trial" [Segnan, *et al.* 2011], en Noruega" Norgewian NORCCAP Trial" [Hol, *et al.* 2009] y el llevado a cabo en Estados Unidos "PLCO Cancer Screening Trial" [Schoen, *et al.* 2012]. En su análisis combinado realizado por la "US Preventive Service Task Force" [Lin, *et al.* 2016] mostró una reducción de la mortalidad por CCR del 27% después de 11 y 12 años de seguimiento (RR 0,73; IC 95% 0,66-0,82). Este beneficio se limitó al CCR de localización distal (RR 0,63; IC 95% 0,49-0,84), así como una reducción de la incidencia de CCR del 21% (RR 0,79; IC 95% 0,75-0,85), con homogeneidad entre los estudios. La disminución de la incidencia fue

estadísticamente significativa solo para el CCR distal (RR 0,71; IC 95% 0,64-0,82).

A pesar de que la sensibilidad de la sigmoidoscopia es inferior a la de la colonoscopia, ésta ha demostrado un efecto protector hasta de 12 años, minimizando los falsos negativos siempre que se realice por personal experto y dentro de los estándares de calidad anteriormente mencionados, además pudiéndose justificar un intervalo de 10 años entre sigmoidoscopias de cribado [Fitzpatrick-Lewis, *et al.* 2016; US Preventive Services Task Force, *et al.* 2016]. En la tabla 9 se pueden apreciar las diferencias respecto a las lesiones encontradas en las diferentes pruebas de cribado.

Tabla 9. Lesiones encontradas en colonoscopia, sensibilidad y especificidad de DNA fecal y SOHg. *Modificado de Imperiale (2012).*

Lesiones encontradas	Colonoscopia (N= 9.989)	DNA Fecal (N=9.989)			SOHi (N=9.989)		
		N	Sensibilidad	Especificidad	N	Sensibilidad	Especificidad
CCR (todos los estadios)	65	60	93,3		48	73,8	
CCR (estadio I y II)	60	56	93,3		44	73,3	
CCR + Displasia severa	104	87	83,7		66	63,5	
Adenoma Avanzado= AA+ adenoma serrado sesil >10mm	757	321	42,4		180	23,8	
Adenomas no avanzados	1.893	498	17,2		220	7,6	
Colonoscopias negativas + Adenomas no avanzados+ no neoplásicos	9.167	1231		86,6	472		94,9
Colonoscopias negativas	4.457	455		89,8	162		89,8

2.2.3.4. Pruebas de imagen

La **cápsula endoscópica** de colon es un método mínimamente invasivo que permite explorar la totalidad de la mucosa colónica de forma prácticamente segura, aunque no exenta de efectos adversos (ver figura 27). Precisa de limpieza colónica exhaustiva, pero sin necesidad de sedación, radiación o insuflación de aire/agua, reduciéndose por tanto las complicaciones.

Consiste en un dispositivo que mide 31,5x11,6 milímetros que se traga con una mínima cantidad de agua con dos cámaras en su interior, unos sensores y una grabadora que emite imágenes. La información se descarga en una estación

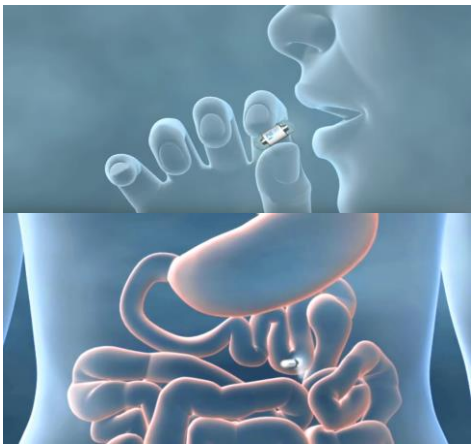


Figura 27. Cápsula endoscópica.

de trabajo para su lectura siendo aproximadamente de unas 5 a 7 horas de visualización de imágenes por un endoscopista. Si detecta pólipos o CCR, es preciso realizar una colonoscopia óptica para confirmar el diagnóstico y posible tratamiento (polipectomía). Este procedimiento ha sido propuesto por la Sociedad Europea de Endoscopia Gastrointestinal como una alternativa a la colonoscopia para el cribado del CCR en población de riesgo intermedio. Sin embargo, no existe evidencia contrastada para su indicación como una prueba de cribado de primera línea, aunque sugieren dicha posibilidad para las personas que se niegan a realizar una colonoscopia óptica o que su estado de salud les impide afrontar una prueba invasiva [Pioche, *et al*. 2018]. Un estudio que comparó la cápsula de colon y la colonoscopia óptica para el cribado del CCR, mostró que la cápsula es más coste-efectiva siempre y cuando la participación supere en un 20% a la de la colonoscopia [Hassan, *et al*. 2008].

La **colonografía** por tomografía computarizada o también llamada colonoscopia virtual (ver figura 28) consiste en la obtención de imágenes tomográficas tras la insuflación del colon con aire o dióxido de carbono, y la posterior reconstrucción de las imágenes por ordenador en dos o tres dimensiones. Su interpretación es relativamente ágil por un radiólogo (20 a 30 minutos). La prueba requiere la misma preparación que para la colonoscopia (aunque existen programas de eliminación de material fecal), sin necesidad de sedación, pero no exenta de complicaciones. Capaz de detectar CCR y pólipos ≥10mm que posteriormente precisarán de una colonoscopia óptica y terapéutica para su extirpación [Senore, *et al.* 2017].

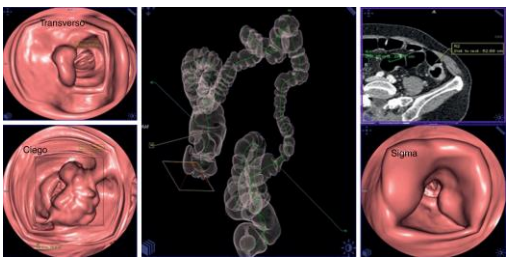


Figura 28. Colonografía.

3. EFECTOS ADVERSOS DEL CRIBADO

No debemos subestimar la aparición de efectos adversos en el cribado, como son las complicaciones derivadas de la colonoscopia y los cánceres de intervalo (CI). De hecho, un programa de cribado poblacional debe evaluar estos aspectos e implementar medidas preventivas cuando el riesgo de la aparición de eventos adversos es superior al beneficio y no sería asumible desde el punto de vista ético, si no es capaz de asegurar la realización del programa con una atención de alta calidad.

3.1. Complicaciones graves de la colonoscopia

En un reciente meta-análisis publicado se combinaron la prevalencia de complicaciones colonoscópicas graves como la perforación posterior a la colonoscopia 0,5 / 1000 (IC 95% 0,4-0,7), hemorragia 2,6 / 1000 (IC 95% 1,7-3,7) y mortalidad 2,9 /100.000 (IC 95% 1.1-5.5) [Reumkens, *et al.* 2016].

En el año 2014, dentro del entorno del programa de cribado, se realizó un estudio caso-control (393/446) sobre mortalidad y complicaciones dentro de los 30 días posteriores a la colonoscopia. Se cruzaron las bases de datos del Centro Coordinador del Programa (PCCR), con el Conjunto Mínimo Básico de Datos (CMBD) y el registro de altas hospitalarias de Osakidetza para conocer de manera certera los ingresos después de la realización de colonoscopia de cribado, tras 6 años de implantación de programa y según fueron definidas las complicaciones a 10 y 30 días posterior a la colonoscopia en la guía europea [von Karsa, *et al.* 2010]: hemorragia grave con transfusión, perforación con o sin intervención quirúrgica, las derivadas de la sedación y síndrome post polipectomía, así como muerte. Se realizaron, 39.254 colonoscopias de cribado siendo la tasa de complicaciones graves del 1,0%. Los predictores independientes fueron sexo (OR 1,68 para hombres; IC 95% 1,18-2,39), riesgo quirúrgico ASA (OR 1,73 para ASA II-III, IC 95% 1,53-3,69), intervención quirúrgica abdominal previa (OR 2,37; IC 95% 1,72 a 4,08), divertículos (OR 2,89; IC 95% 1,94 a 4,30), calidad de limpieza colónica inadecuada (Escala de Boston <6) (OR 29,35; IC 95% 6,52-132,17), hallazgo neoplasia avanzada (OR 4,92; IC 95% 3,29-7,36), hallazgo CCR estadio I (OR 9,44; IC 95% 4,46-20,0), pólipos en el colon derecho (OR 2,27 IC 95% 1,38-3,74) y clasificada por endoscopistas como polipectomía compleja (OR 2,00; IC 95% 1,25-3,20). En dicho estudio se refleja que el PCCR está dentro de las

tasas más altas publicadas hasta la fecha en lo que respecta a complicaciones graves, pero no a mortalidad (ninguna hasta la fecha de inclusión de casos en diciembre 2014) [Rutter CM, *et al.* 2012]. Se deriva pues, de este análisis que la colonoscopia, con o sin extirpación de una lesión, es un procedimiento invasivo con un riesgo innegable de complicaciones severas. Factores como la limpieza inadecuada o el hallazgo de neoplasia avanzada, son determinantes para la aparición de un evento adverso, debiendo implementarse medidas correctoras para reducir el número de complicaciones [Arana-Arri, *et al.* 2018].

3.2. Cáncer de Intervalo

El cáncer de intervalo, es el CCR que se presenta tras un resultado negativo en SOH y antes de la siguiente invitación, y este es el denominado cáncer de intervalo de SOH (CI_FIT). El que se produce antes de la colonoscopia de revisión recomendada por los endoscopistas tras la colonoscopia de cribado diagnóstica se denomina CI_COL. Ambos deben de ser medidos para calcular la sensibilidad y la especificidad del test de cribado, así como de la colonoscopia de cribado. Estos son parámetros de obligada búsqueda para conocer la efectividad del programa, siendo importante seguir los casos que por edad >69 años salen del PCCR en su última invitación al cribado (69 años).

En el estudio realizado en el PCCR de la CAPV entre enero de 2009 y diciembre de 2015 tras la invitación a 1.193.602 personas, fueron diagnosticados dos mil quinientos dieciocho cánceres, 18 IC_COL de 43.542 colonoscopias realizadas y 186 IC-FIT antes de la siguiente invitación a los 769.200 FIT negativos. Como variables predictoras de riesgo de padecer un cáncer de intervalo no se encontró significación en el sexo, la edad y el índice de privación; sí por el contrario en el estadio y la localización. Se observó que había menos riesgo cuando la localización era distal en lugar de proximal (OR 0,28; IC 95% 0,20-0,40) [Portillo, *et al.* 2017].

4. EVALUACIÓN ECONÓMICA DE LOS PROGRAMAS DE CCR

La evidencia científica avala las estrategias de cribado de CCR frente a no realizar cribado mediante cualquiera de sus modalidades. La evidencia existente muestra una sustancial reducción de la incidencia y la mortalidad, así como un incremento de los años de vida ganados ajustados por calidad (AVAC) y de la supervivencia. Hay que destacar, igualmente, que la evidencia disponible refleja una no desdeñable reducción de los costes, especialmente si los comparamos con el coste que suponen los tratamientos del CCR en estadio avanzado, puesto que los estadiajes de los tumores detectados por los programas de cribado se encuentran, principalmente, en estadios iniciales (68%) [Portillo, *et al.* 2013] frente a los CCR detectados en personas sintomáticas de los cuales únicamente el 40% del total se encuentran en dichos estadios [Gil, *et al.* 2012; Morris, *et al.* 2012].

El análisis de coste-efectividad (ACE) es una forma de análisis económico que compara los costes relativos con los resultados de dos o más alternativas terapéuticas. La relación coste-efectividad de una intervención preventiva es la relación que hay entre el coste de la intervención y una medida relevante de su efecto, considerándose en el caso de los CCR, la disminución de la incidencia y mortalidad, así como los AVAC y la supervivencia por la puesta en marcha del cribado CCR como los resultados de interés. Si bien los modelos de simulación para los análisis de coste-efectividad son muy útiles para planificar, organizar y gestionar los programas de cribado en función de los recursos existentes en cada sistema, no debemos de perder de vista que dichos estudios deben valorarse en cada contexto y que estos únicamente representan aproximaciones a la práctica clínica de cada medio [Greuter, *et al.* 2017].

Una revisión sistemática (RS) que incluyó 55 estudios de evaluación económica, analizó el coste-efectividad de diferentes sistemas de cribado, sugiriendo que el cribado con SOHg, SOHi, sigmoidoscopia ó colonoscopia frente a no cribar es coste-efectivo, pero no pudo determinar cuál de las cuatro estrategias era la más efectiva, ya que estaba directamente relacionado con el porcentaje de adherencia a los distintos cribados. Esta misma RS sugirió que los nuevos métodos de cribado (ADN fecal, colonografía y cápsula endoscópica) no son coste-efectivos comparados con el resto de métodos de cribado anteriormente mencionados [Lansdorp-Vogelaar, *et al.* 2011]. Estos resultados son absolutamente concordantes con los de otra RS realizada posteriormente [Patel, *et al.* 2015].

Los estudios de coste-efectividad con información detallada sobre costes obtenidos directamente de ECAs muestran que el cribado con SOHg bienal tiene un

coste incremental por año de vida ganado ajustado por su calidad de 1.584£ (IC 95% 717-8.612) [Whynes, *et al.* 2004]. Otro ECA comparó el coste-efectividad de SOHg, la SOHi y no realizar cribado en población de riesgo intermedio y constató que, después de una invitación completa al cribado, SOHi era la estrategia más coste-efectiva [Rossum, *et al.* 2011].

En el mismo sentido, los modelos de decisión predictivos como el MISCAN-Colon (MIcrosimulation SCreening ANalysis-colon) atribuyen una ganancia similar en Años de Vida Ajustados por Calidad (AVAC) al cribado con colonoscopia cada 10 años, SOHg o SOHi anual, y a la sigmoidoscopia cada 5 años [Zauber, *et al.* 2008].

Un estudio canadiense publicado en 2010 y realizado con un modelo de decisión matemático de Markov, constató que la colonoscopia cada 10 años era la estrategia que reducía más la incidencia y mortalidad, pero también la más costosa. El descenso en la mortalidad tras cribado con colonoscopia cada 10 años, SOHi anual y SOHg fue del 83%, 74% y 55%, respectivamente, mientras que la incidencia se reducía un 81%, 65% y 44% con cada uno de los métodos. La estrategia más coste-efectiva de las evaluadas en este estudio es el cribado mediante test de SOHi anual, con un coste incremental por AVAC ganado de 611$, respecto a los 6.133$ de la colonoscopia cada 10 años y los 9.159$ de SOHg anual [Telford, *et al.* 2010] (ver tablas 10 y 11 y figura 29).

Tabla 10. Resultados del análisis de casos: personas 50 años o más con riesgo medio de CCR que participan o no en una de las distintas estrategias de cribado. *Modificado de Telford, et al. (2010).*

Estrategia	Coste medio $Can. 2007	Media AVAC	Coste Incremental $Can. 2007	Incremento AVAC	Ratio incremental coste-efectividad
No cribado	783	15,2	NA	NA	NA
SOHg/año	1.415	15,26	632	0,069	9.159
SOHi/año	1.437	15,3	22	0,036	611
Colonoscopia/10años	1.529	15,32	92	0,015	6.133

Tabla 11. Comparativa de coste-efectividad de tres diferentes estrategias de cribado CCR comenzando a los 50 años y seguimiento de por vida a 1.000.000 personas frente a no cribado. *Modificado de Telford, et al. (2010).*

Estrategia	Coste $Can 2007	AVAC	Muertes prevenidas	Reducción en Tasa de Mortalidad	Casos CCR prevenidos	Reducción en Tasa de Incidencia
SOHg /año	63.139.823	6.914	2.113	55	2.748	44
SOHi / año	65.429.821	10.491	2.834	74	4.081	65
Colonoscopia/ 10años	76.094.757	12.013	3.157	83	5.082	81

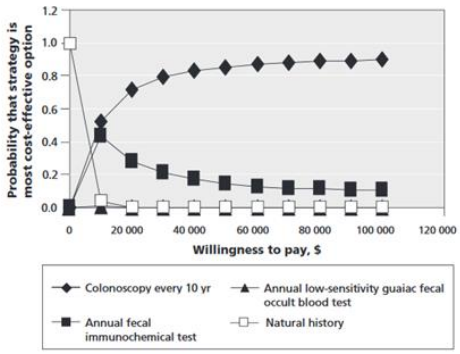


Figura 29. Curva de aceptabilidad de coste-efectividad. El incremento de AVAC estimado con cada una de las estrategias fue ajustado al coste y a la disposición a pagar (del término inglés "willingness to pay"). La probabilidad que una estrategia sea coste-efectiva (eje Y) frente a estrategias alternativas se muestra en los rangos disposición a pagar hasta 100.000 $ por AVAC (eje X). *Tomada de Telford, et al. (2010).*

Otro estudio realizado en Ontario aplicando algoritmos de micro simulación con un modelo de decisión mostró que el cribado bienal con SOHi era más efectivo y de menor coste que el cribado con SOHg. Para la realización del mismo número de colonoscopias necesarias (con un punto de corte positivo de ≥200 ng Hb/ml) en población de 50-74 años, la SOHi comparada con la SOHg obtuvo 11 AVAC extra ganados con un ahorro de 333.300$ canadienses por 1.000 participantes. Sin restricción de número de colonoscopias (punto de corte ≥50 ng Hb/ml) entre los 45-80 años, la SOHi anual es la estrategia más coste-efectiva obteniendo 27 AVAC extra ganados por 1.000 participantes, con un ahorro de 448.300$ canadienses [Goede, *et al.* 2017] (ver figura 30).

Los modelos de decisión aplicados en países europeos se decantan también por el SOHi bienal como modalidad de cribado más coste-efectiva a 10 años, con un coste incremental por AVAC ganado de 1.696€ para población de 55 a 74 años [Lucidarme, *et al.* 2012; Sharp, *et al.* 2012].

En España, López Bastida *et al.* en el 2010 realizaron un ejercicio de evaluación económica con un modelo de decisión de Markov y concluyeron que el cribado del CCR es coste-efectivo y que la estrategia más coste-efectiva es la prueba de SOHi con periodicidad anual, con un coste incremental de 2.154 € por AVAC ganado. Sin embargo, otras estrategias de cribado presentaban costes incrementales similares como podemos observar en las tablas 12 y 13 [Calcerrada, *et al,* 2008; López Bastida, *et al.* 2010].

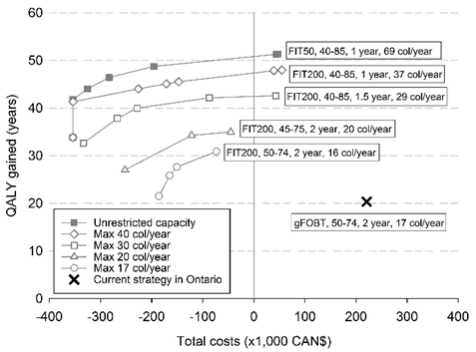


Figura 30. Límites de eficiencia dependiendo de la capacidad para realizar colonoscopias: Costes y AVACs ganados por 1.000 participantes, comparado con no cribado. QUALY = AVACS; col/year= colonoscopias necesarias por cada 1.000 participantes por año; FIT 50/200 = FIT con punto de corte para positividad 50/200. *Tomado de Goede, et al. (2017).*

Tabla 12. Resultados de todas las estrategias de cribado de CCR y de no cribado. *Tomado de López Bastida et al. (2010).*

Estrategia	Costes(€)	Efectividad (AVAC)	ICER
Sin cribado	4.654	15.891	
COLONOSCOPIA (cada 10 años)	5.429	16.218	Dominada
COLONOSCOPIA (1 sola vez a los 50)	5.425	16.216	Dominada
SIGMOIDOSCOPIA (cada 5 años)	5.893	16.419	Dominada
SOHg bienal	5.274	16.158	2.322€/AVAC
SOHg anual	5.378	16.218	1.733€/AVAC
SOHi bienal	5.890	16.444	2.265€/AVAC
SOHi anual	6.004	16.518	1.541€/AVAC

Tabla 13. Resultados de la mejor estrategia de cribado de CCR frente a no cribado. *Tomado de López Bastida et al. (2010).*

Estrategia	Costes €	Efectividad (AVAC)	ICER
Sin cribado	4.654	15.891	
SOHi anual	6.004	16.518	2.154€/AVAC

Todos los estudios recuperados muestran por tanto que el screening poblacional es coste-efectivo frente a no hacer o estrategias oportunísticas, el grado de beneficio es dependiente de la prueba a utilizar y los ratios de participación de la población en los cribados. Estos ratios se relacionan asimismo con la selección de la prueba a utilizar y la aceptabilidad de la misma por la población a riesgo. Es por ello que estrategias con pruebas más cruentas, como es el caso de la colonoscopia o la sigmoidoscopia como prueba inicial, suelen contar con menores ratios de participación por razones obvias. Estos parámetros deben de ser tenidos en cuenta en la selección e implantación de las pruebas a utilizar y las consecuencias en salud y económicas que dichas decisiones pueden tener en la población.

HIPÓTESIS Y OBJETIVOS

II.- HIPÓTESIS Y OBJETIVOS

1. HIPÓTESIS

Se observa una alta tasa de aceptación del programa de prevención del País Vasco por parte de los ciudadanos, tanto en la participación, en la realización de la prueba de cribado, FIT, como en la prueba de confirmación diagnóstica, la colonoscopia. Por otro lado, la también elevada tasa de lesiones pre-malignas y malignas en estadios iniciales detectados en la colonoscopia de cribado tras el FIT positivo, resulta muy determinante en la decisión de utilizar este test como prueba de cribado poblacional. La satisfactoria implantación del programa de cribado en el País Vasco ha permitido alcanzar excelentes resultados al ser comparados con las recomendaciones de la EU, así como de la evidencia científica disponible, y se espera redundará en el beneficio a nivel poblacional. Por otro lado, programas de cribado implementados en otras regiones europeas y con mayor recorrido en el tiempo, presentan resultados de beneficio epidemiológico muy alentadores a la hora de poner en marcha una acción preventiva de elevado coste inicial pero que en un futuro cercano resulta ser coste-efectiva al permitir reducir la morbi-mortalidad que se deriva de los estadios avanzados en el CCR y disminuir la necesidad de utilizar tratamientos oncológicos de alto presupuesto.

Evaluar la efectividad del programa de cribado de CCR mediante la estimación del beneficio epidemiológico (resultados en salud), y conocer la proyección de la carga asistencial y económica que repercutirá en el sistema sanitario (inversión en recursos) es una necesidad para nuestro sistema de salud.

Teniendo en cuenta estas premisas las hipótesis de este trabajo son:

1. **El Programa de prevención de CCR disminuye la incidencia y mortalidad respecto al no cribado.**
2. **El Programa de prevención de CCR mejora la supervivencia y los AVAC respecto al no cribado.**
3. **El Programa de prevención de CCR es coste efectivo respecto al no cribado en el País Vasco.**

2. OBJETIVOS

2.1. Principales

Determinar los beneficios del programa de prevención de cáncer colorrectal de Euskadi en términos de reducción de incidencia, mortalidad y años de vida potencialmente perdidos basado en un ejercicio de micro simulación a 30 años de implementación del cribado

Analizar y comparar la supervivencia de las personas diagnosticadas de cáncer colorrectal dependiendo de la via diagnóstica de detección: programa de cribado poblacional versus diagnosticado por sintomatología

2.2. Secundarios

1. Conocer la efectividad del programa de cribado de CCR.
2. Describir los costes de la implementación del programa de cribado de CCR.
3. Conocer la eficiencia del programa de cribado de cáncer colorrectal a través de los costes de los tratamientos terapéuticos y sus resultados.
4. Analizar las características de los CCR detectados por el programa de cribado poblacional frente a los diagnosticados fuera del programa.
5. Analizar las características de las personas diagnosticadas con CCR dependiendo del tipo de participación en el programa de cribado.
6. Comparar la supervivencia de las subpoblaciones de los participantes en el cribado diagnosticados con CCR tanto de los verdaderos positivos como de los falsos negativos.

MATERIAL Y MÉTODOS

III.- MATERIAL Y MÉTODOS

1. EFECTIVIDAD: BENEFICIOS EPIDEMIOLÓGICOS

Para alcanzar el objetivo principal 1 y los objetivos específicos 1 y 2 planteados en este trabajo de investigación, se describe a continuación la metodología empleada.

1.1. Programa de prevención de cáncer colorrectal del País Vasco

La estrategia principal del programa de cribado de CCR del País Vasco se basa en: a) la puesta en marcha de un centro coordinador para planificar, organizar, gestionar las invitaciones y evaluar los resultados; b) la estrecha relación entre los centros de salud y los hospitales de referencia, a fin de hacer coincidir los casos positivos esperados con la capacidad de la colonoscopia; c) la interconexión de distintas bases de datos entre la población diana a invitar al programa y los registros de pruebas complementarias (colonoscopias) y registro de cáncer para seleccionar individuos elegibles; d) entrenamiento e implicación del personal de Atención Primaria en las distintas actividades y protocolos del programa de cribado; e) envío postal de invitaciones y de exclusiones personalizadas con información sobre el programa CCR antes de enviar el kit y, posteriormente, las instrucciones sobre cómo usarlo y un código de barras individualizado para que la persona identifique la muestra en el domicilio (este código de barras permite identificar la muestra y la persona al procesar el resultado). Las muestras se depositan en los centros de atención primaria y se procesan en laboratorios de los hospitales públicos centralizados; f) la visualización de los resultados por parte de los médicos de atención primaria como si fueran los peticionarios de la prueba y g) el envío de resultados por carta a los domicilios de los participantes. Véase figura 31, el flujograma de la invitación del programa de cribado de CCR.

En los casos positivos, se recomienda a los participantes que visiten a su médico de atención primaria, que los remitirá al hospital para que les realicen la prueba de confirmación diagnóstica, con sedación y pudiendo ser terapéutica “una colonoscopia”. Las colonoscopias se realizan en hospitales públicos bajo sedación profunda por especialistas expertos. El seguimiento de todas las lesiones

se lleva a cabo mediante una estrecha coordinación entre los profesionales de Atención Primaria y los de las Unidades de Atención Especializada. Todos los casos son seguidos y codificados por el personal técnico de la Oficina del Centro Coordinador del Programa siguiendo las directrices de la Unión Europea [von Karsa, et al. 2010] y el consenso de la Red Española de cribado [Salas, *et al.* 2017]. Se registran las complicaciones inmediatas y a 30 días de la colonoscopia, así como el cáncer de intervalo tanto de FIT como de colonoscopia de cribado.

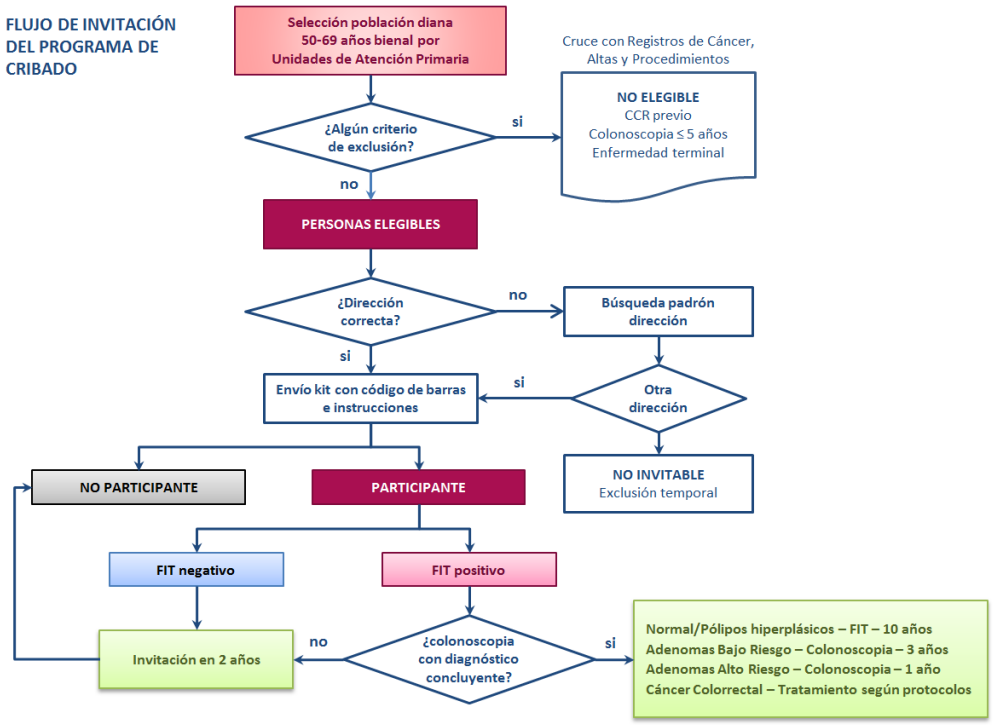


Figura 31. Flujo de invitación del programa de cribado.

El test utilizado fue FobGold® (Sentinel CH. SpA, Milán, Italia) y OC-Sensor® Micro (Eiken Chemical Co. Ltd., Tokyo, Japón), si bien OC-Sensor® Micro (desde 2009 hasta ahora) en el 95% de los invitados al PCCR y FobGold® entre 2009-2010 en 15.000 invitaciones. El punto de corte de positividad de hemoglobina fecal (f-Hb) fue de 20 µg Hb / g de heces en ambos sexos.

Se considera participante la persona que entrega el test y obtiene un resultado válido (positivo/negativo). Se considera una colonoscopia válida y definitiva si se alcanza el ciego y la calidad de la preparación colónica es adecuada (escala de Boston≥6). De acuerdo con esto, los resultados de la colonoscopia se codifican como: 1) Normal / sin patología adenomatosa; 2) pólipos hiperplásicos;

3) adenomas de bajo riesgo (ABR) 4) adenomas de riesgo intermedio (ARM) ; 5) adenomas de alto riesgo (AAR) ; 6) adenoma avanzado: adenoma de riesgo intermedio + adenoma de alto riesgo; 7) Cáncer (CCR), neoplasia que se infiltra en la capa de submucosa a través de la muscularis mucosae ≥pT1. Se utiliza la clasificación TNM de Tumores Malignos en su 7ª edición [Sobin, *et al.* 2009] y para el seguimiento del riesgo el algoritmo propuesto en la guía europea 2010 por Atkin *et al*, 2010 y que a continuación se muestra en la figura 32. En la tabla 14 se definen las categorías de lesiones extirpadas según la guía europea [von Karsa, et al. 2010] y su adaptación para MISCAN-Colon. Para cada lesión se recoge el tipo de test indicado y el tiempo de seguimiento de la lesión.

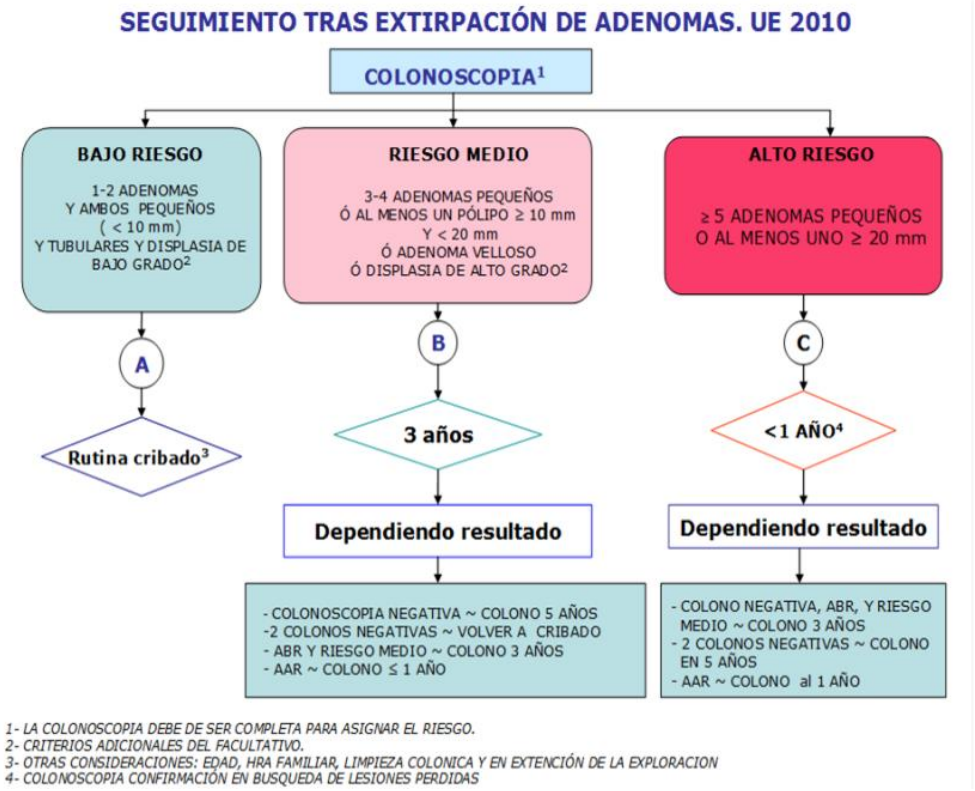


Figura 32. Seguimiento tras extirpación de adenomas. *Modificado de Atkin et al. 2010.*

Tabla 14. Esquema de lesiones y de seguimiento de la guía europea y su adaptación a MISCAN-Colon.

Resultado colonoscopia	Guía europea 2010	Adaptación MISCAN-colon	Siguiente test	Tiempo de seguimiento
Normal	No adenomas	No adenomas	FIT	10 AÑOS
Adenoma bajo riesgo	1-2 adenomas ≤10mm	1-2 adenomas ≤10mm	FIT	5 AÑOS
Adenoma medio riesgo	3-4 adenomas 10-20mm ó displasia severa	>2 adenomas ≤10mm	Colonoscopia cribado control	3 años
Adenoma alto riesgo	≥5 adenomas ó ≥20mm	1 adenoma >10mm	Colonoscopia cribado control	1 año

1.2. Modelización MISCAN-Colon

El modelo de micro simulación de cribado de cáncer colorrectal holandés MISCAN-Colon utilizado estimó los resultados de la estrategia de cribado con test SOHi bienal en la población del País Vasco. MISCAN-Colon es un modelo de microsimulación estocástico para el CCR programado en Delphi (Borland Software Corporation, Scotts Valley, California, Estados Unidos) [Loeve, *et al.* 1998]. Se puede utilizar para explicar y predecir las tendencias en la incidencia y mortalidad de CCR y para cuantificar los efectos y los costes de la prevención secundaria, la detección de CCR y la vigilancia después de la polipectomía de las lesiones pre-malignas, siendo posible conocer de esta manera, la carga asistencial en lo que a colonoscopias de seguimiento se refiere. En dicho modelo se representa la historia de vida de la población en general desde el nacimiento hasta la muerte. El CCR aparece en esta población a partir de los 50 años y de acuerdo a la secuencia adenoma carcinoma [Muto, *et al.* 1975], entendiendo que más de un adenoma puede aparecer en una persona y que cada adenoma puede independientemente desarrollarse en un cáncer invasivo. Los adenomas pueden progresar en tamaño desde uno pequeño (<5 mm) a otro de tamaño mediano (6-9 mm) y a grande (>10 mm). Además, algunos de ellos degenerarán a malignos transformándose en cánceres invasivos en estadio I y otros pudieran progresar a estadios más avanzados, esquema que se muestra en la figura 33 sobre la descripción del modelo conceptual de la historia natural del CCR en la herramienta de micro simulación MISCAN-Colon. En cada uno de los estadios, el CCR puede desarrollar síntomas, aunque en otros casos no lo hará durante la progresión de un estadio al siguiente. Cuando el CCR se desarrolla, la supervivencia tras el diagnóstico clínico depende del estadio, siendo superior en los estadios

iniciales. En cualquier momento de la vida de la persona, el proceso puede ser interrumpido si esta muere por cualquier otra causa. MISCAN-Colon permite el seguimiento de toda la población diana desde la primera invitación al programa de cribado hasta su muerte y medir tanto los beneficios a largo plazo como los costes relacionados con el programa de cribado.

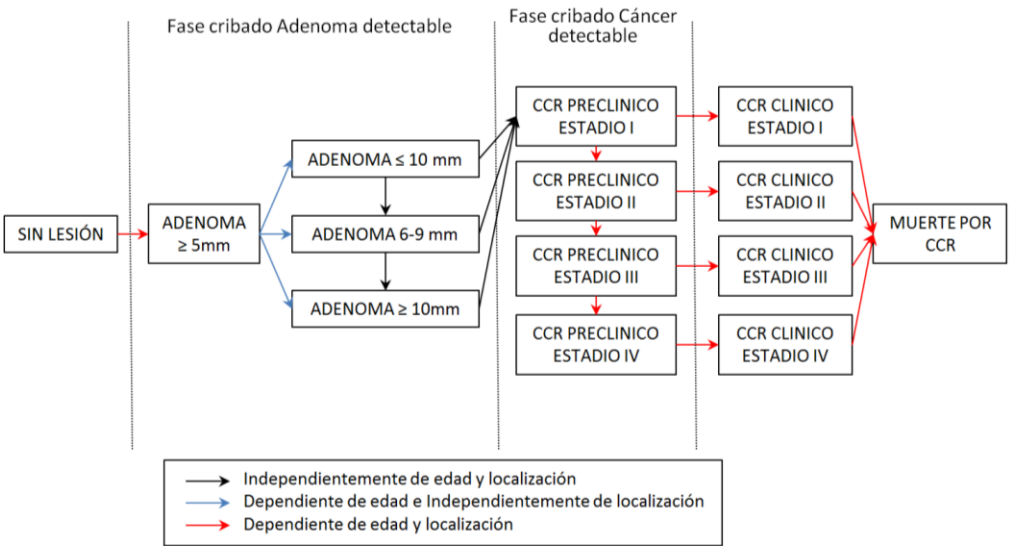


Figura 33. Descripción del modelo conceptual de la historia natural del CCR de MISCAN-Colon. *Modificada de Loeve, et al. 1998.*

Muy posteriormente Rutter*, et al.* en 2016 hacen otra propuesta muy similar donde muestran como el cribado puede modificar la historia clínica personal desde su desarrollo de lesiones premalignas a cáncer, quedando representada en la figura 34 [Rutter, et al. 2016].

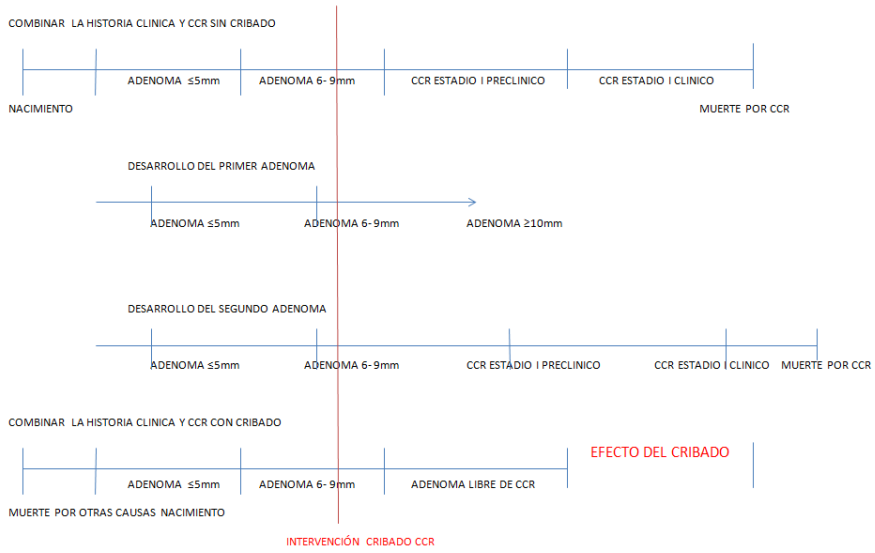


Figura 34. Efecto de la intervención del cribado CCR con la historia clínica personal con y sin cribado y en el desarrollo de adenomas. *Modificado de Rutter et al, 2016.*

Para la calibración del modelo MISCAN-Colon se analizaron los datos de incidencia y mortalidad del Registro Poblacional de Cáncer 2005-2008 por grupos quinquenales de edad y sexo facilitados por el Departamento de Salud de la CAPV, los datos poblacionales estimados según Instituto Vasco de Estadística (EUSTAT), el estudio COLONPREV [Quintero, *et al.* 2012] y los datos procedentes del programa de cribado, además de otros estudios [Arminski y McClean, 1964; Clark, *et al.* 1985].

Los principales resultados de 2009-2014 se utilizaron para describir los principales beneficios del programa. Para el modelo de simulación MISCAN-Colon, se utilizó el período de 2009-2012 de invitación a las personas residentes en el País Vasco de entre 50 y 69 años al PCCR en primera y segunda invitación. Se consideró invitación válida la realizada a la población elegible (población diana menos población excluida por CCR previo, colonoscopia previa en los 5 últimos años y enfermedad grave en el momento de la invitación), y que no había sido devuelta dicha invitación por domicilio desconocido.

Para ajustar los datos al modelo se calculó el intervalo entre dos invitaciones en una media de 2,3 años, dado que las invitaciones no siguen un patrón regular bienal y se distribuyeron los adenomas en menores y mayores de 10mm, designando a éstos las dos únicas categorías de adenomas de bajo y alto riesgo, respectivamente.

La proyección realizada fue a 30 años desde la implementación del programa de cribado. La herramienta matemática

MISCAN-Colon reprodujo a la población viva en Euskadi en el año 2008 con su estructura dividida por edades en diferentes estratos dependiendo de la edad en la cual fueron invitados al programa por primera vez (o nunca fueron invitados si eran mayores de 70 años en el 2008). De esta manera el modelo posibilita la evaluación del cribado como una intervención de salud pública en términos de beneficios en salud relacionada con los costes. En la primera parte del proceso de simulación fueron distinguidas en la adaptación del modelo, primero, la historia natural del cáncer, y en segundo lugar los efectos del cribado. Cuando definimos la historia natural del cáncer, los ciclos de vida (del inglés life histories) son generadas durante la cual los pólipos colorrectales y el cáncer pueden desarrollarse y algunas veces ocasionar la muerte en la cual el cribado no ha tenido lugar. En la segunda parte, el cribado de CCR es simulado y este cambiará algunos ciclos de vida. El sumatorio de esos cambios constituye la efectividad del cribado. El modelo MISCAN-Colon fue desarrollado con el programa Cancer Intervention and Surveillance Modelling Network (CISNET) [Vogelaar, *et al.* 2016] y calibrado con la realidad demográfica y epidemiológica de la población de Estados Unidos. Su posterior aplicación al programa de cribado de CCR holandés fue determinante para su implementación y requirió una nueva calibración, así como la adaptación a las características demográficas y epidemiológicas de la población de interés que en este caso era la población vasca de 2.230.000 personas. Los parámetros que se utilizaron en el modelo para este estudio fueron:

Para la calibración:

- Población
- Distribución por cohortes de nacimiento
- Tablas de vida para la muerte por otras causas
- Incidencia CCR ajustada a población mundial
- Prevalencia de adenomas según el estudio COLON-PREP (muy superior a la prefijada por el modelo)

El modelo tiene especificados:

- Tasas de incidencia en estadio preclínico
- Distribución de adenomas y cáncer en lo que respecta a la localización
- Transición desde cada uno de los estadios
- Duración en los estadios
- Correlación entre las duraciones

Los efectos del cribado:

- Patrón de cribado
- Participación
- Sensibilidad y especificidad del test utilizado
- Sensibilidad y especificidad de las colonoscopias de diagnóstico
- Seguimiento en CCR detectado por cribado

Los datos de resultados del programa son los que se muestran en la tabla 15 relativos a las rondas de invitación desde el plan piloto en el año 2009 hasta el 2014 registrándose un número pequeño con más de 2 invitaciones.

Tabla 15. Principales resultados del PCCR por sexo y ronda de invitación 2009-2014.

	Primera ronda				Segunda Ronda				Tercera Ronda				TOTAL				TOTAL	
	Mujeres		Hombres		Mujeres		Hombres		Mujeres		Hombres		Mujeres		Hombres			
Población Elegible	298.896	%	286.054	%	154.183	%	143.960	%	41.770	%	36.670	%	494,849	%	466,684	%	961,533	%
Población Invitable	288.775	96,6	273.317	95,5	149.234	96,8	137.705	95,7	40.397	96,7	34.988	95,4	478,406	96,7	446,010	95,6	924,416	96,1
Participantes	200.422	69,4	174.968	64	108.776	72,9	93.368	67,8	30.095	74,5	24.427	69,8	339,293	70,9	292,763	65,6	632,056	68,4
FIT+	10.421	5,2	15.671	9	4.659	4,3	6.422	6,9	1.245	4,1	1.717	7,0	16,325	4,8	23,810	8,1	40,135	6,3
VPP		%		%		%		%		%		%		%		%		%
AA		29,4		47,8		23,5		39,0		24,1		40,5		27,3		44,9		37,7
Neoplasia Avanzada		34,4		54,5		27,0		43,5		27,5		44,5		31,7		50,8		43,0
CCR		5,0		6,7		3,5		4,5		3,4		3,9		4,4		5,9		5,3
Colonoscopia Diagnóstica	9.720	93,3	14.678	93,7	4.282	91,9	5.842	91,0	1.176	94,4	1.595	92,8	15,178	93,0	22,115	92,9	37,293	92,9
Lesiones Detectadas		‰		‰		‰		‰		‰		‰		‰		‰		‰
AA	3.063	15,3	7.487	42,8	1.094	10,1	2.504	26,8	300	9,9	696	28,5	4,457	13,1	10,687	36,5	15,144	24,0
Neoplasia Avanzada	3.583	17,9	8.533	48,8	1.257	11,6	2.796	29,9	342	11,4	764	31,3	5,182	15,3	12,093	41,3	17,275	27,3
CCR	520	2,6	1.046	6,0	163	1,5	292	3,1	42	1,4	68	2,8	725	2,1	1,406	4,8	2,131	3,4
CCR Estadio		%		%		%		%		%		%		%		%		
I-II	320	61,5	716	68,5	112	68,7	206	70,5	22	52,4	38	55,9	454	62,6	960	68,3	1,414	66,4
III-IV	157	30,2	279	26,7	45	27,6	76	26,0	20	47,6	25	36,7	222	30,6	380	27,0	602	28,2
Desconocido	43	8,3	51	4,9	6	3,7	10	3,4	0	0	5	7,4	49	6,8	66	4,7	115	5,4

Dadas las diferencias significativas en la epidemiología del CCR entre hombres y mujeres, el modelo MISCAN-Colon se ejecutó por separado para cada sexo por primera vez. Por lo tanto, se realizó una doble validación y calibración para adaptar el modelo MISCAN-Colon a la población vasca en dos pasos. Primero, se ajustó la incidencia de CCR por localización (C18-C21), estadio y edad antes de la implementación del cribado, incluyendo en el modelo los datos demográficos de la población vasca y los datos del Registro Vasco de tumores entre los años 2005-2008. Se utilizó el algoritmo de Newton-Raphson para calcular los parámetros del modelo óptimo, considerando éstos como aquéllos que minimizan el estadístico χ^2. El segundo paso consistió en la calibración de la herramienta, utilizando el mismo algoritmo para los parámetros relacionados con la prevalencia de adenomas. El modelo MISCAN-Colon reproduce la prevalencia de adenomas que se muestra en diferentes estudios ya publicados. Sin embargo, la prevalencia de adenomas calculada para la población vasca con una muestra del estudio COLONPREV fue estadísticamente significativa. Por lo que se consideró el modelo adaptado a los resultados del estudio COLONPREV como el caso base. Esto permitió acercar más la predicción a la realidad en Euskadi con un porcentaje mayor de lesiones pre-malignas, pero no de CCR.

Después de reproducir la historia natural sin cribado, el modelo reprodujo el comportamiento del CCR en condiciones de escenario de cribado considerando el impacto por la extirpación de las lesiones pre-malignas (adenomas) y la anticipación del estadio del CCR en el momento del diagnóstico. Esas consecuencias se tradujeron en años de vida ajustados por calidad y costes evitados en los tratamientos del cáncer. Por el contrario, el cribado genera otros costes debido a las pruebas de cribado y a las colonoscopias de confirmación diagnóstica, así como, a la vigilancia de los adenomas encontrados en el programa.

Como validación externa, fue verificado que el módulo de historia natural reprodujo la incidencia de CCR por estadio y edad en los años anteriores al inicio del programa (2005-2008) y también la prevalencia de adenomas arrojada en el estudio COLONPREV. Se consiguió un buen nivel de concordancia entre la incidencia por CCR observada y la simulada tanto en hombres como en mujeres (figura 35 y figura 36). Como validación interna, el módulo de evaluación fue probado reproduciendo invitaciones, participaciones y resultados de pruebas de cribado vasco. La validación de MISCAN-Colon siguió la misma metodología anteriormente publicada.

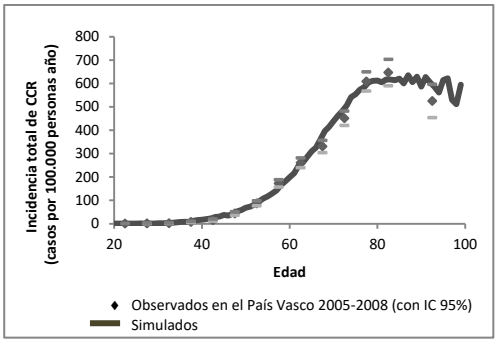


Figura 35. Incidencia CCR observada versus simulada en hombres en 2005-2008 (Base de datos del Registro de Cáncer del País Vasco).

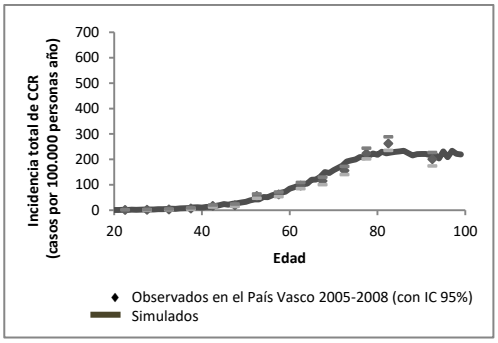


Figura 36. Incidencia CCR observada versus simulada en mujeres en 2005-2008 (Base de datos del Registro de Cáncer del País Vasco).

Los datos extraídos del Registro de Cáncer del País Vasco entre 2005 y 2008, permitió de la misma manera medir el nivel de concordancia entre lo observado y simulado en ambos sexos y por estadios del CCR, mostrando de la misma manera una calibración óptima de la herramienta de micro simulación MISCAN-Colon tal y como se observa en las cuatro imágenes de la figura 37, de los distintos estadios de cáncer.

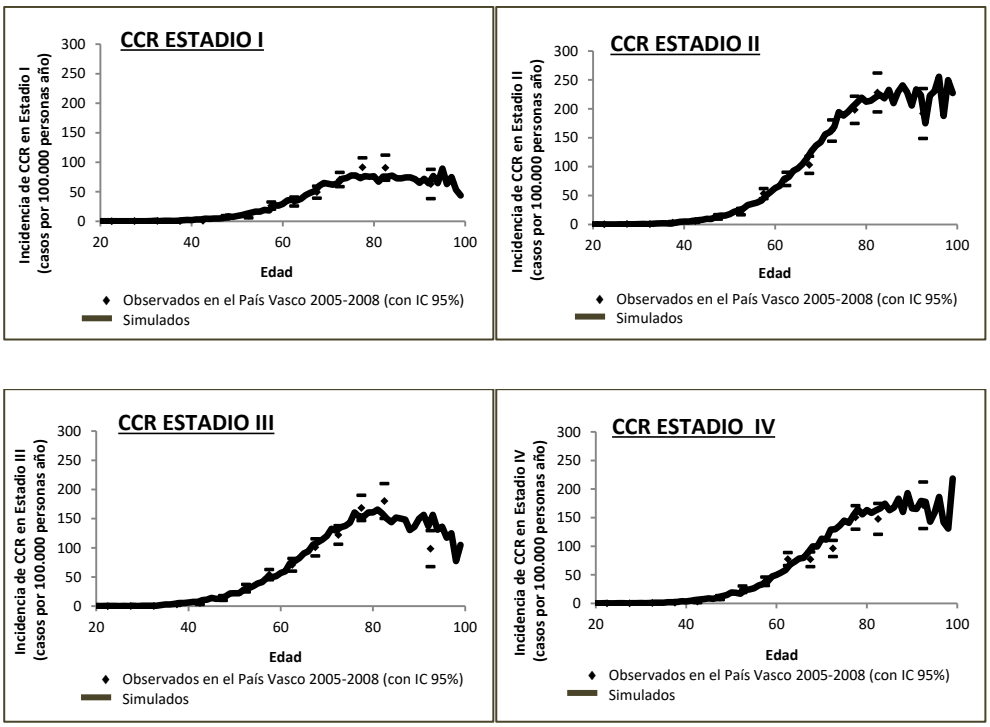


Figura 37. Incidencia CCR observada versus simulada en hombres por detección de los distintos estadios de CCR en 2005-2008 (Base de datos del Registro de Cáncer del País Vasco).

Dada la alta prevalencia de adenomas observada en el estudio COLONPREV tanto en mujeres como en hombres, esta fue enfrentada a lo observado en otros estudios como se representa para los hombres en la figura 38 y para las mujeres en la figura 39.

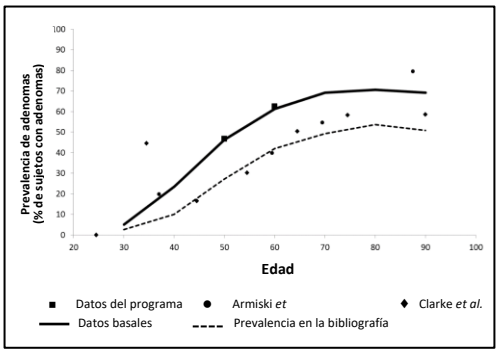


Figura 38. Prevalencia de adenomas en hombres observado en el estudio COLONPREV y otros estudios publicados versus la simulación realizada con MISCAN-Colon.

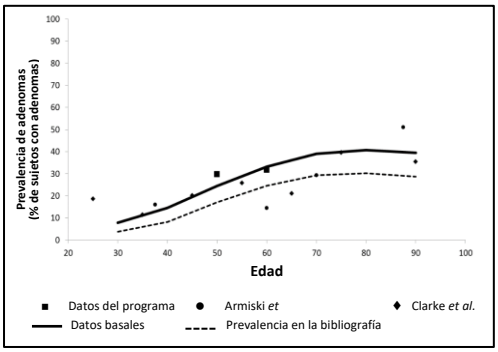


Figura 39. Prevalencia de adenomas en mujeres observado en el estudio COLONPREV y otros estudios publicados versus la simulación realizada con MISCAN-Colon.

2. ANÁLISIS DE COSTES CRIBADO/NO CRIBADO

El estudio sobre coste-efectividad y el análisis de impacto en el presupuesto sobre el programa de cribado de CCR del País Vasco utilizando la herramienta del modelo MISCAN-Colon contó con la financiación del Departamento de Salud del Gobierno Vasco (Expediente 2013111156 de 4/03/2014) y la colaboración de los componentes del equipo investigador, además del Departamento de Evaluación Económica de la Universidad Erasmus Rotterdam. El objetivo del mismo fue realizar una evaluación económica del programa de cribado a partir de los datos epidemiológicos del País Vasco, y los precios de pruebas y tratamientos de CCR actualizados a 2015. Se aplicó también el modelo de análisis de micro simulación MISCAN-Colon para calcular el impacto a corto y largo plazo en términos de resultados y costes de salud [Arrospide, *et al.* 2018].

Para ello se hizo un análisis de micro costes inicial. Los recursos asignados a cada persona examinada fueron desglosados por invitación (6,06€, incluyendo carta de invitación, kit de determinación FIT y recursos de gestión del programa), análisis FIT/participante (0,99€), consulta de atención primaria en caso de resultados FIT positivos (78,00€) y colonoscopias de cribado diagnósticas y control

(461,30€ con polipectomía y 281,30€ sin polipectomía) tal y como se muestra en la tabla 16 donde están detallados los costes del PCCR según las tasas oficiales a fecha 2015 de Osakidetza, y aplicados a los resultados derivados de 6 años desde la puesta en marcha del programa de cribado CCR.

Tabla 16. Costes del programa de prevención del País Vasco.

Costes del PCCR País Vasco	Coste unitario €	% Población
Invitaciones (1)		
Carta informativa	0,6663	100%
Carta + coste kit*	2,5889	97%
Carta resultados (participantes)	0,6325	70%
Carta error (kit incluido)	2,5889	1,30%
Carta recuerdo (para no participantes en 30 días)	0,6048	40%
TOTAL COSTES INVITACIÓN	7,0814	
Proceso colonoscopia (2)		
Visita MAP derivación colonoscopia	54	6% participantes
Visita EAP preparación colonoscopia	24	8% participantes
Evacuantes	6	8% participantes
Colonoscopia sin polipectomía	170	30% colonoscopias
Colonoscopia con polipectomía	350	70% colonoscopias
Biopsia	90	70% colonoscopias
Visita anestesista	198	20% colonoscopias
Test previo a colonoscopia (análisis, ECG, radiología)	81	30% colonoscopias
Visita MAP después de colonoscopia	54	70% colonoscopias
Visita hospital después de colonoscopia de seguimiento	198	10% colonoscopias

También se aplicó un coste promedio de 5.157€ por complicación relacionada con la colonoscopia. Para calcular los costes del tratamiento en caso de CCR, se recopilaron retrospectivamente según el estadio del CCR, los recursos necesarios de una muestra de 529 pacientes tratados en los hospitales de la red pública vasca (Osakidetza). Para los estadios I a III, se midieron los costes iniciales y de seguimiento. El cálculo del coste para la enfermedad en estadio IV combinó modelos lineales generalizados para relacionar el coste con la duración del seguimiento basado en el análisis de supervivencia paramétrica. Los costes unitarios se obtuvieron del sistema de contabilidad analítica del Servicio Vasco de Salud. La muestra incluyó 110 casos en estadio I, 171 en estadio II, 158 en estadio III y en estadio IV 90 pacientes. El coste total inicial varió de 6.968€ para estadio Ia, 12.765€ para estadio II y 13.075€ en estadio III. La estimación del coste anual de la atención de seguimiento incluyó tomografía computerizada, colonoscopia, pruebas analíticas y radiológicas y consultas externas, y se calculó la cantidad de 404€. Para aquellos pacientes en estadio IV, no se consideró el

coste del tratamiento inicial específico y el coste por cada año de seguimiento fue de 24.255€. Se determinó una pérdida de AVAC equivalente a dos días completos de vida, por colonoscopia 0,005 AVAC y dos semanas de vida por complicación 0,0384 AVAC. También se asignó una pérdida de utilidad para cada año de vida con atención al CCR.

Las evaluaciones económicas incluyeron tanto el análisis de coste-efectividad como el análisis de impacto presupuestario del programa para el Sistema Vasco de Salud. El período de evaluación se estableció a 30 años de la puesta en marcha del cribado. La razón coste-efectividad incremental (Incremental cost-effectiveness ratio-ICER) incorporó AVAC adicional obtenido en el denominador y los costes adicionales incurridos por el programa en el numerador [Russell, *et al.* 1996]. Se aplicó un enfoque de múltiples cohortes al incluir todas las cohortes de personas de entre 50-69 años en el programa durante 30 años desde su implementación. Después de este período, a partir de 2039 en adelante, el programa no incluyó más cohortes, pero mantuvo la intervención para todas las personas ya incluidas en el programa de cribado [Sullivan, *et al.* 2014; Arrospide, *et al.* 2016]. Toda la población tuvo un seguimiento de por vida para conocer el impacto a largo plazo. Los costes y AVAC se descontaron al 3% (porcentaje de descuento). Los costes anuales para el diagnóstico y el tratamiento de CCR en las poblaciones participantes en el cribado y las no cribadas desde 2009 a 2038 se tuvieron en cuenta en el modelo. Los recursos de diagnóstico incluyeron pruebas de cribado (análisis de FIT y colonoscopias de confirmación diagnóstica) y colonoscopias de seguimiento de lesiones realizadas en los hospitales de la red pública vasca.

Los valores de desutilidad se muestran en la tabla 17 y fueron incluidos en el modelo tanto para la colonoscopia, las complicaciones derivadas de la misma, así como para los estadios de CCR (I-IV).

En el caso concreto de las personas diagnosticadas con CCR en estadio avanzado (III – IV) se aplicó un modelo lineal generalizado donde se estimó un coste anual de seguimiento (tabla 18).

Tabla 17. Valores de desutilidad.

		Desutilidades
Colonoscopia		0,0055
Complicación		0,0384
CCR estadio I	Fase inicial	0,12
	Seguimiento	0,05
	CCR fase terminal	0,7
	Otras causas fase terminal	0,05
CCR estadio II	Fase inicial	0,18
	Seguimiento	0,05
	CCR fase terminal	0,7
	Otras causas fase terminal	0,05
CCR estadio III	Fase inicial	0,24
	Seguimiento	0,24
	CCR fase terminal	0,7
	Otras causas fase terminal	0,24
CCR estadio IV	Fase inicial	0,7
	Seguimiento	0,7
	CCR fase terminal	0,7
	Otras causas fase terminal	0.70

Tabla 18. Coste anual de seguimiento en pacientes con CCR metastásico.

Parámetros	Coeficientes	p-valor
Constante	5470,4	< 0,001
Seguimiento (años)	3366,9	< 0,001
Coste medio estimado por año	24254,9	
***Familia: Gamma; Función link: Potencia 0.9.**		

Los costes unitarios utilizados en el modelo para el análisis coste-efectividad se observan en la tabla 19 comparando ambas estrategias (cribado y no cribado).

Tabla 19. Costes unitarios utilizados en el modelo para el análisis coste-efectividad.

	Con cribado	Sin cribado
Costes de cribado		
Invitaciones	6,06€	
Participantes	0,99€	
Consulta de atención primaria	78,00€	
Colonoscopias (diagnóstica, de seguimiento o clínica)		
Colonoscopia sin polipectomía	281,30€	281,30€
Colonoscopias con polipectomía	461,30€	461,30€
Complicaciones	5.157,00€	5.157,00€
Costes de tratamiento		
CCR estadio I: Tratamiento inicial	3.963,00€	6.968,00€
Tratamiento en seguimiento	404,00€	404,00€
Cuidados del final de la vida	24.255,00€	24.255,00€
CCR estadio II: Tratamiento inicial	12.765,00€	12.765,00€
Tratamiento en seguimiento	404,00€	404,00€
Cuidados del final de la vida	24.255,00€	24.255,00€
CCR estadio III: Tratamiento inicial	13.075,00€	13.075,00€
Tratamiento en seguimiento	404,00€	404,00€
Cuidados del final de la vida	24.255,00€	24.255,00€
CCR estadio IV: Tratamiento inicial	24.255,00€	24.255,00€
Tratamiento en seguimiento	404,00€	404,00€
Cuidados del final de la vida	24.255,00€	24.255,00€

3. SUPERVIVENCIA

La metodología utilizada para alcanzar el Objetivo Principal 2 y los Objetivos específicos 3, 4 y 5 es la descrita a continuación.

Se optó por un estudio retrospectivo observacional de los CCR diagnosticados en la población vasca de los nacidos entre el 1 de enero de 1940 y el 31 de diciembre de 1964, debido a que era esta la población diana de los 5 años de ejecución del programa de cribado. Como ha sido mencionado con anterioridad, este programa se inició en 2009 como un estudio piloto, completándose su primera ronda de invitación a finales del 2013 para toda la población diana y actualmente se encuentra en curso para las sucesivas invitaciones al programa. El final del reclutamiento para este estudio fue el 31 de diciembre de 2014.

El estudio histológico de todas las lesiones detectadas fue realizado por patólogos expertos especializados en oncología gastrointestinal, de acuerdo con los estándares de calidad de las guías europeas y determinándose como CCR cuando las células neoplásicas invadían a través de la muscularis mucosae la submucosa (≥ pT1). Todos los casos de CCR fueron codificados por personal cualificado en el centro coordinador del programa de cribado siguiendo las pautas del Comité Estadounidense de Cáncer (American Joint Committee on Cancer-AJCC), CIE-O y el consenso de los patólogos endoscopistas de la red nacional de cribados. Los pacientes con CCR detectados son tratados endoscópicamente y/o referidos para tratamientos quirúrgicos u oncológicos. Todos los CCR invasivos (CIE-O: C18-C21) y cuya morfología fue M &&& 3_6 en la codificación de anatomía patológica, fueron incluidos con el objetivo de calcular la incidencia y la mortalidad regional por este tumor, siendo consultadas las bases de datos del registro poblacional de cáncer de Euskadi, así como el registro de altas hospitalarias y el registro de mortalidad hasta el 20 de octubre de 2017. Para el análisis se excluyeron los 39 casos de CCR encontrados, cuya localización fue canal anal y ano (C21) puesto que son tumores bien diferentes a los del resto de regiones del colon y recto cuya histología (carcinomas epidermoides con sus variantes (cloacogénico, basaloideo, de transición o pavimentoso) y están asociados a distintos factores de riesgo, como papiloma virus, y son considerados cánceres de piel en más del 80% [Ferrer Márquez, *et al.* 2013].

3.1. Población a estudio

Se utilizaron las diferentes bases de datos interrelacionadas entre sí para establecer los siguientes grupos:

1. CCR no detectados por el PCCR: Las personas que siendo población diana del programa de cribado (50-69 años), no fueron invitadas, dado que todavía no se estaba realizando el cribado en el lugar donde vivían o la invitación fue incorrecta (error postal) o hubo un error de exclusión en la base de datos, además de las personas invitadas al PCCR, que decidieron no participar.

2. CCR detectados por el PCCR: Personas invitadas y participantes en el PCCR, con CCR diagnosticado después de un resultado FIT positivo y cuyo diagnóstico fue confirmado por la colonoscopia de cribado. También se incluyeron los CCR detectados en la colonoscopia de vigilancia, también llamada colonoscopia de seguimiento o control, según pautas de seguimiento establecidas por el riesgo según algoritmo de la guía europea de Atkin, *et al.* 2010.

3. Cáncer de Intervalo. Fueron considerados dos entidades diferentes:

a. CI_FIT: CCR diagnosticado después de un resultado en FIT negativo y antes de la siguiente invitación al cribado. Todos los casos FIT negativos (FIT <20 µg Hb / gr de heces) de una ronda previa fueron consultados en las bases de datos del registro de altas hospitalarias con CIE-9 1530-1548, en diagnóstico primario y secundario, CIE-O (C18-C21) de registros hospitalarios y registro poblacional de cáncer basados en la población, así como a los códigos de anatomía patológica terminados en M &&& 3_6. En todos los casos coincidentes, el personal cualificado del PCCR revisó las historias clínicas, (casos que cumplían con los criterios de tener un resultado FIT negativo en la invitación previa (0-24 meses o más en caso de retraso en la invitación al programa de cribado) e incluso aquellos que estaban fuera del PCCR por ser mayores de 69 años para una siguiente invitación, pero con diagnóstico CCR antes de los 72 años. Para disminuir las posibles pérdidas, este proceso se repite anualmente, ya que los registros pueden tener un cierto retraso en la captación de los datos.

b. IC_COL (colonoscopia): Son los CCR detectados antes de la colonoscopia de vigilancia por el riesgo asignado en la colonoscopia diagnóstica y recomendada por el endoscopista. Se utilizaron las mismas bases de datos de control y búsqueda activa que en el grupo anterior.

Por otro lado, las personas diagnosticadas de CCR por el programa de cribado fueron estratificadas en 3 grupos de acuerdo con su tipo de participación en el PCCR según las distintas invitaciones:

1. Participante inicial: aquellos con un resultado positivo válido en la prueba de detección (FIT) en la primera invitación al PCCR.

2. Participante regular: las personas con un resultado en primera invitación válido y negativo en la prueba de detección (FIT) y resultado positivo en la 2ª invitación ó invitaciones sucesivas al PCCR.

3. Participante irregular: los que en el cribado obtuvieron un resultado positivo/negativo en la prueba de detección (FIT) en una ó dos participaciones no consecutivas en el cribado.

3.2. Variables a estudio

Los diferentes tipos de CCR estudiados fueron comparados por sexo, grupo de edad (menores y mayores de 60 años), índice de privación a partir de la sección censal donde se establecen 5 niveles siendo el 1) los más favorecidos y el 5 los menos favorecidos socio económicamente; índice de morbilidad con 4 niveles, siendo el de mayor dependencia el denominado "manejo del paciente" y el de mayor autonomía el etiquetado como "prevención y promoción de la población sana"; fecha de defunción (sólo casos relacionados con CCR); tipo de CCR según topografía (C18- C20); grado de diferenciación celular en 2 grupos (bien a moderadamente diferenciado y pobre a indiferenciado) y estadio tumoral en el momento del diagnóstico (según la clasificación de Dukes, 1932); por el tipo de invitación y participación en el programa de cribado de acuerdo con las fechas en que se enviaron las pruebas de cribado (FIT) y la ronda de invitación.

Desde los programas de cribado se consideran que los casos Cáncer de Intervalo tanto del test como de la colonoscopia (CI_FIT y CI_COL) forman parte de los efectos adversos del cribado (falsos negativos), entendiendo que los beneficios de los programas de cribado son los CCR detectados por el mismo, incluyendo entre estos los casos de CCR diagnosticados en el seguimiento de adenomas de la colonoscopia de cribado diagnóstica.

El índice de morbilidad se clasificó en 4 grupos dependiendo de su grado de severidad y siendo de mayor a menor dependencia:

1. Manejo del paciente
2. Manejo de la enfermedad
3. Automanejo de la enfermedad
4. Prevención y promoción de la población sana

La topografía del tumor se dividió en 3 grandes bloques:

- Colon proximal: de C18.0 a C18.4
- Colon distal: desde el ángulo esplénico C18.5 a 19.9, excluyendo C18.8 y C18.9 como no específicos de esta región distal topográfica
- Recto: C20

Los grados de diferenciación del tumor se agruparon según descriptivo del informe de anatomía patológica en:

- Bien o moderadamente diferenciado
- Pobremente diferenciado e indiferenciado
- Desconocido o no aplicado

El estadio tumoral se agrupó en 2 grupos, independientemente de que fuera patológico (determinado por la pieza quirúrgica) o radiológico (determinado por pruebas diagnósticas radiológicas):

- estadio inicial (desde IA a IIB)
- estadio avanzado (desde IIIA a IVB)

3.3. Análisis estadístico

Para el análisis estadístico se han utilizado el programa estadístico SPSS 23.0 y STATA. Han sido utilizados las variables continuas que se han descrito: media y desviación estándar. Las variables categóricas se han descrito en frecuencias y porcentajes. Las comparaciones entre variables categóricas se realizaron con la prueba de chi-cuadrado o la prueba de Fisher cuando las frecuencias esperadas fueron < 5. Las tasas de incidencia específicas por sexo se calcularon a partir del número de casos nuevos dividido por el número de personas/año en riesgo por 100.000 para el período 2001-2014. Se obtuvieron tasas de incidencia estandarizadas por sexo para el grupo de edad de 50-69 años utilizando el método directo según la población mundial (estándar mundial OMS). El tiempo se subdividió en dos periodos de 2001-2008 y de 2009-2014 para estudiar los datos. Los modelos de regresión de Poisson se usaron para analizar las tasas de incidencia por sexo y período de tiempo incluidos en el modelo, así como para estimar la tendencia temporal en las tasas de incidencia global. Los resultados se informan como índices de frecuencia (IC del 95%). El análisis de supervivencia se ha estimado utilizando tablas de Kaplan-Meier y las supervivencias de cada grupo se han comparado utilizando la prueba de log-rank. Para ver qué variables influyen en la supervivencia, inicialmente se realizó un análisis de regresión de Cox univariante. Aquellas variables que tenían un valor de p <0,20 se han incluido en un modelo de Cox multivariante. La variable con un valor p más alto se ha eliminado del modelo y el modelo se ha repetido hasta que todas las variables hayan sido significativas (p<0,005).

RESULTADOS

1. BENEFICIOS EN SALUD: INCIDENCIA, MORTALIDAD, AVAC

Según los datos del Registro de tumores del País Vasco en el periodo previo al cribado 2005-2008, se registraron 4.519 nuevos casos de CCR en hombres, 47% de los cuales fueron en estadios iniciales. En mujeres los casos nuevos fueron 2.350, siendo en estadios iniciales el 43,6%. La localización más frecuente en ambos sexos fue colon sigmoide (61,5%) seguida de recto (48,4%).

En la tabla 20 se observan las proyecciones futuras en hombres, mujeres, total de invitaciones, participación y lesiones detectadas en diferentes años, siendo el año 2038 el año en el que se realiza la última proyección. En todos los casos se observan diferencias entre hombres y mujeres, tanto en participación como en lesiones detectadas, con un aumento de la participación en todos los quinquenios. Se observa que a partir de la proyección de 2020 hay una tendencia a la estabilización en todos los parámetros.

Tabla 20. Futuras proyecciones por sexo: invitaciones, participantes y lesiones detectadas.

	INVITACIONES Y PARTICIPANTES								
	Hombres			Mujeres			Total		
Año	Invitaciones	Participantes	%	Invitaciones	Participantes	%	Invitaciones	Participantes	%
2012	93.822	58.994	62,9	99.099	68.045	68,7	192.921	127.039	65,9
2015	130.983	85.337	65,2	139.006	98.553	70,9	269.989	183.889	68,1
2020	137.436	91.543	66,6	144.522	104.610	72,4	281.958	196.153	69,6
2025	132.995	88.238	66,3	137.473	99.219	72,2	270.468	187.457	69,3
2030	133.678	88.969	66,6	137.485	99.935	72,7	271.164	188.904	69,7
2035	123.789	83.234	67,2	127.178	93.397	73,4	250.966	176.630	70,4
2038	114.699	77.577	67,6	118.248	87.204	73,7	232.947	164.781	70,7
	COLONOSCOPIAS DIAGNOSTICAS Y LESIONES DETECTADAS								
	Hombres			Mujeres			Total		
Año	Colonoscopias	Detección adenomas	CCR detectados	Colonoscopias	Detección adenomas	CCR detectados	Colonoscopias	Detección adenomas	CCR detectados
2012	4.070	2.658	295	2.786	1.231	142	6.856	3.888	437
2015	5.580	3.620	347	3.973	1.730	185	9.553	5.350	532
2020	5.764	3.638	348	4.120	1.745	159	9.884	5.384	508
2025	5.397	3.372	304	3.839	1.597	148	9.236	4.969	452

2030	5.394	3.354	310	3.839	1.587	148	9.233	4.941	458
2035	5.073	3.199	288	3.627	1.505	140	8.700	4.704	428
2038	4.766	3.041	289	3.406	1.427	134	8.172	4.468	424

COLONOSCOPIAS DE SEGUIMIENTO Y LESIONES DETECTADAS

	Hombres			**Mujeres**			**Total**		
Año	**Colonos-copias**	**Detección adenomas**	**CCR detec-tados**	**Colonos-copias**	**Detec-ción adeno-mas**	**CCR detecta-dos**	**Colo-nosco co-pias**	**Detección adeno-mas**	**CCR de-tec-ta-dos**
2012	941	259	2	380	101	1	1.321	360	3
2015	1.971	459	7	900	185	3	2.871	644	10
2020	3.801	787	16	1.832	338	4	5.634	1.115	20
2025	5.190	1.172	25	2.511	523	9	7.701	1.695	34
2030	5.757	1.310	27	2.743	571	8	8.500	1.881	35
2035	5.666	1.278	25	2.706	551	10	8.371	1.829	35
2038	5.523	1.233	31	2.638	544	9	7.561	1.777	40

TOTAL COLONOSCOPIAS (Diagnosticas y Seguimiento) y LESIONES DETECTADAS

	Hombres			**Mujeres**			**Total**		
Año	**Colonos-copias**	**Detección adenomas**	**CCR detec-tados**	**Colonos-copias**	**Detec-ción adeno-mas**	**CCR detecta-dos**	**Colo-nos-copias**	**Detección adeno-mas**	**CCR de-tec-ta-dos**
2012	5.011	2.917	297	3.166	1.332	143	8.177	4.248	440
2015	7.551	4.079	354	4.872	1.915	188	12.424	5.994	542
2020	9.566	4.425	364	5.952	2.083	163	15.517	6.499	528
2025	10.586	4.544	328	6.350	2.120	157	16.937	6.664	485
2030	11.151	4.664	337	6.582	2.158	156	17.733	6.822	493
2035	10.738	4.477	313	6.333	2.056	150	17.071	6.533	463
2038	10.289	4.274	320	6.044	1.971	143	15.734	6.245	463

En las figuras 40 y 41 se observan los gráficos con los resultados del ajuste en la herramienta MISCAN-Colon entre lo observado y lo simulado, mostrando una buena concordancia de los datos tanto para hombres como para mujeres de ambos parámetros: invitaciones y participación. Se observa un aumento para el año 2013, tanto en invitaciones como en la participación debido a la extensión al 100% de la población diana del programa, con una disminución hacia la estabilización a partir de ese año. Por consiguiente, se produce una disminución drástica de las primeras invitaciones al programa de prevención dado que sólo se producen nuevas entradas en el cribado de aquellos que van cumpliendo 50-51 años y estimándose un número de invitaciones totales para 2014 de 271.447 personas: 131.447 hombres y 140.030 mujeres y correspondiendo un 72,1% a invitaciones sucesivas.

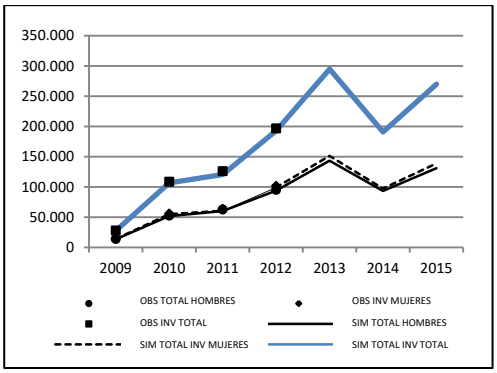


Figura 40. Invitaciones observadas y simuladas 2009-2014 por sexo.

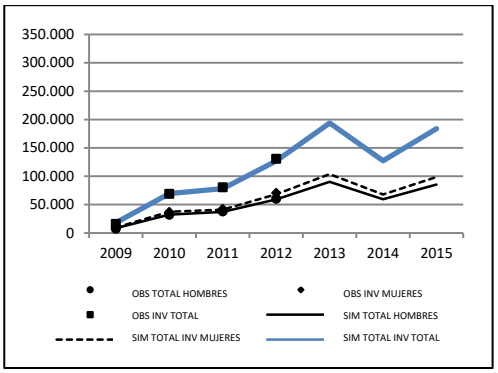


Figura 41. Participaciones observadas y simuladas 2009-2014 por sexo.

En el periodo 2009-2012 se realizaron un total de 459.382 invitaciones, válidas. 224.050 a hombres y 235.332 a mujeres entre 50 y 69 años, encontrándose diferencias estadísticamente significativas en cuanto a participación y siendo superior en mujeres (67,5%) respecto a hombres (61,2%), con una tasa de positividad y de lesiones detectadas mayor en hombres.

Se observa la disminución de incidencia a 30 años, siendo superior en hombres (17,2%) (figura 42) que en mujeres (14,7%) (figura 43). En ambos casos se aprecia que esta disminución de número de casos comienza a partir del décimo año de puesta en marcha del programa. Si consideramos ambos sexos, la media de disminución se sitúa en 16,3%.

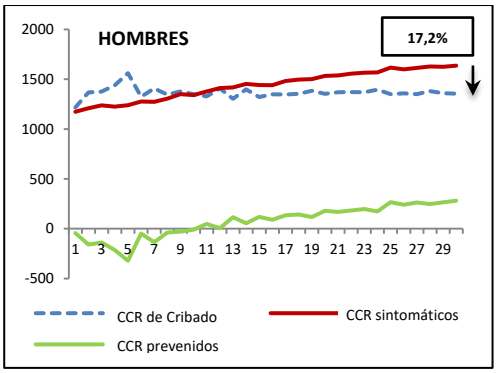


Figura 42. Disminución de la incidencia en hombres en 30 años de programa de cribado.

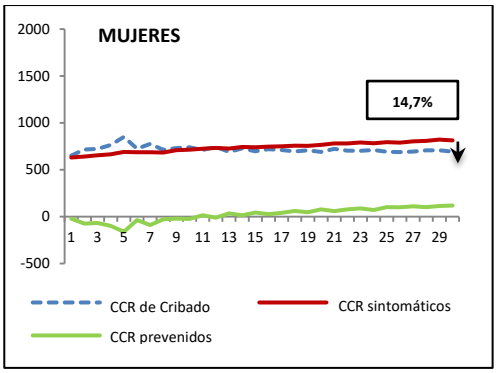


Figura 43. Disminución de la incidencia en mujeres en 30 años de programa de cribado.

En las figuras 44 para hombres y 45 para mujeres observamos la disminución de la mortalidad para esa misma proyección. La disminución en hombres se situó en 28,1% y en mujeres en 22,4%, con una tendencia creciente desde el inicio del programa, siendo la media de disminución en ambos sexos de 26,1%.

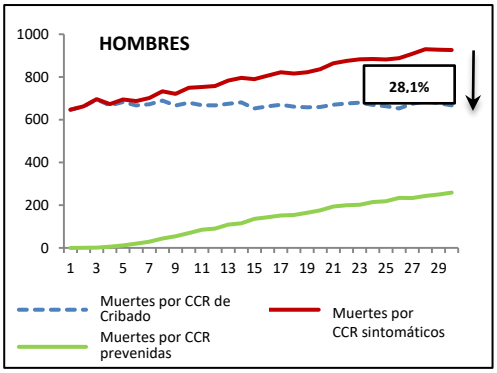


Figura 44. Descenso de la mortalidad en hombres en 30 años.

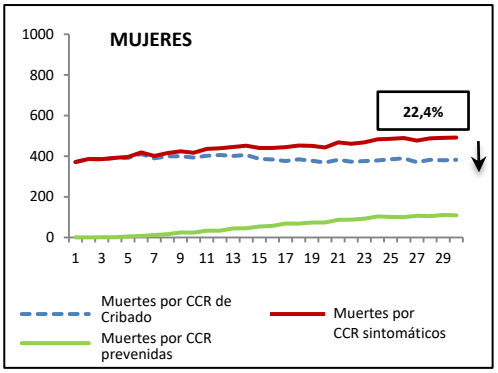


Figura 45. Descenso de la mortalidad en mujeres en 30 años.

La disminución de años de vida potencialmente perdidos se observa en la figura 46, donde queda reflejada que es mayor en hombres que en mujeres (22,6% vs 18,4%) (figura 47), con una tendencia creciente desde el inicio del programa y una media para ambos sexos de 21%.

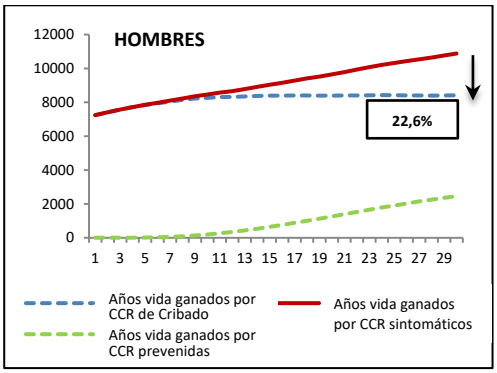


Figura 46. Disminución en años de vida perdidos en hombres en 30 años.

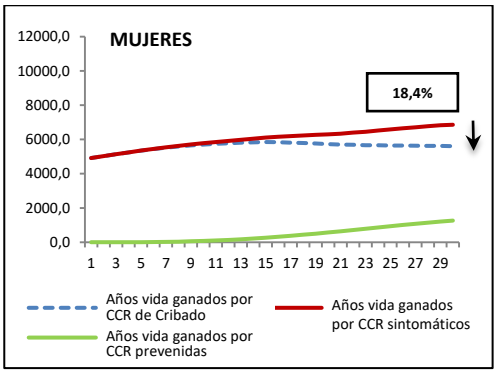


Figura 47. Disminución en años de vida perdidos en mujeres en 30 años.

2. COSTES DEL PROGRAMA

En el análisis de coste-efectividad se puede decir que, sin programa de cribado, se esperaba que la población vasca objetivo del mismo en 2008 viviera un promedio 41,1 años. Tras la implementación del programa de detección, esa expectativa de vida aumentó en 29,3 días por persona. Esta ganancia en términos de años de vida implicó una efectividad incremental de 56.664,8 AVAC (con un descuento del 3%) debido a la detección precoz del CCR. El coste total del cribado, el seguimiento diagnóstico y el tratamiento, durante el horizonte temporal aplicado, fue de 2.057,2 millones de euros. Sin embargo, debido a que el cribado produjo una reducción sustancial de la incidencia de cáncer colorrectal, hubo una gran reducción en los costes de tratamiento del mismo, 256,3 millones de € y un ahorro neto de 93,1 millones de € en comparación con la población no cribada, tal y como se ve en el análisis de sensibilidad para el estudio de coste-efectividad tras la puesta en marcha del cribado (tabla 21). En general, el ahorro en el tratamiento fue mucho mayor que los costes del cribado y, por lo tanto, el programa de cribado vasco fue dominante en comparación con no hacer cribado.

Tabla 21. Análisis de Sensibilidad para el estudio de coste-efectividad por la puesta en marcha del cribado.

		Costes de la población cribada		Coste incremental		AVAC ganados	ICER
Coste por invitación	Prevalencia adenoma	Costes tratamiento	Costes totales	Coste tratamiento	Coste total		
€6.06	Caso base						
	Hombres	1.199,90	1.317.0	-179,1	-81,7	37.132,50	Dominante
	Mujeres	664,2	740,2	-77,1	-11,4	19.532,30	Dominante
	Total	1.864,10	2.057.2	-256,3	-93,1	56.664,80	Dominante
	Prevalencia bibliografía						
	Hombre	1.227,50	1.318.9	-168,6	-97,2	36.616,90	Dominante
	Mujer	661	726,9	-77,6	-21,8	20.438,50	Dominante
	Total	1.888,50	2.045,70	-246,2	-119	57.055,40	Dominante
15€ por invitación	Caso base total	1.864,10	2.103,20	-256,3	-47,1	56.664,80	Dominante
20€ por invitación	Caso base total	1.864,10	2.128,90	-256,3	-21,4	56.664,80	Dominante
25€ por invitación	Caso base total	1.864,10	2.154,60	-256,3	4,2	56.664,80	74,1
30€ por invitación	Caso base total	1.864,10	2.180,30	-256,3	30	56.664,80	529,4
40€ por invitación	Caso base total	1.864,10	2.231,80	-256,3	81,5	56.664,80	1.438,30
50€ por invitación	Caso base total	1.864,10	2.283,20	-256,3	132,9	56.664,80	2.345,40

En lo que respecta a los análisis de impacto presupuestario, podemos decir que los costes totales e incrementales relacionados con el cribado, diagnóstico y tratamiento del CCR en ambos escenarios (cribado y no cribado) son similares tal y como se muestra por año en la tabla 22. Los altos costes del cribado pudieran ser debidos a la alta prevalencia de adenomas que precisan de mayor número de colonoscopias de vigilancia y los casos de CCR en los primeros cuatro años desde la introducción del cribado hasta 2013, cuando se logró la extensión del programa, cosa lógica ya que al no haber habido programa preventivo hasta ese momento, se produce un incremento en la prevalencia, diagnosticándose mayor número de lesiones pre-malignas y malignas en los primeros años de implementación. Durante los primeros cinco años se necesitaron 69,2 millones de euros de promedio para financiar anualmente el cribado. Los ahorros en el Análisis de impacto presupuestario aparecen en 2023, 10 años después de la implementación completa del programa. A pesar de que el ahorro fue pequeño al principio, aumentó a medida que se hizo evidente el impacto del programa.

En la tabla 22 quedan reflejados los costes totales de los dos distintos tipos de poblaciones: la de la población cribada, añadiendo el plus de los costes del cribado, y la de la no cribada, sin los costes anteriormente mencionados y con los costes de diagnóstico y tratamiento para cada una de las dos poblaciones, así como el sumatorio de los costes.

Tabla 22. Costes para población cribada y no cribada.

	Población cribada				Población no cribada		
Año	Cribado	Diagnóstico clínico	Tratamiento	Costes totales	Diagnóstico clínico	Tratamiento	Costes totales*
2009	0,68	0,85	60,9	62,5	0,9	60,3	61,1
2010	2,75	0,86	63,5	67,1	0,9	61,2	62
2011	3,37	0,86	64,5	68,7	0,9	62,5	63,4
2012	5,17	0,83	65,5	71,5	0,9	62,7	63,6
2013	7,93	0,81	67,7	76,4	0,9	63,4	64,4
2014	5,75	0,8	64,6	71,1	0,9	64,8	65,7
2015	7,54	0,78	65,4	73,7	0,9	65,1	66
2020	8,69	0,77	65,5	75	1	71	72
2025	9,02	0,74	63,4	73,2	1,1	73,8	74,8
2030	9,3	0,75	63,9	74	1,1	78,1	79,2
2035	8,87	0,75	63,5	73,1	1,1	80,7	81,9
2038	8,43	0,75	63,7	72,9	1,2	81,7	82,9
***Sin costes de cribado en la población no cribada**							

La tabla 23 muestra cómo el aumento en el presupuesto anual para cubrir el envejecimiento de la población no cribada desaparece cuando se realiza el cribado, y así se logró un presupuesto anual estable de 73,4 millones de euros en promedio desde el año 2023 hacia adelante.

Además, el modelo predijo el número de colonoscopias durante un período de 30 años que alcanzó su máximo en 2032 con 19.384 pruebas. De promedio, el número anual estimado de colonoscopias (incluidas las colonoscopias diagnósticas, de control y clínicas) necesarias en el caso base desde 2029 hasta 2038 fue de 18.843 (52,5% de estas son colonoscopias de control del seguimiento de los adenomas desde la colonoscopia diagnóstica).

Tabla 23. Análisis de impacto presupuestario del PCCR en millones de euros.

	Con cribado	Sin cribado	Diferencia
Costes totales (millones de Euros)	3.576,36	3.681,12	-104,77
Costes de cribado	305,53	0	305,53
Invitaciones	47,77	0	47,77
Participantes	3,46	0	3,46
Test con resultado positivo	9,13	0	9,13
Colonoscopias de diagnóstico	115,17	0	115,17
Colonoscopias de seguimiento	97,21	0	97,21
Polipectomías	25,59	0	25,59
Complicaciones	7,21	0	7,21
Costes del diagnostico clínico	63,01	81,07	-18,06
Colonoscopias clínicas	51,39	66,13	-14,73
Polipectomías	10,21	13,13	-2,93
Complicaciones	1,40	1,81	-0,40
Costes de tratamiento	3.207,82	3.600,06	-392,24
Tratamiento inicial	1.011,39	1.092,42	-81,03
Tratamiento en seguimiento	820,02	890,79	-70,76
Cuidados del final de la vida	1.376,40	1.616,85	-240,45
Millones de AVACs perdidos	1,16	1,34	-0,18
Ratio coste-efectividad incremental			Dominante

La figura 48 muestra cómo el impacto presupuestario se va reduciendo hasta que en 2034 supone un ahorro de costes debido al menor coste por el tratamiento CCR. Por este motivo el análisis coste-efectividad es dominante cuando el horizonte temporal alcanza toda la vida de la población diana.

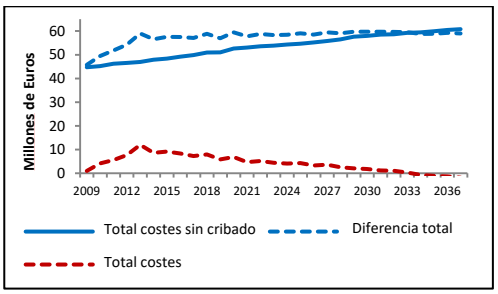


Figura 48. Análisis del impacto presupuestario para los primeros 30 años.

3. SUPERVIVENCIA DE PERSONAS DIAGNOSTICADAS DE CCR Y LAS DISTINTAS SUBPOBLACIONES

Los siguientes resultados responden al objetivo principal 2 y a los objetivos específicos 3 al 6.

Durante el período de estudio 5.909 personas fueron diagnosticadas de CCR en Euskadi. En la figura 49, podemos observar las tendencias en las tasas de mortalidad e incidencia para ambos sexos. En ambos períodos se encontró una tendencia creciente estadísticamente significativa en hombres. En el caso de las mujeres, se encontró una tendencia creciente estadísticamente significativa sólo para el segundo período. Para la tasa de mortalidad, sólo observamos una tendencia decreciente estadísticamente significativa en hombres en el segundo período, pero todas las tasas de mortalidad tuvieron una tendencia decreciente. Los modelos de regresión de Poisson confirmaron que las tendencias de incidencia y mortalidad cambian después de la implementación del programa de cribado. La tasa de incidencia tiene un aumento promedio anual de 2,6% en el primer período frente al 2,2% en el segundo en hombres, y 1,2% frente al 4,8% en mujeres. La tasa de mortalidad tiene una disminución promedio anual del 0,3% en el primer período frente al 4,3% en el segundo en hombres, y 0,10% frente al 1,9% en mujeres.

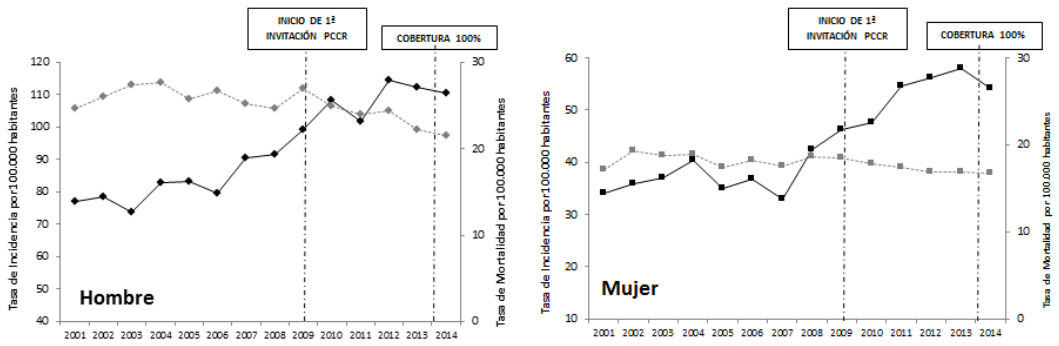


Figura 49. Tendencias en las tasas de mortalidad e incidencia para ambos sexos (2001-2014).

Podemos ver en la tabla 24 las características socio-demográficas, de estado de salud, económicas, así como las características del tumor en cuanto a localización, estadio y grado de diferenciación de las personas diagnosticadas de CCR, tanto dentro como fuera del programa de cribado. Cabe destacar la significación estadística encontrada enfrentando ambos grupos en lo que respecta a las ca-

racterísticas y localización del tumor como en el índice de morbilidad y la edad, siendo la media en el grupo de CCR de no cribado ligeramente más alta 62,3 ± 6,0 y 61,9 ± 5,4 respectivamente.

Tabla 24. Características socio-demográficas, de salud, económicas, del tumor en cuanto a localización, estadio y grado de diferenciación de las personas con CCR diagnosticado dentro y fuera del programa de cribado.

Variables		Detectados fuera PCCR* (n = 3.764)	Detectados PCCR (n = 2.145)	p Valor
Sexo	Hombre; n (%)	2.499 (66,4)	1.410 (65,7)	0,313
	Mujer; n (%)	1.265 (33,6)	735 (34,3)	
Edad	Media (DE); años	62,3 (6,0)	61,9 (5,4)	**0,025**
	50-54 años; n (%)	489 (13,0)	276 (11,9)	0,137
	55-59 años; n (%)	736 (19,6)	455 (21,2)	
	60-64 años; n (%)	976 (25,9)	587 (27,4)	
	≥ 65 años; n (%)	1.563 (4157)	847 (39,5)	
Índice privación	Más favorecidos 1-2; n (%)	1.308 (34,8)	855 (39,9)	**0,009**
	3; n (%)	630 (16,7)	477 (22,2)	
	Menos favorecidos 4-5; n (%)	1.260 (33,5)	755 (35,2)	
	Desconocido; n (%)	566 (15,0)	58 (2,7)	
Índice de Morbilidad	Manejo del paciente; n (%)	1.812 (48,1)	486 (22,7)	**< 0,001**
	Manejo de la enfermedad; n (%)	1.086 (28,9)	855 (41,3)	
	Automanejo de la enfermedad; n (%)	701 (18,6)	685 (31,9)	
	Prevención y promoción población sana; n (%)	93 (2,6)	84 (3,9)	
	Desconocido; n (%)	69 (1,8)	5 (0,2)	
Localización del tumor	Proximal; n (%)	994 (26,4)	427 (19,9)	**< 0,001**
	Distal; n (%)	1.634 (43,4)	1.377 (64,2)	
	Recto; n (%)	995 (26,4)	330 (15,4)	
	Colon no especificado; n (%)	141 (3,7)	11 (0,5)	
Estadio del tumor	Estadio inicial pT1-pT2; n (%)	1.675 (44,5)	1.514 (70,6)	**< 0,001**
	Estadio avanzado pT3-pT4; n (%)	2050 (54,5)	627 (29,2)	
	Desconocido; n (%)	39 (1,0)	4 (0,2)	
Grado de diferenciación	Bien-Moderado; n (%)	2.657 (70,6)	1.671 (77,9)	**< 0,001**
	Pobre-Indiferenciado; n (%)	255 (6,8)	80 (3,7)	
	Desconocido; n (%)	852 (22,6)	394 (18,4)	

DE: desviación estándar

Las características entre los participantes en el programa de cribado quedan reflejadas en la tabla 25, donde difieren entre los distintos tipos de participación en el programa de prevención, a excepción de la localización, en la que en los participantes regulares es más frecuente que sea en colon proximal. Es interesante ver que no hay diferencias estadísticamente significativas en cuanto al estadio del tumor y por tanto al pronóstico entre los distintos tipos de participantes en el programa.

Tabla 25. Características de los CCR según tipo de participación en PCCR.

Variables		Inicial (n= 1.615)	Regular (n =347)	Irregular (n= 164)	p-Valor
Sexo	Hombre; n (%)	1.076 (66,6)	217 (62,5)	105 (64,0)	0,308
	Mujer; n (%)	539 (33,4)	130 (37,5)	59 (36,0)	
Edad	Media (DE); años	61,8 (5,5)	62,8 (4,9)	61,4 (5,5)	**<0,001**
	50-54 años; n (%)	220 (13,6)	24 (6,9)	10 (6,1)	**<0,001**
	55-59 años; n (%)	336 (20,8)	65 (18,7)	51 31,1)	
	60-64 años; n (%)	438 (27,1)	101 (29,1)	39 (23,8)	
	≥ 65 años; n (%)	621 (38,5)	157 (45,2)	64 (39,0)	
Indice Privación	Más favorecidos 1-2; n (%)	641 (39,7)	142 (40,9)	66 (40,2)	0,579
	3; n (%)	368 (22,8)	68 (19,6)	36 (22,0)	
	Menos favorecidos 4-5; n (%)	552 (34,2)	133 (38,3)	62 (37,8)	
	Desconocido; n (%)	54 (3,3)	4 (1,2)	0 (0,0)	
Indice Morbilidad	Manejo del paciente; n (%)	339 (21,0)	96 (27,7)	46 (28,0)	**0,011**
	Manejo de la enfermedad; n (%)	661 (41,0)	143 (41,2)	71 (43,3)	
	Automanejo de la enfermedad; n (%)	548 (34,0)	94 (27,2)	39 (23,8)	
	Prevención y promoción población sana; n (%)	63 (3,9)	13 (3,8)	8 (4,9)	
	Desconocido; n (%)	4 (0,2)	1 (0,3)	0 (0,0)	
Localización Tumor	Proximal; n (%)	291 (18,0)	100 (28,8)	30 (18,3)	**<0,001**
	Distal; n (%)	1.070 (66,3)	188 (54,2)	109 (66,5)	
	Recto; n (%)	245 (15,2)	58 (16,7)	24 (14,6)	
	Colon no especificado; n (%)	9 (0,6)	1 (0,3)	1 (0,6)	
Estadio Tumor	Estadio inicial pT1-pT2; n (%)	1.151 (71,3)	235 (67,7)	113 (68,9)	0,338
	Estadio avanzado pT3-pT4; n (%)	460 (28,5)	112 (32,3)	51 (31,1)	
	Desconocido; n (%)	4 (0,2)	0 (0,0)	0 (0,0)	
Grado de Diferenciación	Bien-Moderado; n (%)	1.237 (76,6)	290 (83,6)	130 (79,3)	0,196
	Pobre-Indiferenciado; n (%)	64 (4,0)	13 (3,7)	2 (1,2)	
	Desconocido; n (%)	314 (19,4)	44 (12,7)	32 (19,5)	

DE: desviación estándar

Observamos en la tabla 26 una distribución diferente en lo que respecta a la localización del tumor entre los pacientes en el grupo de CI_FIT, siendo la más habitual la localización recto, y en los casos de CI_COL el 68,8% es colon distal, no encontrando ningún caso en recto.

Tabla 26. Características de los Cánceres de Intervalo CI_FIT frente a CI_COLonoscopia.

Variables		CI_FIT; (n=223)	CI_COL; (n=16)	p-valor
Sexo	Hombre; n (%)	146 (65,5)	9 (56,3)	0,456
	Mujer; n (%)	77 (34,5)	7 (43,8)	
Edad	Media (DE); años	62 (5,2)	64,1 (6,3)	0,108
	50-54 años; n (%)	19 (8,5)	0 (0,0)	
	55-59 años; n (%)	57 (25,6)	1 (6,3)	0,098
	60-64 años; n (%)	62 (27,8)	8 (50,0)	
	≥ 65 años; n (%)	85 (38,1)	7 (43,8)	
Índice de privación	Más favorecidos 1-2; n (%)	92 (41,3)	4 (25)	0,140
	3; n (%)	39 (17,5)	6 (37,5)	
	Menos favorecidos 4-5; n (%)	80 (35,9)	6 (37,5)	
	Desconocido; n (%)	12 (5,4)	0 (0)	
Índice de Morbilidad	Manejo del paciente; n (%)	105 (47,1)	8 (50,0)	0,216
	Manejo de la enfermedad; n (%)	64 (28,7)	6 (37,5)	
	Automanejo de la enfermedad; n (%)	51 (22,9)	1 (6,3)	
	Prevención y promoción población sana; n (%)	3 (1,3)	1 (6,3)	
Localización del tumor	Proximal ; n (%)	82 (36,8)	5 (31,3)	**0,009**
	Distal ; n (%)	69 (30,9)	11 (68,8)	
	Recto; n (%)	63 (28,3)	0 (0)	
	Colon no especificado; n (%)	9 (4)	0 (0)	
Estadio del tumor	Estadio inicial pT1-pT2; n (%)	96 (43)	8 (50)	0,588
	Estadio avanzado pT3-T4; n (%)	169 (75,8)	13 (81,3)	
Grado de diferenciación	Bien-Moderado; n (%)	23 (10,3)	2 (12,5)	0,877
	Pobre-Indiferenciado; n (%)	31 (13,9)	1 (6,3)	

DE: desviación estándar

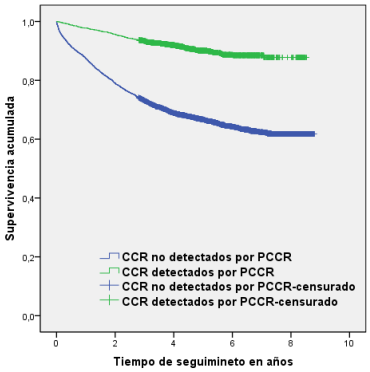
En la tabla 27 se describen las características de las personas nunca invitadas y de los no participantes en el programa de cribado y se muestra que en las personas que no participan en el programa tras la invitación, el estadio es más avanzado que en el grupo de los nunca invitados al mismo.

Tabla 27. Características de las personas con CCR nunca invitadas y de los invitados pero no participantes en el PCCR.

Variables		CRC No invitados* (n = 3.056)	CRC No participantes (n = 465)	p-Valor
Sexo	Hombre; n (%)	2.038 (66,7)	304 (65,4)	0,303
	Mujer; n (%)	1.018 (33,3)	161 (34,6)	
Edad	Media (DE); años	62,3 (6,1)	62,1 (5,7)	0,387
	50-54 años; n (%)	423 (13,6)	47 (11,4)	
	55-59 años; n (%)	586 (18,8)	92 (22,2)	0,252
	60-64 años; n (%)	796 (25,6)	110 (26,6)	
	≥ 65 años; n (%)	1.306 (42,0)	165 (39,9)	
Indice Privación	Más favorecidos 1-2; n (%)	1.048 (34,3)	162 (34,8)	0,445
	3; n (%)	508 (16,6)	77 (16,6)	
	Menos favorecidos 4-5; n (%)	993 (32,5)	179 (38,5)	
	Desconocido; n (%)	507 (16,6)	47 (10,1)	
Indice Morbilidad	Manejo del paciente; n (%)	1.492 (49,0)	207 (50,7)	0,854
	Manejo de la enfermedad; n (%)	900 (29,5)	116 (28,4)	
	Automanejo de la enfermedad; n (%)	576 (18,9)	73 (17,9)	
	Prevención y promoción población sana; n (%)	80 (2,6)	12 (2,9)	
	Desconocido; n (%)	63 (2,0)	6 (1,4)	
Localización Tumor	Proximal; n (%)	793 (25,9)	111 (23,9)	**0,020**
	Distal; n (%)	1.360 (44,5)	194 (41,7)	
	Recto; n (%)	792 (25,9)	139 (29,9)	
	Colon no especificado; n (%)	111 (3,6)	21 (4,5)	
Estadio Tumor	Estadio inicial pT1-pT2; n (%)	1.370 (44,8)	198 (42,6)	**< 0,001**
	Estadio avanzado pT3-pT4; n (%)	1.651 (54)	263 (56,6)	
	Desconocido; n (%)	35 (1,1)	4 (0,9)	
Grado de Diferenciación	Bien-Moderado; n (%)	2.165 (70,8)	307 (66,0)	0,809
	Pobre-Indiferenciado; n (%)	201 (6,6)	29 (6,2)	
	Desconocido; n (%)	690(22,6)	129 (27,8)	

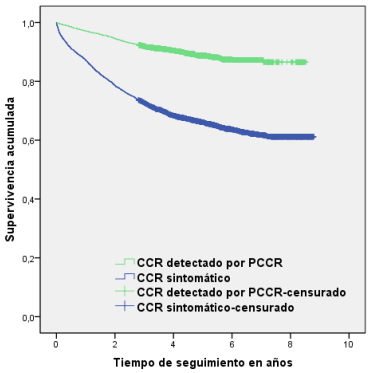
DE: desviación estándar

Para el análisis de supervivencia, el tiempo medio de seguimiento de todos los casos fue de 4,57 ± 2,23 años (rango 0-9 años). En la figura 50 se puede apreciar una diferencia superior al 22% en la supervivencia a 5 años en el grupo de CCR detectado por el cribado frente al de no cribado. Cabe destacar cómo en la figura 51, cuando se incluyen los CI en el grupo de no cribado, intentando de esta manera, estimar la supervivencia en la población que participa en el programa frente al resto, se aprecia cómo el peso que aporta la imputación de los CI es mínimo.



	1 año	3 años	5 años	p valor
CCR detectados por PCCR %	97,8	93,4	90,1	**<0,0001**
CCR no detectados por PCCR %	87,4	73,0	66,7	

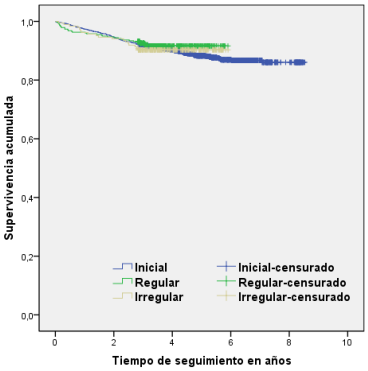
Figura 50. Curva de supervivencia Kaplan–Meyer de los distintos tipos de CCR: imputando los casos codificados de CI_FIT y CI_COL y los hallados en la colonoscopia de seguimiento a los CCR de no cribado.



	1 año	3 años	5 años	p valor
CCR detectados por PCCR %	97,1	91,9	88,7	<0,0001
CCR sintomático %	87,1	72,6	66,1	

Figura 51. Curva de supervivencia Kaplan–Meyer de los distintos tipos de CCR: imputando los casos de CI_FIT y CI_COL a los CCR detectados por cribado y también en la colonoscopia de seguimiento.

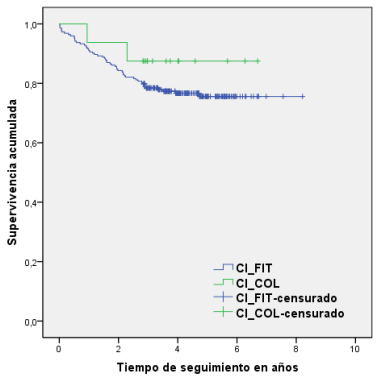
Lograr una alta participación en el cribado es fundamental sea cual fuera su adherencia al mismo, puesto que por tipo de participación la supervivencia no muestra diferencias estadísticamente significativas según se aprecia en la figura 52.



Participación	1 año	3 años	5 años	p valor
Regular %	96,3	93,1	91,6	0,970
Irregular %	95,7	91,5	91,5	
Inicial %	98,3	93,6	88,3	

Figura 52. Curva de supervivencia Kaplan–Meyer de los CCR detectados en el PCCR según distintos tipos de participación en el cribado.

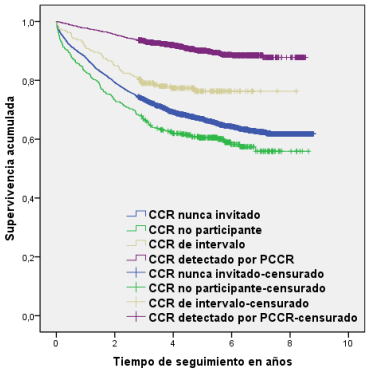
Analizando por separado los CI, apreciamos como la supervivencia a cinco años es mayor en los CI de colonoscopia, aunque la diferencia no sea estadísticamente significativa.



	1 año	3 años	5 años	p valor
CI_COL %	93,8	87,5	87,5	0,354
CI_FIT %	91,0	78,4	75,6	

Figura 53. Curva de supervivencia Kaplan–Meyer de los distintos tipos de Cáncer de Intervalo: FIT versus Colonoscopia.

Aun entendiendo los CI como efectos adversos del programa, vemos que la supervivencia a cinco años está por encima del 15% respecto a los no participantes en el programa.



	1 año	3 años	5 años	p valor
CCR detectado por PCCR %	97,8	93,4	90,1	<0,0001
CCR de intervalo %	91,2	79,0	76,3	
CCR nunca invitado %	87,6	73,4	66,9	
CCR no participante %	83,1	66,7	60,5	

Figura 54. Curva de supervivencia Kaplan–Meyer, comparación de porcentajes de supervivencia entre los distintos grupos: nunca invitado al PCCR, no participante, Cáncer de Intervalo y CCR detectado por PCCR.

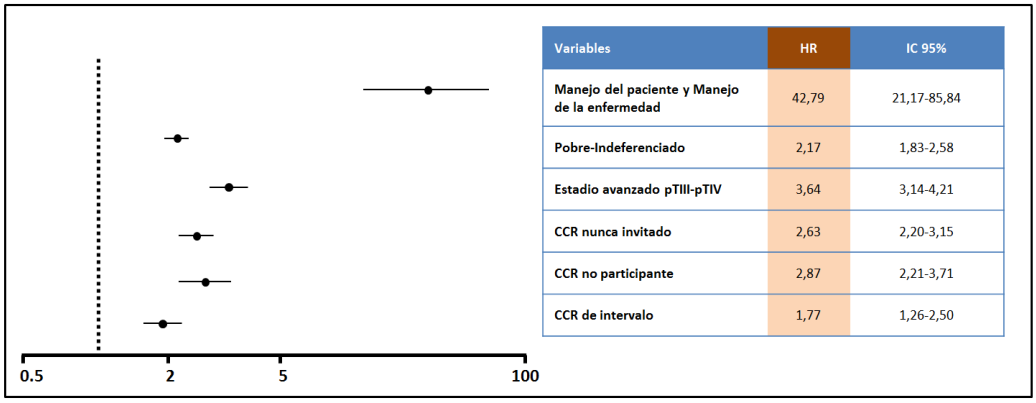
En el análisis univariante, tal y como muestra la tabla 28, se identificaron distintas variables que se relacionaban con la supervivencia: ser mujer, <60 años, en el índice de morbilidad las más sanas en la clasificación; tener un tumor de localización distal, con un grado de diferenciación tumoral de bien a moderadamente diferenciado y en estadio inicial. Los CCR diagnosticados por el PCCR tienen una probabilidad de supervivencia muy superior al resto, llamándonos la atención que a éstos le siguen los CI, seguidos de los nunca invitados al programa, y los de menor supervivencia a 5 años son los no participantes en el mismo.

Tabla 28. Análisis univariante.

Variables	HR	IC 95%	p-valor
Sexo (Ref. mujer)			
Hombre	1,13	1,01-1,26	**0,025**
Edad (Ref. <60 años)			0,128
>60 años	1,12	1,00-1,25	**0,043**
Índice de privación (Ref. 1-2 menos desfavorecidos)			0,159
3	1	0,85-1,18	0,999
4-5 (más desfavorecidos)	1,13	0,98-1,29	0,081
Índice de morbilidad (Ref. Manejo del paciente - Manejo de la enfermedad)			
Automanejo de la enfermedad - Prevención y promoción de población sana	48,4	28,60-81,95	0
Localización del tumor (Ref. Distal)			0
Proximal	1,34	1,19- 1,52	0
Recto	1,21	1,07-1,38	**0,003**
Estadio Tumor (Ref. Estadio inicial pTI-pTII)			
Estadio avanzado pTIII-pTIV	5,8	5,12-6,57	**0**
Grado de diferenciación (Ref. Bien-Moderado)			
Pobre-Indeferenciado	3,094	2,61-3,67	**0**
Tipo de población (Ref. CCR detectado por PCCR)			**0**
CCR nunca invitado	4,04	3,47-4,69	**0**
CCR no participante	5,04	4,10-6,18	**0**
CCR de intervalo	2,73	2,02-3,68	**0**
Cáncer de intervalo (Ref. CI_COL)			
CI_FIT	2	0,47-7,92	0,312
Tipo de población (Ref. CCR detectado por PCCR)			
CCR no detectado por PCCR	4,06	3,50-4,71	**0**

Ref. : Referencia

Después de incluir todas las variables, el análisis de regresión logística multivariante muestra que el índice de morbilidad (manejo del paciente y manejo de la enfermedad), el grado de diferenciación del tumor (pobre-indiferenciado), el estadio del tumor (avanzado), junto a no ser invitado al PCCR, no participante, o ser un CI_FIT o CI_COL en el PCCR fueron consistentemente asociados como predictores independientes con menor supervivencia (figura 55).



Variables	HR	IC 95%
Manejo del paciente y Manejo de la enfermedad	42,79	21,17-85,84
Pobre-Indeferenciado	2,17	1,83-2,58
Estadio avanzado pTIII-pTIV	3,64	3,14-4,21
CCR nunca invitado	2,63	2,20-3,15
CCR no participante	2,87	2,21-3,71
CCR de intervalo	1,77	1,26-2,50

Figura 55. Análisis multivariante.

DISCUSIÓN

V.- DISCUSIÓN

La estrategia del programa de cribado de CCR en el País Vasco se puso en marcha siguiendo las recomendaciones de la Unión Europea y teniendo en cuenta las características de la población vasca, el sistema de salud y los profesionales de la salud en esta región europea (adaptación al contexto).

En las tres rondas de invitación desde 2009 hasta 2014, dicho programa mostró una alta tasa de participación en ambos sexos. Esta alta tasa de participación se relaciona muy probablemente con la estrategia de invitación implementada, tal y como refiere McGregor, [McGregor, *et al.* 2007], que demostró una relación entre la participación en ambos sexos (hombres OR 5,0; IC 95% 2,9 a 8,3 y mujeres OR 3,8; IC 95% 2,3 a 6,5) y el consejo médico sobre la participación en el programa. Igualmente, Tinmouth, *et al.* 2013 refieren como predictores de la participación la importancia de la invitación contando con el médico, enfermera y personal administrativo de los centros de atención primaria al proporcionar información sobre el programa para incentivar la participación en el mismo. El equipo investigador de van Roosbroeck [van Roosbroeck, *et al.* 2012] demostró, asimismo, una tasa de participación más alta relacionada con el tipo de invitación, siendo esta superior cuando los kits se envían a la casa de la población elegible al programa que cuando son entregados por un médico de atención primaria (OR 2,96; IC 95% 2,78 a 3,14). Las estrategias combinadas podrían ser también eficientes para lograr una mayor tasa de participación. Además, garantizar la alta calidad en todo el proceso de cribado, juega un papel importante para su éxito [von Karsa, *et al.* 2013].

El punto de corte para positividad elegido del kit en FIT ha generado mucha presión en términos del número de colonoscopias que se tendrán que realizar. Esto fue una limitación inicial para la extensión total del programa en la CAPV. Sin embargo, no se ha modificado, pero se debe tener en cuenta en rondas sucesivas de invitación, según el equipo holandés de cribado [van Rossum, *et al.* 2009].

El análisis de la tasa de detección de lesiones en la CAPV arrojó una tendencia alta en la primera ronda de invitación con una disminución significativa en las rondas sucesivas, siguiendo el mismo patrón que la prueba de cribado (FIT positivo). La disminución más grande ocurrió principalmente en hombres y en la tasa de detección de adenomas avanzados. Denters *et al*., 2012 encontraron una disminución significativa en el VPP para neoplasia avanzada entre la primera y la segunda ronda del 55% (132/239) al 44% (112/252), (p = 0,017). El VPP para CCR fue del 8% (20/239) en la pri-

mera ronda frente al 4% (9/252) en la segunda ronda (p = 0,024).

Los casos de CCR detectados mediante cribado en el País Vasco se encontraron en estadios iniciales (I-II) en 66,4%, contrastando con datos previos a implementarse el cribado (45,8%) [https://www.osakidetza.euskadi.eus, 2017]. En el programa del País Vasco, considerando la rápida extensión de dicho programa poblacional, su alta tasa de participación tanto en el FIT como en la realización de colonoscopia de cribado tras FIT positivo y de lesiones detectadas, se podría esperar un impacto positivo a medio y largo plazo. Este impacto fue apuntado en un programa similar por el equipo italiano de Zorzi, *et al.* 2015 que encontraron un mayor impacto dependiendo de las áreas locales y la implementación del cribado, con mayores reducciones en la mortalidad en las mujeres (RR = 0,64; IC del 95% = 0,51-0,80) que en los hombres RR = 0,87; IC del 95%: 0,73-1,04), pero con resultados significativos en ambos sexos.

1. MODELIZACIONES PARA LA PREDICCIÓN DEL IMPACTO

La elección del modelo de simulación MISCAN-Colon para predecir el impacto del programa, tanto a medio como a largo plazo, brindó la oportunidad de establecer un escenario futuro basado en datos reales, con respecto a la incidencia y mortalidad antes del cribado en nuestro medio, así como los resultados del programa tras su inicio en 2009. Una característica sobresaliente de este método fue poder contar con registros de Cáncer reconocidos internacionalmente, que hacen factible el estudio de la efectividad del cribado [Anttila, *et al.* 2015].

Para ello el modelo tuvo en cuenta las tasas de incidencia y de mortalidad en el País Vasco que son diferentes a las de otras regiones europeas. Así, en comparación con los registros europeos, el País Vasco mostró una mayor tasa de incidencia en los hombres y una tasa intermedia en las mujeres en comparación con la hallada en los Países Bajos, Italia o Escocia y el norte del Támesis en el Reino Unido. La tasa de mortalidad en los hombres también fue más alta. Sin embargo, para las mujeres la tasa de mortalidad mostró una posición intermedia [Steliarova-Faoucher, *et al.* 2015].

La simulación aplicada a ambos sexos ofreció una visión más amplia del CCR, que no se reflejó en la mayoría de las investigaciones y que, sin embargo, es importante para calcular el impacto de los programas de cribado. En nuestro estudio, fue claro que estábamos tratando con diferentes grupos de población, no solo con respecto a la incidencia y mortalidad de CCR, sino también cómo se comportaron ambos sexos en cuanto a participación, tasa de positividad del FIT y tasa de lesiones detectadas en la

colonoscopia de cribado. Por lo tanto, el impacto del programa ha demostrado ser mayor en los hombres que en las mujeres, pero éstos participaron menos que las mujeres.

Después de estimar una proyección de 30 años, y con tasas de participación ajustadas a los resultados del programa, la disminución en la incidencia y la mortalidad encontradas parece compatible con lo que se refleja en la literatura actual [Zauber, *et al.* 2015], aunque es difícil comparar los resultados, debido a las diferencias en el contexto, puesto que muchos de estos estudios incluyen simulaciones con un 100% de participación y por períodos cortos o no determinados de seguimiento [Joseph, *et al.* 2016]. Sin embargo, la calidad de la simulación y la adaptación de nuestros parámetros resultó exitosa debido a que los datos son el resultado de la realidad en esta región y proporcionados por tanto por el PCCR como por los distintos registros de Cáncer y de mortalidad.

Según los resultados de la modelización, la reducción en la incidencia comenzaría en los primeros diez años tras la implantación del programa con aumentos significativos a lo largo del tiempo. Como afirman otros autores, el cribado del CCR no sólo reduce la mortalidad, sino que previene nuevos casos [Ventura, *et al.* 2014], que contribuyen a minimizar la carga de la enfermedad en el futuro y a la disminución de su incidencia. Esto es debido a la interrupción de la secuencia adenoma carcinoma tras la extirpación de todas las lesiones adenomatosas en la colonoscopia de cribado. Sobre la base de tasas de incidencia más altas, el impacto a medio y largo plazo podría representar una reducción importante tanto en el número de casos como en muertes, según Parente, et al. 2015 que encontraron una tasa de mortalidad significativamente menor en el cribado en 5 años en comparación con pacientes con cáncer colorrectal no participantes en el cribado o con CCR antes de la implantación del mismo (19% frente a 37% y 41%; p <0,001).

En este sentido, la disminución de los años de vida perdidos para ambos sexos es muy alta y dicho parámetro mostró ser una herramienta importante para las autoridades sanitarias tanto regionales como nacionales, así como para los gerentes sanitarios, para invertir y apoyar este tipo de programas preventivos, teniendo en cuenta a la organización sanitaria y sus indicadores de calidad, tal y como sugieren van Hees, *et al.* 2015 desde los programas de los Países Bajos. Las comparaciones entre programas son difíciles, como fue sugerido por Klabunde, *et al*. 2015 que encontraron una amplia variación en la cobertura de invitación desde el 30 al 100% y la tasa de participación global entre el 7 y el 67,7%, y en concreto en la primera invitación, del 7 al 64,3%. Estas diferencias podrían minimizarse implementando diferentes medidas en el modelo de invitación para aumentar la cobertura y la captación de personas participantes a fin de maximi-

zar la igualdad de acceso y el impacto en la salud pública recomendado por Senore, *et al.* 2015.

Una fortaleza importante de este estudio es un modelo bien validado basado en varios años de datos de un programa poblacional con alta tasa de participación, aportados por los responsables del programa del País Vasco, muy similares y en consonancia con los observados por el propio programa.

En el futuro, se deberían de tener en cuenta algunos de los hallazgos realizados en la prueba de cribado (FIT) con respecto a las rondas repetidas para aumentar la eficiencia [van der Meulen, *et al.*2016]. Así, hoy en día todavía tenemos dificultades para comparar datos de diferentes modelos de invitación, así como de pruebas de cribado, debemos aceptar que no tenemos ensayos controlados aleatorios sobre la eficacia del FIT, así como la falta de datos sobre la participación en las colonoscopias de seguimiento y la incertidumbre en la prevalencia de adenomas en algunas regiones. Por lo tanto, es necesario llevar a cabo estudios prospectivos de cohortes pragmáticos para evaluar el impacto de la efectividad de estos programas en un contexto real de implementación y tomando en consideración todos los parámetros posibles y su influencia.

De acuerdo con los parámetros de simulación de MISCAN-Colon y por medio de los primeros años del programa, el cribado parece ser una estrategia efectiva para reducir la incidencia, la mortalidad y los años de vida perdidos. Estos resultados están en línea con los estudios publicados sobre análisis de coste-efectividad [Lansdorp-Vogelaar, *et al.* 2011]. Esta información respalda por tanto la continuidad del PCCR.

2. ANÁLISIS ECONÓMICO

En lo que respecta al análisis de coste-efectividad apuntar que éste presentó el programa de cribado de CCR vasco como una intervención dominante porque produjo un ahorro neto de costes y un aumento de los beneficios para la salud [Russell, *et al.* 1996]. El análisis de impacto presupuestario también mostró un ahorro consistente después de 10 años de su implementación completa, destacando la capacidad de asumir su coste por el sistema sanitario [Sullivan, *et al.* 2014]. Ambos enfoques de la evaluación económica revelan que sólo un largo seguimiento puede establecer el beneficio económico tardío del cribado basado en la disminución del número de casos de CCR en estadios iniciales y avanzados y la consecuente reducción en la necesidad de tratamientos oncológicos. Hasta ahora en Europa, ningún otro programa de cribado de PCCR poblacional ha sido evaluado con un enfoque integral que incluya análisis de coste-efectividad y de

impacto presupuestario para demostrar su eficiencia y su viabilidad en un sistema sanitario. Obviamente, nuestros resultados apoyan la continuidad de esta política preventiva para mejorar el beneficio epidemiológico de los ciudadanos. Dos revisiones de la literatura confirmaron este hallazgo, haciendo hincapié en que el cribado del cáncer colorrectal es rentable o dominante en comparación con no realizar ninguna estrategia de cribado [Lansdorp-Vogelaar, *et al.* 2011; Patel, *et al.* 2015]. Los programas de salud pública deben reevaluarse periódicamente para confirmar que han logrado los resultados planificados [Tappenden, *et al.* 2013]. Dichos estudios de evaluación también pueden ser útiles a otros países para asesorar a la hora de hacer una planificación sobre la conveniencia o no de implementar un programa poblacional. El análisis de sensibilidad realizado con los datos particulares del cribado vasco mostró el impacto por la prevalencia real de adenoma sobre la necesidad de colonoscopias de seguimiento. Una estimación realista sobre el número de colonoscopias necesarias se podría hacer sobre la base de los primeros informes producidos por los resultados del estudio COLONPREV [Quintero, *et al.* 2012]. Cualquier evaluación debe tener en consideración si el sistema sanitario tiene la capacidad de absorber tal demanda creciente de colonoscopias de seguimiento para asegurar la continuidad del PCCR. Hay que tener en cuenta no sólo el número de colonoscopias diagnósticas tras la prueba de cribado positiva, sino el número requerido de colonoscopias de seguimiento, dato que está directamente relacionado con la prevalencia de adenomas en la población específica [Wilschut, *et al.* 2011; Corley, *et al*. 2014]. Para explicar el ahorro de costes a largo plazo, es necesario subrayar que, aunque el programa de cribado y las colonoscopias derivadas significaron un gasto importante, (máxime por la alta prevalencia de adenomas), más del 90% del gasto total se originó por los costes de tratamiento oncológico fundamentalmente en estadios avanzados.

Los costes totales en el escenario de no cribado crecieron constantemente durante los años analizados debido a que el número de casos de CCR en la población vasca aumentó con el envejecimiento derivado del aumento demográfico en la década de los 70. El principal coste fue el del tratamiento que fue proporcional a la incidencia.

Cabe destacar que el impacto del cribado significó la estabilización de los costes totales porque se mantuvo la incidencia bruta y, por lo tanto, las tasas ajustadas por edad del CCR disminuyeron. En el análisis sólo se consideraron los costes relacionados con el PCCR y el tratamiento de CCR, sin tener en cuenta el coste de la atención de enfermedades no relacionadas que podrían aparecer debido al aumento del tiempo de supervivencia de las personas. La inclusión de estos costes podría hacer aumentar el ICER final y reducir la eficiencia del cribado. Sin em-

bargo, puede ser observado como positivo ya que probablemente se corresponda con patologías similares en el rango de edad de estudio, por lo que únicamente la morbilidad derivada del programa y los tratamientos subsecuentes debieran contabilizarse. Igualmente en un análisis más profundo y fino, se podría argumentar que no se cuentan los costes indirectos reducidos por el incremento de la productividad en los años de vida recuperados en población todavía activa.

También es importante contextualizar los costes relativos al programa de cribado "per se", ya que representan entre el 6% y el 8% del coste total, cuando agregamos los costes de todo el seguimiento de las lesiones. Además, ese rango porcentual probablemente disminuirá, ya que los costes de tratamiento tienden a crecer como consecuencia de la introducción de nuevos tratamientos oncológicos mucho más caros que los actualmente disponibles en el mercado [Corley, *et al.* 2015]. Por lo tanto, los resultados apoyan la idea de que el refuerzo en la prevención secundaria parece una opción futura plausible en el actual escenario de manejo. La consideración de las desigualdades en el acceso a la atención de la salud también sostiene la política de inversiones encaminadas a medidas de prevención, en lugar de tratamiento una vez se presenta la enfermedad, ya que el caso de CCR suele ser detectada en estadios avanzados fundamentalmente [Gil, *et al.* 2012; Morris, *et al.* 2012] y los costes son superiores en dichos casos. De hecho, aunque se han encontrado diferencias en la participación por nivel de privación en el programa de cribado, es más fácil proporcionar a los grupos desfavorecidos un mejor acceso a los programas de cribado que proporcionar a toda la población los últimos fármacos oncológicos [Hurtado, *et al.* 2015]. Esta afirmación que pudiera ser considerada como utilitarista, sin embargo presenta una ventaja a futuro y una decisión sobre dónde se obtiene un mejor resultado sobre la base de prioridades a establecer. Es decir, no quiere referirse a que no se deben procurar terapias avanzadas a los pacientes que lo necesiten, sino que la inversión en prevención representa una ventaja y un mejor coste-oportunidad frente a la inversión en tratamientos. Estos hechos deberían compartirse con la sociedad cuando se establezcan las prioridades y se definan los presupuestos en salud y las acciones a realizar no ya menos costosas sino más eficientes.

3. COMPARACIÓN EN TÉRMINOS DE RESULTADOS EN SALUD

Las intervenciones de salud pública siempre han sido criticadas por su escasa especificidad, dudosa eficiencia (no soportada en datos) y porque sus resultados probablemente se obtengan a largo plazo. Posiblemente se pueda aplicar a programas de cribado poblacionales que, desde su inicio, han tenido grandes defensores, pero también detractores [Sackett, *et al.* 1975]. Sin embargo, uno de los factores clave que determina la implementación o no, de un programa de detección basado en toda la población, es la existencia, o no, de un factor de riesgo modificable o la capacidad de detectar y tratar cambios anormales que podrían ocurrir posteriormente, es decir, convertirse en una enfermedad. De hecho, el principal objetivo de esos programas es detectar patología en su etapa temprana. Sin embargo, promover cualquier intervención en su fase inicial, sólo tiene sentido cuando se obtiene un mejor resultado que con el tratamiento en su etapa avanzada [Petticrew, *et al.* 2000; UK National Screening Committtee, 2015]. En el caso del CCR, se cumplieron tanto los criterios establecidos por la OMS para establecer un cribado poblacional, así como aquellos referidos al coste-efectividad o al coste-oportunidad [UK National Screening Committtee, 2015], y el establecimiento de programas de cribado poblacional se consideró por lo tanto que merecía la pena [Wilson and Junger 1968]. El Consejo de la Unión Europea definió una serie de recomendaciones para el cribado del cáncer [von Karsa, *et al.* 2013]. Sobre la base de dichas recomendaciones, los diferentes ministerios de salud y los proveedores de servicios en diferentes países de Europa promovieron programas de cribado y estrategias nacionales [UK National Screening Committtee, 2016-2017]. Sin embargo, los promotores de los programas no sólo deberían considerar el valor teórico (la eficacia) y los costes de implementar los programas, sino también la evaluación continua de los resultados de los programas, y determinar así el valor pragmático (la efectividad), especialmente considerando que en la mayoría de los casos los resultados finales se obtienen a medio y largo plazo y las inversiones a realizar impactan sobre los presupuestos actualmente y deben ser sustentadas en argumentos de coste-oportunidad.

Diferentes autores han afirmado que, para maximizar los posibles beneficios de los programas de prevención, la tasa de participación es crítica [Klabunde, *et al.* 2015; Borowski, *et al.* 2018]. Además, Borowski, *et al.* 2018 afirman que, aunque la disminución acumulada de la mortalidad puede lograrse fácilmente con el programa de cribado del Reino Unido en hasta el objetivo del 25%, tanto en los cánceres de intervalo como en las lesiones de colon derecho no detectadas,

enfatizan la necesidad de una mejora adicional en la participación, así como la investigación en métodos de detección alternativos más sensibles. De hecho, las recomendaciones del Grupo de Trabajo Europeo en la guía de cribado de CCR, [von Karsa, *et al*. 2010] establecieron una participación del 45% como aceptable y del 65% como deseable y en la comparación no exhaustiva realizada por Klabunde y su equipo de investigadores, [Klabunde, *et al*. 2015], sólo tres programas se acercaban u obtuvieron tasas de participación por encima del 65%, siendo estos el programa Finés (67,7%), el sueco (65%) y el del País Vasco (64,3%). Los datos recogidos en dicho estudio fueron de finales de 2013, una vez completada la primera ronda de invitación al total de la población elegible. Actualmente, la tasa de participación del programa vasco es mucho más alta (71,3%), mostrando tendencias crecientes en ambos sexos y en todos los quinquenios además de en todas las rondas de invitación [https://www.osakidetza.euskadi.eus, 2017]. Los datos del estudio actual indican que, con la participación obtenida, la reducción de la tasa de mortalidad de entre el 20 y el 30%, así como el aumento de la supervivencia a 5 años, se pueden lograr de manera realista en un corto período de tiempo, incluso más corto que el esperado en la modelización [Idigoras, *et al.* 2017].

La efectividad de la mayor parte de los programas de detección colorrectal se ha sustentado sobre la base de resultados intermedios (sensibilidad y especificidad, falsos positivos y falsos negativos y los números necesarios de cribar) con el fin de detectar una lesión. Algunos autores también han informado sobre la reducción de las tasas de mortalidad una vez que los programas de detección se han implementado en condiciones ideales como las que refieren los ensayos clínicos [Lansdorp-Vogelaar, *et al*. 2011] o sobre la base de programas de detección poblacionales [Klabunde, *et al*. 2015]. De hecho, Zorzi *et al.* en el 2015 comparando la población cribada con la no cribada, refirieron una disminución en la mortalidad del 13 al 22% entre la población procedente del cribado. El estudio actual en la CAPV ha demostrado que participar en el programa de cribado puede reducir la mortalidad a 5 años entre 33,4% (90,1% vs 66,7%) y 22,6% (88,7% vs 66,1%), dependiendo de cómo sean consideradas las poblaciones a estudio. En el peor escenario, en el que el grupo de los no cribados es considerado como los que nunca se invitaron al cribado y a los que fue imposible localizar por un error de exclusión en la base de datos ó error en la dirección postal, frente a los de cribado que incluían a los invitados y participantes en el programa, los CCR detectados en la colonoscopia de vigilancia, así como los cánceres de intervalo tanto de FIT como de colonoscopia, la diferencia en mortalidad a 5 años es mayor del 20%. Dichos resultados demuestran que las predicciones de mortalidad realizadas con modelos de simula-

ción y los realizados en marcos teóricos se pueden conseguir para períodos de tiempo más cortos que los esperados. Esto es consistente con lo observado en otros estudios [Gill, *et al*. 2014; Zorzi, et al. 2015, Borowski, *et al*. 2018]. Sin embargo, debido a las características del programa vasco de cribado, su tasa de participación y la posibilidad de interoperatibilidad entre las diferentes bases de datos y registros de cáncer y mortalidad, se han podido analizar las tasas de mortalidad por tipo de invitación, participación, localización y estadio del tumor entre otros parámetros. Los datos actuales del estudio han demostrado que la detección en etapas tempranas y la participación en el PCCR son variables protectoras cuando se consideran las tasas de supervivencia a 5 años. De forma consistente, otras variables tales como: el índice de morbilidad, el grado de diferenciación del tumor, el estadio avanzado del tumor, así como no haber sido invitado al programa, optar por no participar en el mismo, o ser un falso negativo tanto de FIT como de Colonoscopia (CI_FIT ó CI_COL), se asociaron con una peor supervivencia a los 5 años.

En cuanto al pronóstico de los cánceres detectados por o fuera del programa, Gill, *et al*. en 2012 demostraron que los CCR detectados a través del programa de cribado del Reino Unido tuvieron un pronóstico más favorable en comparación con los cánceres no detectados por el programa. Además, este mismo equipo de investigadores dos años después [Gill, *et al*. 2014] demostró que la estrategia de cribado que sigue la mayoría de los programas de cribado en el mundo, el test de sangre oculta en heces, es mejor para detectar cánceres en colon izquierdo y en los hombres. Curiosamente, los mismos autores concluyeron en lo que respecta al CI, que los detectados por el cribado, no tuvieran un mejor resultado en comparación con la población no cribada. En el estudio actual, se observó, por el contrario, que los CI tienen tasas de supervivencia más altas en comparación con los CCR de no cribado. Algunos de los argumentos para estas diferencias podrían ser las diversas características biológicas de los tumores, a pesar de que Walsh, *et al.* 2016 no identificaron evidencia de diferencias biológicas entre el CI y los CCR detectados por cribado, lo que es consistente con la baja sensibilidad de SOHi para los CI_FIT. Las principales causas, por lo tanto, están relacionadas con el sexo y con la localización del tumor.

El presente estudio muestra que una estrategia de prevención secundaria de cáncer colorrectal poblacional no sólo muestra ventajas desde el punto de vista de resultados en salud, sino que ofrece una ventaja económica frente a estrategias alternativas como el cribado oportunístico, sólo de población a riesgo o la inversión en tratamientos innovadores una vez detectada la patología. Sin embargo, la aparición de nuevas pruebas diagnósticas, la determinación de perfiles de riesgo y la irrupción de terapias

curativas o prolongadoras de la esperanza de vida deberán ser consideradas para poder remodelizar las diferentes alternativas y seleccionar aquéllas que presenten mejores valores de efectividad y eficiencia. Los programas de cribado poblacional no se pueden acomodar en estos resultados exitosos y deben mejorar su personalización especialmente en los casos de los falsos positivos, cánceres de intervalo (especialmente colon derecho) y pruebas confirmatorias. Es más, el simple hecho de que la participación una única vez en el programa ya mejoraba la supervivencia hace reflexionar sobre si en todos los casos se deben realizar los tests de FIT cada dos años o probablemente en algunos casos sea innecesario o se pueda realizar en periodos más dilatados.

4. LIMITACIONES

Limitaciones del estudio 1:

- Para la modelización con la herramienta MISCAN-Colon se tuvieron que ajustar parámetros como el relativo a los datos de hallazgos de la colonoscopia de cribado, a las características predeterminadas por el modelo matemático donde exclusivamente se clasifican por su tamaño en adenomas ≤ 10mm en ABR y los > 10mm en AAR, cuando la clasificación de las lesiones por la Guía Europea de calidad de colonoscopias sintomáticas y de cribado (2010) y seguida por los técnicos del Centro Coordinador del PCCR, más allá del tamaño de los adenomas, contempla otros parámetros como el grado de displasia y el número de adenomas y en base de dichos ítems establece el riesgo en ABR, ARM y AAR .
- Por otro lado, sería necesario poder ajustar el modelo de micro simulación MISCAN-Colon a la realidad global de otros parámetros específicos del programa de cribado vasco, como lo que respecta a los efectos adversos: complicaciones, falsos positivos, falsos negativos, ya que los parámetros utilizados fueron los que muestra la literatura a nivel mundial y son diferentes a los del programa evaluado.

Limitaciones del estudio 2:

- Se requiere un período prolongado para que se manifieste el impacto de las extirpaciones de las lesiones premalignas (adenomas) en muertes evitadas y tratamientos contra el CCR y, por lo tanto, los primeros años del programa pueden ser engañosos porque el cambio en la historia natural del CCR no ha alcanzado un estado estable en términos poblacionales.

Limitaciones del estudio 3:

- Pudieran resultar escasos los 6 años de recorrido de programa de cribado y será muy interesante ver a más largo plazo de tiempo los beneficios poblacionales de dicha acción preventiva a pesar de que ya se vislumbran a corto-medio plazo.
- Es necesario realizar más investigaciones para mejorar la eficiencia de los programas a fin de proponer estrategias diferenciales para aumentar la participación en los mismos. Por lo tanto, los coordinadores de los programas y los gestores de las actividades preventivas deben trabajar juntos para identificar los factores que aumentan el riesgo para el individuo o los distintos grupos, y por lo tanto requieren de estrategias de selección y de cribado personalizadas y personalizables.
- Esperamos que la repercusión del programa será algo diferente y de mejor pronóstico para las personas etiquetadas como participantes regulares, dado que a fecha del análisis de los datos el número de invitaciones en sucesivas rondas fue aún pequeño, lo mismo que probablemente se establezca una diferencia en la supervivencia para los participantes irregulares en el PCCR.
- La no detección de algunas de las lesiones pre malignas y malignas colónicas, además de la insuficiente calidad en el seguimiento, pudieran a futuro hacer que tan esperanzadores beneficios epidemiológicos poblacionales se vean disminuidos, por lo que se deben establecer medidas estrictas de calidad de realización de las colonoscopias así como de realización de los seguimientos no seguidos por el total de la población vasca.

CONCLUSIONES

VI.- CONCLUSIONES

Los resultados obtenidos permiten concluir que:

1. Los resultados del PCCR del País Vasco se ajustan a su estrategia y son comparables con otros programas de cribado en Europa. Se puede concluir que el modelo MISCAN-Colon es una herramienta útil para predecir los beneficios del programa.
2. De acuerdo con los parámetros de micro simulación de MISCAN-Colon y a través de los resultados de los primeros años del programa de prevención, el cribado parece ser una estrategia efectiva para reducir la incidencia de CCR en un 17,2% y un 14,7% en hombres y mujeres respectivamente, la mortalidad en un 28,1% y 22,4% en hombres y mujeres respectivamente a 30 años de su implantación.
3. La evaluación económica mostró que, con la intervención de cribado sobre el CCR, se obtiene un importante beneficio en salud y que también produjo ahorros netos cuando se utilizó un seguimiento prolongado (30 años), para calcular el beneficio económico tardío.
4. Del análisis de coste-efectividad podemos extraer que el ahorro en el tratamiento del CCR fue mayor que los costes de tratamiento adicionales debido a la extirpación de lesiones pre-malignas. El ahorro apareció 10 años después de la implantación completa del programa. El presupuesto anual promedio fue de 73,4 millones de € desde el año 2023.
5. El programa de cribado aplicado durante 30 años y con seguimiento de por vida resulta dominante, esto es, ahorra costes y proporciona más años de vida ajustados por calidad a la población. La esperanza de vida aumentó en 29,3 días por persona.
6. La diferencia en la supervivencia a 5 años de los participantes en el programa de cribado, es el 23,1% más alta que en el grupo de no cribado. Esto hace pensar que las tasas de incidencia y mortalidad de CCR disminuirán en un futuro cercano.
7. Lograr una alta tasa de participación en el programa vasco de cribado es esencial para lograr beneficios en salud independientemente del tipo de participación en el programa, dado que no se han encontrado diferencias estadísticamente significativas en la superviviencia.
8. La información extraída de los 3 diferentes estudios presentados, avala la continuidad del programa de prevención de CCR del País Vasco.

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VII.- BIBLIOGRAFÍA

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ANEXOS

ANEXO I: Informe favorable del Comité de Ética de Investigación Clínica de Euskadi

INFORME DEL COMITE ETICO DE INVESTIGACION CLINICA DE EUSKADI (CEIC-E)

Dª. Iciar Alfonso Farnós como Vicepresidenta del CEIC de la Comunidad Autónoma del País Vasco (CEIC-E)

CERTIFICA

Que este Comité, de acuerdo a la ley 14/2007 de Investigación Biomédica, Principios éticos de la declaración de Helsinki y resto de principios éticos aplicables, ha evaluado el proyecto de investigación, titulado **EVALUACIÓN A NIVEL POBLACIONAL DEL BENEFICIO EN SALUD Y COSTE DEL PROGRAMA DE DETECCIÓN PRECOZ DEL CÁNCER DE COLON Y RECTO EN LA CAPV,** Código interno: PI2014171

Versión del Protocolo: Versión 1. Septiembre 2014
Versión de la HIP:
DONANTE / Versión 29 de Septiembre de 2014
PACIENTE/ Versión 29 de Septiembre de 2014

Y que este Comité reunido el día 29/10/2014 (recogido en acta 10/2014) ha decidido emitir **informe favorable** a que dicho proyecto sea realizado por los siguientes investigadores:

- Isabel Idigoras Rubio *Organización Central de Osakidetza*

Lo que firmo en Vitoria, a 4 de noviembre de 2014

Fdo:

Dra. Iciar Alfonso Farnós
Vicepresidenta del CEIC de la Comunidad Autónoma del País Vasco (CEIC-E)

ANEXO II: Glosario de términos

- **Adenoma Avanzado (AA):** sumatorio de adenomas de riesgo medio + adenoma de alto riesgo
- **Adenoma de Bajo Riesgo (ABR):** 1-2 adenomas y ambos pequeños (< 10 mm) y tubulares y displasia de bajo grado
- **Adenoma de Riesgo Alto (AAR):** ≥ 5 adenomas pequeños o al menos uno ≥ 20 mm
- **Adenoma de Riesgo Medio (ARM):** 3-4 adenomas pequeños o al menos un pólipo ≥ 10 mm y < 20 mm o adenoma velloso o displasia de alto grado
- **Cáncer Colon y Recto:** tumor que invade la submucosa a través de la Muscularis Mucosa (pT1)
- **Cáncer de Intervalo COL (CI_ COL):** CCR diagnosticado tras una colonoscopia de cribado sin CCR y antes de realización de colonoscopia de seguimiento recomendada por endoscopistas a la vista del riesgo establecido en la colonoscopia de cribado

- **Participante inicial invitación sucesiva en PCCR:** Participa en el programa por primera vez, pero no en invitaciones previas
- **Participante Inicial primera invitación en PCCR:** Participa en el programa en la primera invitación
- **Cáncer de Intervalo FIT (CI_FIT):** CCR diagnosticado tras un FIT negativo ya antes de la siguiente invitación al PCCR, incluyendo a las personas que tras resultados FIT negativo, no cumplen criterios de edad para volver a invitarles al cribado, es decir personas de 68 y 69 en la última participación
- **Especificidad:** proporción de personas sin enfermedad que tienen un resultado negativo
- **KRAS:** Describe un gen cuando se encuentra en su forma natural, sin mutaciones, este produce una proteína llamada KRAS, que participa en las vías de señalización celular que controlan el crecimiento y la muerte de las células
- **Neoplasia Avanzada (NA):** engloba el sumatorio de Adenomas avanzados + CCR
- **NNS:** número de personas que necesitarían ser examinadas para identificar a una persona con la enfermedad
- **Participante Irregular en PCCR:** Participa en el programa de manera intermitente
- **Participante regular en PCCR:** Participa en el programa al menos 2 invitaciones consecutivas. Se utiliza dicho término para el estudio de los CCR relacionados con su modo de participación en el PCCR

- **Población diana PCCR:** Personas entre 50-69 años y con médico de atención primario en el Centro de Salud donde se pone en marcha el programa de cribado
- **Población elegible PCCR:** Personas entre 50-69 años, con médico de atención primario en el Centro de Salud donde se pone en marcha el programa de cribado y sin ningún motivo e exclusión en el programa de cribado
- **Población invitable PCCR:** Personas entre 50-69 años, con médico de atención primario en el Centro de Salud donde se pone en marcha el programa de cribado, sin ningún motivo e exclusión en el programa de cribado y cuya carta de invitación al programa no es devuelta por error postal

- **Sensibilidad:** proporción de personas con la enfermedad que tienen un resultado positivo
- **Tasa de falsos negativos (1 menos sensibilidad):** proporción de personas con enfermedad que tienen un resultado negativo
- **Tasa de falsos positivos (1 menos especificidad):** proporción de personas sin enfermedad que tienen un resultado positivo
- **Valor predictivo negativo:** proporción de personas sin enfermedad entre las personas con una prueba negativa
- **Valor predictivo positivo:** proporción de personas con enfermedad entre las personas con una prueba positiva

ANEXO III: Índice de abreviaturas

AA: Adenoma Avanzado

AAR: Adenoma de Alto Riesgo

ABR: Adenoma de Bajo Riesgo

ACE: Análisis de Coste-Efectividad

ADN: Ácido Desoxirribonucleico

AJCC: American Joint Committee on Cancer

APC: Adenomatous Polyposis Coli

ARM: Adenoma de Riesgo Medio

ARN: Ácido Ribonucleico

AVAC: Años de Vida Ajustado por Calidad

CAPV: Comunidad Autónoma Vasca

CCAA: Comunidades Autónomas

CCR: Cáncer Colorrectal

CEA: Antígeno Carcinógeno- Embrionario

CI: Cáncer de Intervalo

CIE-O: Clasificación Internacional de Enfermedades para Oncología

CIMP: CpG island methylation phenotype

CIN: Vía de Inestabilidad Cromosómica

CISNET: Cancer Intervention and Surveillance Modelling Network

CMBD: Conjunto Mínimo Básico de Datos

DE: desviación estándar

ECA: Ensayo Clínico Aleatorizado

EMS: Estabilidad Micro-Satélites

ERR: Exceso de riesgo relativo

EUSTAT: Instituto Vasco de Estadística

f-Hb: Hemoglobina fecal

FIT: Faecal Inmunochemical test

Hb: Hemoglobina

HR: Hazard Ratio

IC: Intervalo de Confianza

ICER: Incremental cosst-effectiveness ratio

IMS: Inestabilidad Micro-Satélites

INE: Instituto Nacional de Estadística

MISCAN-Colon: Microsimulation Screening Analysis-colon

mSEPT9: Metilado de Septina9

MVHP: pólipos hiperplásicos microvesiculares

OR: Odds Ratio

PCCR: Centro Coordinador Programa

RR: riesgo relativo

RS: revisión sistemática

SNst : Supervivencia Neta estandarizada por edad

SOH: Sangre oculta en Heces

SOHg: Test de guayaco de Sangre oculta en Heces

SOHi: Test inmunoquímico de Sangre oculta en Heces

TAE: Tasa Ajustada por Edad

TB: Tasa Bruta

VPP: Valor Predictivo Positivo

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PUBLICACIONES RELEVANTES DE LOS ÚLTIMOS 5 AÑOS

IX.- PUBLICACIONES RELEVANTES DE LOS ÚLTIMOS 5 AÑOS

1. **Idigoras I,** Arana-Arri E, Portillo I, Bilbao I, Martínez-Indart L, Imaz-Ayo N, de Castro V, López de Munain A, Torrejón I, Gutiérrez-Ibarluzea I. Evaluation of the Effectiveness of the Colorectal Cancer Screening Programme in the Basque Country in terms of 5 year survival rates. J Gastroenterol. [Enviado].
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5. **Idigoras I,** Arrospide A, Portillo I, Arana-Arri E, Martínez-Indart L, Mar J, de Koning HJ, Lastra R, Soto-Gordoa M, van der Meulen M, Lansdorp-Vogelaar I. Evaluation of the colorectal cancer screening Programme in the Basque Country (Spain) and its effectiveness based on the Miscan-Colon model. BMC Public Health. 2017; 18(1):78.
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Screening colonoscopy and risk of adverse events among individuals undergoing fecal immunochemical testing in a population-based program: A nested case-control study

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Abstract

Background: Screening by means of biennial fecal occult blood test has provided a reduction in overall colorectal cancer mortality. Notwithstanding, we should not underestimate the harms that it can produce.

Aim: The aim of this article is to identify the independent risk factors of complications after a screening colonoscopy.

Methods: A six-year, nested case-control study was conducted. Mortality/complications within 30 days after colonoscopy were registered and its predictors identified through logistic regression.

Results: After 39,254 colonoscopies, the complication rate was 1.0%. Independent predictors were sex (OR 1.68 for men; CI 95% 1.18–2.39), ASA physical status classification system (OR 1.73 for ASA II–III; CI 95% 1.53–3.69), history of abdominal surgery (OR 2.37; CI 95% 1.72–4.08), diverticulosis (OR 2.89; CI 95% 1.94–4.30), inadequate cleansing (OR 29.35; CI 95% 6.52–132.17), detection of advanced neoplasia (AN) (OR 4.92; CI 95% 3.29–7.36), detection of stage I adenocarcinoma (OR 9.44; CI 95% 4.46–20.0), polyps in right colon OR 2.27 CI 95% 1.38–3.74) and complex polypectomy (OR 2.00; CI 95% 1.25–3.20). The logistic model explained 82% of the complications (CI 95% 0.798–0.854, $p < 0.001$).

Conclusions: Colonoscopy, with or without removal of a lesion, is an invasive procedure with a non-deniable risk of major complications. Factors like inadequate cleansing or detection of AN are determinants. Therefore, it is vital to know which aspects predict their appearance to implement countermeasures.

Keywords

Colorectal cancer, screening colonoscopy, complication, fecal immunochemical test, independent risk factors

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Key summary

1. Summarize the established knowledge on this subject:
- Screening colonoscopy with polypectomy has shown to be a diagnostic and therapeutic procedure that reduces the incidence and mortality of colorectal cancer (CRC) and it is considered the gold standard in colorectal cancer detection.

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- Although endoscopic techniques have improved over the years, they are not exempt from damage and adverse events, and different publications have shown diverse complication rates, ranging from 0.04% to 8%.
- Different independent factors have been identified to be related to these complications and could lead to the implementation of countermeasures. The issue is how to prioritize them by their importance.

2. What are the significant and/or new findings of this study?

- As far as we know, this is one of the few published studies that tries to identify risk factors related to the occurrence of adverse events when performing a colonoscopy in a population-based screening program with a fecal immunochemical test.
- This study reflects the risk associated with colonoscopies within the framework of a well-established, high participation rate and real-world practice CRC population-based screening program.
- The outcomes observed provide insights as to how to minimize adverse events rates, prioritize countermeasures to be established and increase the efficiency of existing programs while ensuring that the goals of reducing CRC-related morbi-mortality are reached.

Introduction

Once lesion suspicion is determined, colonoscopy is the final common denominator of all colorectal cancer (CRC) screening strategies and today is the gold standard for the detection of CRC and premalignant lesions. According to the results of a population-based case-control study, about 75%–80% of CRC cases could be prevented by colonoscopy, with a stronger effect on distal than on proximal CRCs.[1] However, this estimate was not corrected for self-selection bias.

Since well-designed and implemented screening programs demonstrate effectiveness, CRC is one of the most preventable cancers. Several studies have shown that CRC screening programs in average-risk individuals reduce the incidence and mortality.[2–8] In contrast with other screening programs, such us lung, prostate or breast cancer, CRC screening focuses not only on early-stage cancer detection, but also on detecting and removing precancerous lesions (adenomas).[9] Moreover, CRC screening programs have been shown to be a highly cost-effective health care strategy.[10,11]

However, we must not underestimate the occurrence of adverse effects such as colonoscopy complications. In fact, a population-based screening program should not be implemented when the risks of the diagnostic and management tests required to run the program are not assumable from the ethical point of view, in order to ensure high-quality care. Overall pooled colonoscopy complication prevalence in a recent published meta-analysis for post-colonoscopy perforation, bleeding and mortality is 0.5/1000 (95% confidence interval (CI) 0.4–0.7), 2.6/1000 (CI 95% 1.7–3.7) and 2.9/100,000 (CI 95% 1.1–5.5) colonoscopies.[12]

Different risk factors have been reported to be related to colonoscopy complications. The main factors are related to the size, location and shape of the polyp.[13–20] Other reported risk factors include cardiovascular or chronic renal disease,[19] age,[16,18] anticoagulant treatment,[19] poorer bowel preparation[19] and body mass index.[14] Cutting mode of the electrosurgical current and the inadvertent cutting of a polyp before current application have also been proved to be independent risk factors for immediate post-polypectomy bleeding.[19] The risks of serious adverse events following colonoscopy performed as part of screening are low, but there are also related risk factors, such as age and polypectomy.[20]

Based on the recommendations of the European guidelines of 2010[8] and the Spanish Strategy against Cancer validated in 2009,[21] population-based screening for CRC was approved by the Basque Autonomous Government and implemented in 2009. One of the challenges of CRC screening programs and, therefore, that implemented in the Basque Country, is efficiency; hence, the reduction of incidence and morbi-mortality is the main scope, but embracing the minimum if any and acceptable adverse events. For this purpose, it is critical not only to identify and analyze screening colonoscopy complications, but also to try to implement strategies to reduce them. That is the reason why the aim of this study is to identify the independent risk factors of complications after a colonoscopy in the Basque CRC Screening Program. At the same time, this analysis could guide other similar programs when considering the risks in order to act on and minimize them.

Patients/Material and methods

Design and setting

We conducted a nested case-control study in the Basque Colorectal Cancer Screening Program (BCCSP). The screening is based on the detection of occult blood in feces using a biennial quantitative immunochemical test (FIT), targeting women and men between 50 and 69 years of age (approximately 977,819 invitations) and a colonoscopy under sedation for FIT-positive cases.

The colonoscopies were performed in publicly funded hospitals by qualified and trained specialists. All colonoscopies are reviewed and codified within 10 days to assess possible complications. Every three months, all cases are linked to the register of hospital discharges in order to identify all cases that have had an episode of admission within 30 days after colonoscopy.

Study participants

We included participants in the program with a positive FIT and who had had a colonoscopy performed. It was considered a case when a complication was identified as defined in the European guide on CRC screening:[8] hospitalization within 30 days for serious hemorrhage involving transfusion, or for perforation, vagal syndrome or peritonitis-like syndrome and death attributed to complications of a screening colonoscopy.

Cases were randomly selected from colonoscopies performed by the same endoscopy unit over the same week, matching each with the identified complication (Figure 1).

Potential independent factors

As potential independent factors, we collected the following data: age, sex, weight and height, comorbidities, deprivation index, American Society of Anesthesiologists physical status classification system (ASA), anticoagulant/antiplatelet treatments, previous abdominal surgery, diverticulosis, bowel cleansing, cecal intubation, polypectomy, lesions detected in the colonoscopy and the location/size/morphology. Size of the polyp was recorded in millimeters as informed in the histopathologic report; in those cases in which this was not documented the size estimated by the colonoscopist was recorded. To determine the number of polyps, we took the number of polyps resected. Location was categorized as rectum, distal colon (sigmoid, descending colon and splenic flexure), proximal colon (transverse, hepatic flexure and ascending colon) and cecum. Complex colon polypectomy was considered as defined by Gallegos-Orozco and Gurudu[22] as polypectomy of sessile/pedunculated polyps more than 2 cm and difficult to treat endoscopically. Adequate bowel preparation was assessed with the Boston Bowel Preparation Scale (score >6) as recommended by the European Society of Gastrointestinal Endoscopy (ESGE).[23] Adenomas ≥10 mm, adenoma with a villous component (i.e. tubulovillous/villous adenoma) or adenomas with severe/high-grade dysplasia were classified as advanced adenomas (AA).[8] Advanced neoplasia (AN) was defined as CRC plus AA.

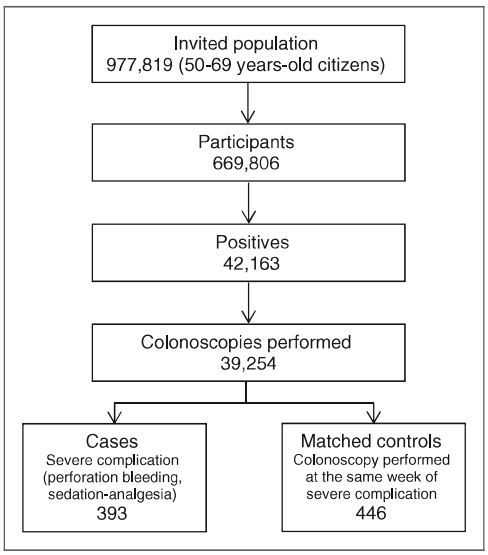

Figure 1. Selection of cases and controls for the study, 2009–2014.

Statistical analysis

Data are expressed as mean ± standard deviations or median and interquartile range (IQR) for quantitative variables and qualitative variables by frequency tables and percentages. For comparison between two groups Fisher's exact test or χ^2 was used. To compare quantitative variables and categorical variables with two categories *t*-test or the non-parametric Mann–Whitney *U* test was used. Logistic regression analysis was performed with complications as the outcome variable (dichotomous variable). Significance was set at the 5% level. The analysis was performed by IBM SPSS 23.0 and SAS 9.4.

Results

During the study period 39,254 colonoscopies under sedation were performed. The average number of colonoscopies per person was 1.08 (range 1–5). A total of 393 severe complications were identified (complication rate 1.0%). We can see that the rate for each type of complication is different, as shown in Table 1.

The mean age of the individuals with complications was 61.7 ± 5.4 years and 70.2% were men. The characteristics of patients with and without complications can be seen in Table 2.

The BCCSP has a high participation rate, 68.5%, and high colonoscopy compliance rate, 93.1%, above desirable levels of the European guidelines (65% and 90%, respectively). In 90.5% of the colonoscopies in which a complication was identified, AA or CRC was

Table 1. Adverse events registered.

	Our series $N = 39{,}254$ colonoscopies			Literature
	All *N*; (%) (CI 95%)	Post-polypectomy *N*; (%) (CI 95%)	Without polypectomy *N*; (%) (CI 95%)	% range
Severe complications				
Perforation	106; (2.7) (2.2–3.3)	91; (2.3) (1.9–3.0)	15; (0.4) (0.2–0.6)	0.01–4.6[12]
Bleeding	245; (6.2) (5.5–7.1)	242; (6.2) (5.4–7.0)	3; (0.08) (0.02–0.2)	0.01–15.3[12]
Sedation analgesia	38; (1.0) (0.7–1.3)	30; (0.8) (0.5–1.1)	8; (0.2) (0.09–0.4)	0.8–20.0[8]
Other[a]	4; (0.1) (0.03–0.3)	4; (0.1) (0.03–0.3)	0	0.003–1.0[8]
Minor complications[b]	47; (1.2) (0.9–1.6)	27; (0.7) (0.5–1.0)	20; (0.5) (0.3–0.8)	0.02–0.4[8]

[a]Post-polypectomy syndrome, diverticulitis and peritonitis-like syndrome.
[b]Complications that improve spontaneously without hospitalization or emergency treatment, which can lead to interruption of the colonoscopy, such as abdominal pain, abdominal discomfort, agitation, nausea/vomiting, desaturation or heart rhythm disorder.
CI: confidence interval.

detected. The characteristics of the colonoscopies performed in patients with and without complications can be seen in Table 3.

In univariate analysis, as shown in Table 4, we identified different variables as risk factors: male sex, medium level deprivation index, ASA II–III, heart disease, previous abdominal intervention, diverticular disease, antiplatelet therapy, inadequacy of colon cleansing, diagnosis of stage I adenocarcinoma, polyps in right colon, polyp size ≥ 10 mm, polypectomy, complex colon polypectomy and stage I adenocarcinoma detection rate at the endoscopy units.

After including all the variables, the multivariate logistic regression analysis indicated that male sex, II–III ASA, previous surgical abdominal intervention, diverticular disease, inadequate colon cleansing, diagnosis of AA, diagnosis of stage I adenocarcinoma, polyps in right colon and a complex polypectomy were consistently associated as independent predictors with a colonoscopy complication (Table 5). The area under a receiver operating characteristic curve of the model was 0.826 (CI 95% 0.798–0.854, $p < 0.001$) (Figure 2).

Admitted patients had a median hospital stay of 5.0 days (IQR = 3–7 days). In post-colonoscopy bleedings in 47.6% a therapeutic colonoscopy was performed and in 1.2% surgery. Of the bleedings, 21.1% required transfusion. A total of 59.1% of post-colonoscopy perforations were managed with conservative treatment. No deaths were reported.

Discussion

Screening colonoscopy with polypectomy has been shown to be a diagnostic and therapeutic procedure capable of reducing the incidence and mortality of CRC.[2–8] However, although endoscopic techniques have greatly improved, they are not exempt from damage, and different publications show diverse complication rates, ranging from 0.04% to 8%.[14–21] In our study we have observed that our outcomes are close to the highest rates published to date. Nevertheless, it should be emphasized that most of the published studies are retrospective, which underestimates the complication rates[17] because of the lack of records with proven quality, which could influence the completeness of the data. In the BCCSP, all colonoscopy data are collected prospectively and routinely within 10 days of their completion. In addition, all hospital discharges are linked with the program database, ensuring record quality as recommended by the European CRC guidelines.[8] The effectiveness of the screening colonoscopy depends not only on its compliance, which in our program is above the desirable level (>90%) recommended by the European guide,[8] reaching 92.7%, but also in the quality of its performance and record keeping. It is therefore of paramount importance this registry, as well as the quality of the data collected within it, be able to carry out analysis and identify independent factors related to complications, to be able to implement measures that improve the efficiency of the program.

One risk factor described extensively in the literature is the location of polyps, demonstrating how polypectomy in the proximal colon is an independent risk factor.[14–21,24,25] The Munich Polypectomy Study (MUPS) study reported that proximal location of polyps had a substantial risk of major complications (odds ratio (OR) 2.40, CI 95% 1.34–4.28).[16] After performing the multivariate analysis, we estimated an OR of 2.27 (CI 95% 1.38–3.74) for severe complication after polypectomy in the proximal colon. However, other authors such as Rutter et al.[24] were able to analyze the risk that each segment of the colon had, estimating an OR of 13.5 (CI 95% 3.9–46.4) for bleeding

Table 2. Characteristics of patients with and without adverse events (AE).

Variables	AE ($n = 393$)	No AE ($n = 446$)	p
Sex: men; *n* (%)	276 (70.2)	210 (47.1)	<0.001
Age			
Mean (SD); years	61.7 (5.4)	61.3 (5.5)	0.228
50–54 years; *n* (%)	60 (15.3)	73 (16.4)	
55–59 years; *n* (%)	82 (0.9)	99 (22.2)	0.420
60–64 years; *n* (%)	119 (30.3)	148 (33.2)	
≥ 65 years; *n* (%)	132 (33.6)	126 (28.3)	
Body mass index:			
Mean (SD); kg/m^2	28.6 (4.2)	29.3 (4.9)	0.087
Normal range; *n* (%)	60 (17.5)	87 (22.3)	
Overweight; *n* (%)	155 (45.2)	160 (40.9)	0.790
Obese; *n* (%)	128 (37.3)	144 (36.8)	
Privation index:			
1 (least deprived); *n* (%)	72 (18.8)	82 (18.7)	
2; *n* (%)	71 (18.5)	95 (21.6)	0.104
3; *n* (%)	103 (26.8)	85 (19.1)	
4; *n* (%)	67 (17.4)	91 (20.7)	
5 (most deprived); *n* (%)	71 (18.5)	87 (19.8)	
Morbidity index:			
Patient management; *n* (%)	20 (5.2)	9 (2.0)	
Disease management; *n* (%)	73 (18.8)	60 (13.5)	<0.001
Self-management support; *n* (%)	182 (46.9)	219 (49.4)	
Prevention and promotion of healthy population; *n* (%)	113 (29.1)	155 (35.0)	
ASA physical status classification system			
I; *n* (%)	79 (20.3)	146 (32.9)	<0.001
II; *n* (%)	231 (59.2)	249 (56.1)	
III; *n* (%)	80 (20.5)	49 (11.0)	
Heart disease: yes; *n* (%)	154 (39.2)	235 (52.7)	<0.001
Pulmonary disease: yes; *n* (%)	29 (9.5)	14 (5.8)	0.078
Previous surgical abdominal intervention: yes; *n* (%)	104 (26.5)	52 (11.7)	<0.001
Diverticular disease: yes; *n* (%)	143 (36.6)	65 (14.8)	<0.001
Anticoagulant therapy: yes; *n* (%)	37 (9.4)	48 (10.8)	0.298
Antiplatelet therapy:			
Single; yes; *n* (%)	75 (19.1,8)	51 (11.4)	0.419
Dual; yes; *n* (%)	10 (2.5)	1 (0.2)	
Colon cleansing:			
Adequate; *n* (%)	353 (90.7)	429 (99.5)	<0.001
Inadequate; *n* (%)	36 (9.3)	2 (0.5)	

ASA: American Society of Anesthesiologists.

requiring transfusion after cecal snare polypectomy and an OR of 12.2 (CI 95% 1.2–119.5) for perforation after cecal non-pedunculated polypectomy. In the referred study, 7.7% of the procedures were performed in the cecum, and in our study these were 15.2% of the total polypectomies (almost double), so we could assume a higher risk for major complications while performing polypectomies in the cecal location (univariate analysis, OR 2.98, CI 95% 1.57–5.67). A reasonable explanation for this may be the biological structure of the cecum; this is the finest and distensible part of the colon with saccular pouches between the linear tenia coli. Insufflation during colonoscopy to distend the wall leaves the cecum more susceptible to damage.[14,24]

The risk of severe complications also increases with polyp size. Our study showed that a complex colon

Table 3. Characteristics of colonoscopies with and without adverse events (AE).

Variables	AE ($n = 393$)	No AE ($n = 446$)	p
Endoscopic centers			
Screening colonoscopies performed per year			
300–600; *n* (%)	139 (35.4)	169 (37.9)	0.473
≥600; *n* (%)	254 (64.6)	277 (62.1)	
Time from positive FIT to colonoscopy, mean (SD); days	65.2 (55.1)	60.5 (42.5)	0.170
Colonoscopy yield:			
Normal; *n* (%)	11 (3.1)	178 (40.4)	
Not advanced adenoma; *n* (%)	23 (6.5)	59 (13.4)	< 0.001
Advanced adenoma; *n* (%)	281 (79.2)	182 (41.3)	
Cancer; *n* (%)	40 (11.3)	22 (5.0)	
Stage I cancer: yes; *n* (%)	29 (72.5)	14 (63.6)	0.568
Location of the largest number of polyps:			
Rectum; *n* (%)	23 (7.6)	25 (10.9)	
Distal colon; *n* (%)	41 (13.5)	24 (10.5)	0.001
Proximal colon; *n* (%)	193 (63.7)	168 (73.4)	
Cecum; n (%)	46 (15.2)	12 (35.2)	
Location of the largest polyp:			
Rectum; *n* (%)	29 (9.6)	28 (12.2)	
Distal colon; *n* (%)	40 (13.2)	24 (10.5)	0.003
Proximal colon; *n* (%)	187 (61.9)	164 (71.6)	
Cecum; *n* (%)	46 (15.2)	13 (5.7)	
Number polyps removed:			
Mean (SD); *n*	3.2 (3.4)	2.96 (2.5)	0.266
Median (IQR); *n*	2.0 (3.0)	2.0 (3.0)	
1; *n* (%)	116 (29.6)	89 (34.4)	
2; *n* (%)	66 (16.8)	64 (24.7)	0.004
2 >; *n* (%)	210 (53.6)	106 (40.9)	
Major polyp removed:			
Mean (SD); *n*	11.8 (9.4)	15.9 (11.6)	< 0.001
Median (IQR); *n*	15.0 (12.0)	10.0 (10.0)	
1–5 mm; *n* (%)	65 (16.8)	70 (27.1)	
6–9 mm; *n* (%)	42 (10.9)	42 (10.9)	< 0.001
≥10 mm; *n* (%)	279 (72.3)	139 (53.9)	
Polypectomy: yes; *n* (%)	369 (93.4)	284 (63.7)	< 0.001
Complex polypectomy: yes; *n* (%)	107 (35.0)	37 (15.5)	< 0.001
Cecal intubation: yes; *n* (%)	361 (96.5)	415 (98.8)	0.027
Colonoscopist detection rates:			
Polyps: median (SD); %	64.0 (8.5)	63.4 (9.7)	0.344
Adenoma: median (SD); %	59.1 (8.2)	58.3 (8.9)	0.181
Advanced adenoma: median (SD); %	42.4 (10.1)	41.7 (11.0)	0.366
Advanced neoplasia: median (SD); %	47.9 (10.7)	46.9 (11.6)	0.242
Pt 1: median (SD); %	2.8 (1.3)	2.7 (1.3)	0.034

FIT: fecal immunochemical test; IQR: interquartile range.

Table 4. Univariate analysis of risk factors of colonoscopy complication.

Variables	OR	CI 95%	*p*
Sex (female) Male	2.65	1.99–3.52	<0,001
Age (50–54 years)			0.421
55–59 years	1.01	0.64–1.58	0.973
60–64 years	0.99	0.64–1.49	0.918
≥ 65 years	1.27	0.84–1.94	0.257
Body mass index (normal weight)			0.790
Over weight	1.05	0.67–1.66	0.827
Obesity	0.92	0.58–1.48	0.747
Deprivation index (1–2); (least deprived)			0.032
3	1.52	1.06–2.18	0.024
4–5 (most deprived)	0.80	0.70–1.31	0.796
Morbidity index (prevention and promotion of healthy population)			0.010
Self-management support	3.05	1.34–6.94	0.008
Disease management	1.67	1.10–2.54	0.017
Patient management	1.14	0.83–1.59	0.441
ASA physical status classification system (I)			<0.001
II	1.71	1.24–2.38	0.001
III	3.02	1.93–4.73	<0.001
Heart disease (yes)	1.73	1.3–2.27	<0.001
Pulmonary disease (yes)	0.59	0.30–1.15	0.120
Previous surgical abdominal intervention (yes)	2.74	1.90–3.94	<0.001
Diverticular disease (yes)	3.31	2.37–4.62	<0.001
Anticoagulant therapy (yes)	1.16	0.74–1.82	0.519
Antiplatelet therapy (no therapy)			<0.001
Single	1.88	1.28–2.77	0.001
Dual	12.79	1.63–100.47	0.015
Colon cleanliness (adequate) Inadequate	21.87	5.23–91.49	<0.001
Stage I adenocarcinoma (yes)	2.28	1.18–4.42	0.015
Advanced adenomas (yes)	5.76	4.17–7.96	<0.001
Advanced neoplasia (yes)	10.87	7.28–16.21	<0.001
Polyps in right colon (yes)	2.16	1.40–3.33	0.001
Largest polyp in right colon (yes)	0.99	0.66–1.49	0.970
Number of polyps removed (one polyp) ≥2 polyps	1.25	0.89–1.74	0.200
Polyp size (<10 mm) ≥10 mm	2.23	1.60–3.11	<0.001
Polypectomy (yes)	8.05	5.17–12.53	<0.001
Complex colon polypectomy (yes)	2.91	1.91–4.45	<0.001
Cecal intubation (yes)	2.99	1.05–8.46	0.039
Polyp detection rate	1.01	0.99–1.02	0.344
Adenoma detection rate	1.01	0.99–1.03	0.182
Advance adenoma detection rate	1.01	0.99–1.02	0.242
Stage I adenocarcinoma detection rate	1.13	1.01–1.26	0.035

ASA: American Society of Anesthesiologists; OR: odds ratio; CI: confidence interval.

Table 5. Multivariate analysis of risk factors of colonoscopy complication.

Variables	OR	CI 95%	*p*
Sex (female) Male	1.68	1.18–2.39	0.004
ASA physical status classification system (I) II–III	1.73	1.53–3.69	<0.001
Previous surgical abdominal intervention (yes)	2.37	1.72–4.08	<0.001
Diverticular disease (yes)	2.89	1.94–4.30	<0.001
Colon cleanliness (adequate) Inadequate	29.35	6.52–132.17	<0.001
Advanced adenomas (yes)	4.92	3.29–7.36	<0.001
Stage I adenocarcinoma	9.44	4.46–20.0	<0.001
Polyps in right colon (yes)	2.27	1.38–3.74	0.001
Complex colon polypectomy (yes)	2.00	1.25–3.20	0.004

ASA: American Society of Anesthesiologists; OR: odds ratio; CI: confidence interval.

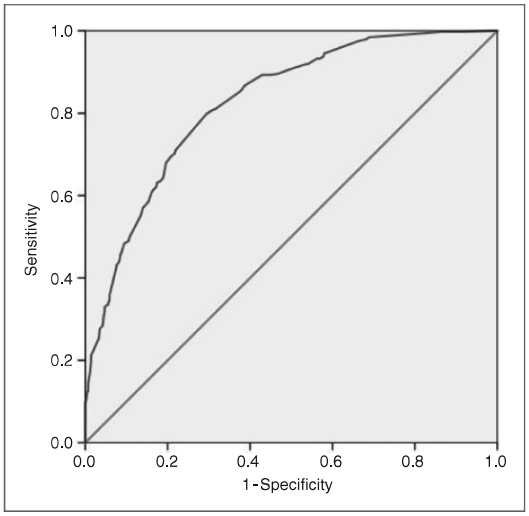

Figure 2. Receiver operating characteristic curve for the logistic model.

polypectomy had an estimated OR of 2.00 (CI 95% 1.25–3.20) for the risk of severe complication. In the definition of complex colon polypectomy, one of the main characteristics is to have a polyp bigger than 20 mm. Our study supports several studies that had estimated the polyp size in relation to severe complications.[14–21,24–26] In the MUPS study[16] the main risk factor for major adverse events reported was polyp size, with an OR of 31.01 (CI 95% 7.53–128.1). Buddingh et al.[13] reported that the risk increased by 13% (CI 95% 5–20) per millimeter, similar to the 9% per millimeter found by Sawhney et al.[27] In this context, Dobrowolski et al.[28] reported that polyp size greater than 17 mm, pedunculated polyps with a stalk diameter >5 mm, sessile polyps, and malignant lesions of the colorectal region are at high risk of hemorrhage after endoscopic excision. Gimeno-García et al.[17] also stablished a cutoff point of 14 mm polyp size as the most important predictor of post-polypectomy bleeding. Using this cutoff would have allowed a prediction of 70% of post-polypectomy bleeding episodes.

We have also identified as independent risk factors the malignancy of the lesions detected. The detection of an AA had an OR of 4.92 (CI 95% 3.29–7.36) and the detection of stage I adenocarcinoma 9.44 (CI 95% 4.46–20.0). Related to histology and malignancy, Consolo et al.[29] reported that post-polypectomy bleeding was associated with large polyps, malignancy, heart disease and hyperplastic polyps.

Male sex has a 1.68 (CI 95% 1.18–2.39) higher risk of an adverse event. This result is not in accordance with the OR of 2.85 (CI 95% 1.17–7.09) for female sex reported by Buddingh et al.[13] However, some studies report that complications are more common in men than women.[17,21] In a univariate analysis, Heldwein et al.[16] reported the relation of ASA as an independent factor (OR 1.10, CI 95% 0.63–1.93), but not statistically significant. However, we have estimated an OR of 1.73 (CI 95% 1.53–3.69) for ASA $\geq$ II.

Related to the participant characteristics, we have identified two independent factors: on the one hand, previous surgical abdominal intervention (OR 2.37, CI 95% 1.72–4.08) and on the other diverticular disease (OR 2.89, CI 95% 1.94–4.30). We have also estimated an OR of 1.73 (CI 95%, 1.3–2.27) for history of heart disease. In this context we have not identified as risk factors hypertension as Watabe et al.[26] described, nor body mass index >25 kg/m^2.

According to the ESGE guidelines[30] for the management of antiplatelet/anticoagulant therapy in patients undergoing a high-risk endoscopic procedure (polypectomy), all patients in the BCCSP followed the recommendations. In the univariate analysis, we did not identify anticoagulant therapy as a risk factor. In the case of antiplatelet therapy, we found a significant relation in single (OR 1.88, CI 95% 1.28–2.77) and dual treatment (OR 12.79, CI 95% 1.63–100.47) while comparing with no antiplatelet treatment. Also, Kim et al.[19] identified anticoagulant therapy as a risk factor (OR 3.71, CI 95% 1.05–13.05) and Heldwein et al.[16] non-steroidal anti-inflammatory drug intake (OR 4.00, CI95% 0.55–29.41), but these were not statistically significant.

Cecal intubation rates and bowel cleansing scores are very important quality indicators in colorectal

screening programs, as reported in several studies.[31–34] In fact, the quality of bowel preparation is important for the efficacy of colonoscopy. As pointed out in the ESGE guidelines,[23] the quality of bowel preparation is associated with two other important performance measures, adenoma detection rate and cecal intubation rate. Suboptimal bowel preparation results in further costs and inconvenience, because the examination has to be repeated or an alternative examination has to be arranged.[35] In the BCCSP the cecal intubation rate was 97.7%, higher than the desirable level in the European guidelines,[8] and the rate of adequate bowel preparation 95.1% (target standard rate for an adequate bowel preparation is 95% by ESGE).[34] In the univariate analysis, we identified lack of cecal intubation as a risk factor (OR 2.99, CI 95% 1.05–8.46) and in the multivariate analysis, inadequate bowel cleansing had almost 30 times more risk of severe complications than adequate cleansing (OR 29.35, CI 95% 6.52–132.17).

Bearing in mind the results of this and other studies, it would be interesting to carry out future studies in which, based on the risk of suffering a complication, different strategies are implemented and analyzed when considering which individuals should undergo a colonoscopy. Today there are less-invasive tests such as the endoscopic capsule or computed tomography colonography. These tests could be considered in those individuals with a higher risk of complication.

Finally, our study has some limitations. One of the most important limitations is that this is a retrospective study nested to a cohort prospective study. However, it should be noted that the quality and completeness of the screening electronic records in the BCCSP is very high. It has already been indicated that colonoscopies, once performed, are recorded prospectively, collecting all the data from endoscopies' reports, as well as reports of pathological anatomy, with all data regarding the polyps and lesions identified.

It should be noted as one of the main strengths of the study that we present is that it is one of the few published studies, as far as we know, that tries to identify risk factors related to the performance of a colonoscopy in a population screening program with FIT. Furthermore, the study has been carried out in the context of real-world practice. This increases the interest for the figures provided and the importance of the countermeasures, in order to improve the quality and minimization of the risks of the program itself.

CRC population-based screening program analyses have been centered on the assessment of major outcomes and costs of required colonoscopies without paying much attention to the risks associated with the procedures themselves and related costs. This study reflects the risk associated with colonoscopies within the framework of a well-established program with a high participation rate and real-world conditions. The outcomes observed provide insight as to how to minimize the adverse event rates of colonoscopies and how to increase the efficiency of existing programs while ensuring that the goals of morbi-mortality are reached.

Declaration of conflicting interests

None declared.

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Ethics approval

This study was approved by the Basque Country's Ethics Committee (no. PI2014171; November 4, 2014). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institutions' human research committee.

Informed consent

All participants provided written informed consent.

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Cost-effectiveness and budget impact analyses of a colorectal cancer screening programme in a high adenoma prevalence scenario using MISCAN-Colon microsimulation model

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Abstract

Background: The Basque Colorectal Cancer Screening Programme began in 2009 and the implementation has been complete since 2013. Faecal immunological testing was used for screening in individuals between 50 and 69 years old. Colorectal Cancer in Basque country is characterized by unusual epidemiological features given that Colorectal Cancer incidence is similar to other European countries while adenoma prevalence is higher. The object of our study was to economically evaluate the programme via cost-effectiveness and budget impact analyses with microsimulation models.

Methods: We applied the Microsimulation Screening Analysis (MISCAN)-Colon model to predict trends in Colorectal Cancer incidence and mortality and to quantify the short- and long-term effects and costs of the Basque Colorectal Cancer Screening Programme. The model was calibrated to the Basque demographics in 2008 and age-specific Colorectal Cancer incidence data in the Basque Cancer Registry from 2005 to 2008 before the screening begun. The model was also calibrated to the high adenoma prevalence observed for the Basque population in a previously published study. The multi-cohort approach used in the model included all the cohorts in the programme during 30 years of implementation, with lifetime follow-up. Unit costs were obtained from the Basque Health Service and both cost-effectiveness analysis and budget impact analysis were carried out.

Results: The goodness-of-fit of the model adaptation to observed programme data was evidence of validation. In the cost-effectiveness analysis, the savings from treatment were larger than the added costs due to screening. Thus, the Basque programme was dominant compared to no screening, as life expectancy increased by 29.3 days per person. The savings in the budget analysis appeared 10 years after the complete implementation of the programme. The average annual budget was €73.4 million from year 2023 onwards.

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Conclusions: This economic evaluation showed a screening intervention with a major health gain that also produced net savings when a long follow-up was used to capture the late economic benefit. The number of colonoscopies required was high but remain within the capacity of the Basque Health Service. So far in Europe, no other population Colorectal Cancer screening programme has been evaluated by budget impact analysis.

Keywords: Colorectal Cancer, Mass screening, Cost-effectiveness analysis, Budget impact analysis

Background

The cost effectiveness of colorectal cancer (CRC) screening has been widely documented [1–4]. However, specific evaluations for different programmes are necessary because local CRC epidemiology (cancer incidence and adenoma prevalence) and the actual implementation of screening (type of test, attendance rate, and surveillance schedule) can cause variations in efficiency [4–6]. CRC in Basque country is characterized by unusual epidemiological features given that CRC incidence is similar to other European countries while adenoma prevalence is higher [7]. Therefore the need for independent evaluation is especially noteworthy. As with all public health interventions, cancer screening programmes must measure their value, i.e., the health outcomes achieved per euro spent for the whole population [8, 9].

The Basque CRC Screening Programme began in 2009 at the suggestion of the Cancer Advisory Council, which took into account the significant increase of both CRC incidence and mortality in the Basque Country from 1986 through 2008 [10–12]. Like most European programmes, it uses faecal immunochemical testing (FIT) to detect microscopic bleeding from adenomas or preclinical CRC [10, 13]. Individuals with positive test results are referred for a diagnostic colonoscopy and can then be assigned to a surveillance schedule [13]. As more cohorts are included in the programme, the number of colonoscopies grows, and programme feasibility relies on its capacity to respond to that demand [3, 5, 14]. The Basque CRC epidemiology of high adenomas prevalence may constitute a challenge because it may mean that the number of colonoscopies required in the CRC screening programme will be higher. Experts have underscored the need to tailor the implementation of CRC screening in populations within the context of organized programmes [6, 15].

During the first four years of implementation, the Basque programme performed 295,934 screening tests, and 17,146 diagnostic colonoscopies were carried out to confirm positive FIT results. Such marked resource consumption alone justifies conducting an economic assessment that takes into account the results in the middle and long term [5, 9]. Besides the cost effectiveness, for a comprehensive economic evaluation, it is essential analysing the programme's affordability regarding the global budget impact [16]. This analysis addresses the expected changes in the expenditure of a healthcare system after the adoption of a new intervention [16]. As with other CRC screening programmes, sustainability analysis must also tackle the demand for colonoscopies to avoid future inability to meet the need [2–6, 15]. To carry out the economic evaluation of cancer screening programmes, widespread use of decision models has been the rule generally, [2–6] as well as in the Basque Country [17, 18].

Because the implementation of the Basque CRC programme has been complete since 2013, decision-makers should now be informed as to whether the resources are appropriately allocated and the programme is sustainable given the high prevalence of adenomas. The object of our study was to economically evaluate the programme compared to no screening via cost-effectiveness and budget impact analyses with microsimulation models calibrated to the Basque epidemiological features of CRC incidence and adenoma prevalence [11, 19, 20].

Methods

As the programme targeted the population between 50 and 69 years of age and used biennial FIT screening and complete colonoscopy to confirm positive results, its evaluation required follow-up of the target population at middle and long term. To estimate the economic results of the screening strategy implemented in the Basque Country, the Microsimulation Screening Analysis model for colorectal cancer (MISCAN-Colon) was applied. MISCAN-Colon is a stochastic microsimulation model for colorectal cancer (CRC) developed using Delphi programming language (Borland Software Corporation, Scotts Valley, California, United States). The aim of the model was to explain and predict CRC incidence and mortality trends, as well as, assessing the effect of primary prevention of CRC, screening for CRC, and surveillance after polypectomy in terms of both health and costs. The structure of the MISCAN-Colon model and the sources that inform the parameters of the model have been fully described in previous publications, [21–25] as well as in a standardised model profile of the Cancer Intervention and Screening Network (CISNET) [26]. A full description of the model was also included in the Model Appendix section of the Additional file 1.

Individuals of a large population were simulated using MISCAN-Colon. They were created at birth and lifelong follow-up was applied. Natural history of CRC was included according to the adenoma–carcinoma sequence [27, 28]. The model assumes the possibility for more than one adenoma at the same time in each individual. Each adenoma can independently progress in size (≤5 mm, 6–9 mm, ≥10 mm) and develop into CRC. In addition, some will become malignant, transforming to stage I CRC; some cases of CRC may even progress to more advanced stages. At any stage, CRC may be diagnosed due to the development of symptoms. When CRC finally develops, the survival rate after diagnosis depends on the stage at which the cancer was detected. In addition, at any time during the individual's life, the process may be interrupted by his/her death from other causes. With this model, the entire target population can be followed from birth to death to measure both the long-term costs and health outcomes related to the programme.

Simulated population

We reproduced the entire Basque population in 2008: 2,230,000 people, 51% women. The screening programme begun in 2009 was fully implemented by 2013. In order to reproduce the implementation strategy, the population was divided into different strata based on its age structure and the calendar year at which individuals were invited into the programme for the first time (or never invited in the event that they were 70 or older in 2009). In the model the continuation of the screening programme was set to 30 years (2009–2038). In this way the model enabled the evaluation of the screening as a public health intervention by estimating both lifetime costs and health benefits. Table 1 shows the data and sources used in the model. This study was approved by the Basque Country's Ethics Committee.

As the MISCAN-Colon model was developed within the CISNET group, [26] it was first calibrated to CRC epidemiology and demographics of the United States population. Therefore, to use it for the Basque population, the age-specific CRC incidence by location (colon and rectum) and stage distribution were calibrated to the incidence data from the Basque Cancer Registry for the years 2005–2008, prior to the implementation of the CRC screening programme. Simultaneously, the MISCAN-Colon model was calibrated to the adenoma detection rates calculated for the Basque population from the COLONPREV study [20]. Separate models were built for men and women due to epidemiological differences in the natural history of CRC.

Screening scenario simulated

Screening was simulated according to the design of the Basque colorectal cancer screening programme.

Table 1 Sources of parameters used in the adaptation of the MISCAN-Colon model to the Basque population and screening programme

Data	Source
Demographics 2008	EUROSTAT – Basque Institute of Statistics
CRC incidence 2005–2008	Basque Cancer registry
Adenomas prevalence Base case	COLONPREV study [19]
Adenomas prevalence Low Prevalence case	[28, 29]
Costs screening	Basque CRC screening programme
Costs colonoscopy	Basque Health Service accounting system
Costs treatment	Basque Health Service accounting system
Utilities	[30]
Invitations 2009–2013	Basque CRC screening programme
Participation 2009–2012	Basque CRC screening programme
Test features 2011–2012	Basque CRC screening programme

EUROSTAT Statistical Office of the European Union, *CRC* colorectal cancer

All individuals within the programme's age range biennially received an invitation letter that included a FIT. Delivering a sample to the assigned primary care health centre was necessary to have it analysed for microscopic bleeding. The cut-off was established at 20 μg/g faeces. Those participants with a positive test result were referred for colonoscopy. Furthermore, patients with at least one adenoma > 20 mm or five or more adenomas were recalled within a year for a surveillance colonoscopy and those with one adenoma > 10 mm or more than three adenomas or any adenomas with a villous component or high degree of dysplasia were invited for surveillance colonoscopy in three years, and all individuals with adenomas < 10 mm or 1 to 2 adenomas or tubular component or low degree of dysplasia were invited for regular FIT screening in 5 years. All recommendations were based on the European surveillance guidelines [13] adapted to the size-dependent classification in the model. A description of the surveillance protocol appears in the Additional file 2: Table S1. Participation rates both for FIT and colonoscopy were estimated for initial and successive invitations, depending on the individual's age as determined by available data from the Basque CRC Screening Programme in the period 2009–2012 (Table 1).

Test characteristics

Test characteristics were fitted to the positivity and detection rates of advanced neoplasia observed in the Basque programme between 2011 and 2012 (Additional file 2: Table S2). Advanced neoplasia included CRC and advanced adenomas, which were defined as adenomas ≥10 mm in size, with a 25% or greater villous component and/or high-

grade dysplasia. The screening module was tested by reproducing invitations, participation and test results.

After the natural history of CRC without detection by screening was reproduced, the behaviour of CRC was reproduced according to the screening scenario, in which the impact of removing adenomas and anticipation of the CRC stage at diagnosis were considered. Those consequences were translated in quality-adjusted life years (QALY) gained and avoided costs in treatment.

Costs and utilities

We applied the perspective of the Basque Health Service, which is responsible for delivering screening to the entire Basque population between 50 and 69 years old. Unit costs were obtained in Euros (Sep 2012: 1 Euro = 1.25 US dollars) from the accounting systems in the service. The resources assigned to each screened person were disaggregated by invitation (€6.06 including invitation letter, FIT and programme management resources), FIT analysis in participants (€0.99), primary care consultation in case of positive results (€78.00) and colonoscopies (€461.30 with polypectomy and €281.30 without polypectomy). We also applied an average cost of €5157.00 for complications related to colonoscopy. To calculate the costs of CRC treatment, we retrospectively collected stage and resource use from a sample of 529 patients [29]. For stages I to III the initial and follow-up costs were measured. The calculation of cost for stage IV disease combined generalized linear models to relate the cost to the duration of follow-up on the basis of parametric survival analysis. Unit costs were obtained from the analytical accounting system of the Basque Health Service. The sample included 110 cases in stage I, 171 in stage II, 158 in stage III and 90 in stage IV. The initial total cost ranged from €6968 for stage I to €12,765 for stage II and €13,075 for stage III. The estimation of the annual cost for follow-up care included computed tomography, colonoscopy, tests and external consultations, and an amount of €404 was rendered. For those patients in stage IV specific initial treatment cost was not considered, however, the cost for each year of follow-up was €24,255. The details of the generalized linear model are reported in the Additional file 2: Table S3.

As specific preference values for the different stages of CRC were not available for the Basque or Spanish population, we incorporated utilities that were already in the MISCAN-Colon model (Additional file 2: Table S4) [29]. We assumed a utility loss (i.e., a loss of QALY) equivalent to two full days of life per colonoscopy (0.0055 QALY) and two weeks of life per complication (0.0384 QALY). We also assigned a utility loss to each life-year with CRC care (Additional file 2: Table S4) [30].

Economic evaluation

The economic evaluations included both the cost-effectiveness analysis and the budget impact analysis (BIA) of the programme from the perspective of the Basque Health System. The evaluation period was defined as 2009 through December 31, 2038. The incremental cost-effectiveness ratio (ICER) incorporated the additional QALY gained in the denominator and the additional costs incurred by the programme in the numerator [9]. We applied a multi-cohort approach by including all the cohorts in the programme during 30 years of implementation from its beginning in 2009. After this period, from 2039 onwards, the programme did not include more cohorts, but maintained the intervention for all individuals already included in the screening programme. The entire population had lifetime follow-up in order to capture the long-term impact. Costs and QALYs were discounted by 3%.

The microsimulation model was used simultaneously for BIA. The annual costs for CRC diagnosis and treatment in both the screened and unscreened populations from 2009 to 2038 were calculated in the model [16, 18]. Diagnostic resources included screening tests (FIT and diagnostic and surveillance colonoscopies) and clinical colonoscopies implemented in the reference hospital. It was not necessary to discount the costs because the BIA showed financial streams over time without aggregation [16].

Sensitivity analysis

To assess the impact of model assumptions in our results, three main sensitivity analyses were carried out: 1) A scenario including a lower prevalence of adenomas based on the literature [31–40] was run in addition to the base case model; 2) Because individuals with a false negative test result have a higher than average probability of another false negative test result at a successive screening, we also developed a new scenario in which dependency of FIT results in sequential screening rounds was assumed (Additional file 2: Table S2) [41]; 3) The impact of increasing the cost of screening was also estimated.

Results

Goodness-of-fit

Goodness-of-fit obtained in the MISCAN-Colon model adaptation for adenoma prevalence by age and gender, respectively, is shown in Fig. 1a and b and Model Appendix contain further validation details such as CRC incidence fitting. The model showed good concordance with the number of diagnostic colonoscopies observed in the Basque programme from 2009 to 2014 (Fig. 2a and b), validating the base scenario of high adenoma prevalence. Only in 2013 observed participation and positivity rates exceeded those simulated and the number of diagnostic colonoscopies carried out in the programme was also higher than forecasted. In 2014

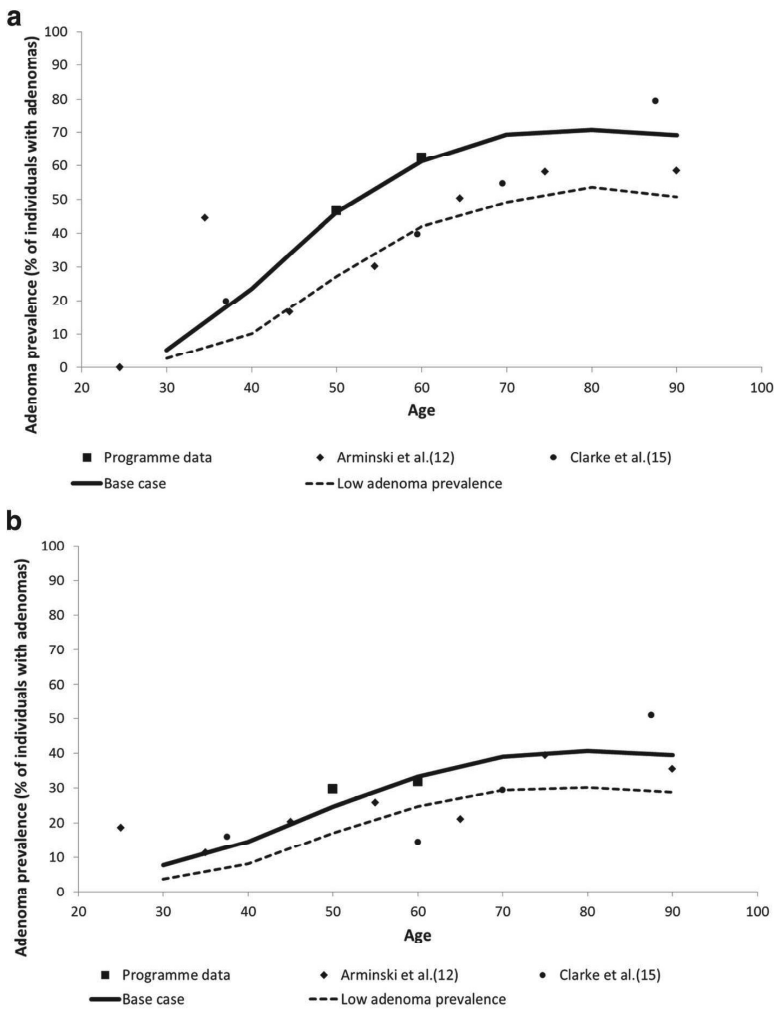

Fig. 1 Adenomas Prevalence Observed in COLONPREV study and other published studies Versus Simulated by MISCAN-Colon (% of individuals with adenomas)*. **a**) Men; **b**) Women. *Observed results are only shown for the two largest studies on which the model has been calibrated. MISCAN-Colon has additionally been calibrated to 8 other autopsy studies

the fit was better. Some other internal validation results, such as invitations and adherence to the programme and FIT characteristics in the period 2009–2014 were also used to validate model fitting and prediction behaviour (Additional file 2: Figure. S1 and Additional file 2: Figure S2). All these comparisons pointed to the good fit achieved in the adaptation of the MISCAN-Colon model to the Basque population and screening programme.

Cost-effectiveness analysis

Without screening, the target Basque population in 2008 was expected to live on average 41.1 years (Table 2). After the implementation of the screening programme, that life expectancy increased by 29.3 days per person. This gain in terms of life-years involved an incremental effectiveness of 56,664.8 QALY (with 3% discount) due to screening. The total cost for screening, diagnostic follow-up, surveillance and treatment, during the applied time horizon, was €2057.2 million (Table 2). However, because screening resulted in a substantial reduction of colorectal cancer incidence, there was a large reduction in the costs of treating CRC (256.3 m€) and a net saving of €93.1 million (Table 2) compared to that in the unscreened population. Overall, these savings from treatment were larger

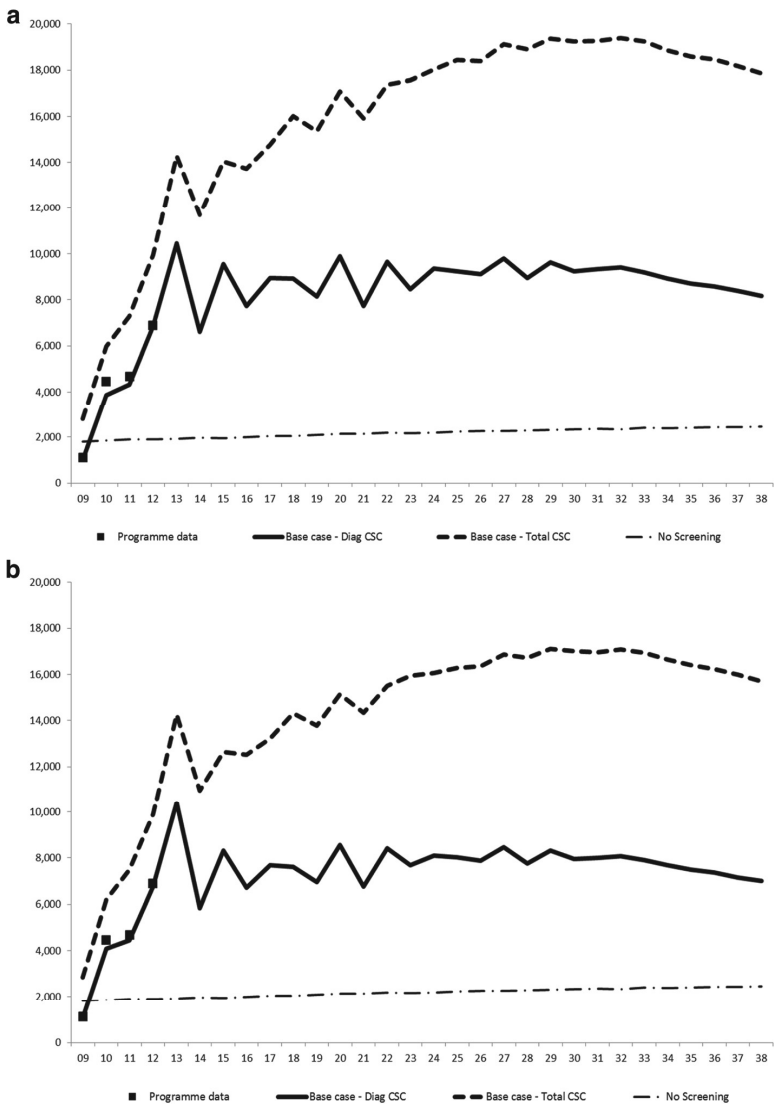

Fig. 2 Predicted number of diagnostic and total colonoscopies needed each year in base-case scenario. **a**) Independent successive screening tests; **b**) Correlated successive screening tests. Diag: diagnostic; CSC: colonoscopies

than the costs for screening, and thus, the Basque screening programme was dominant compared to no screening.

Budget impact analysis

Total and incremental costs related to screening, diagnosis and treatment of CRC in both scenarios (screened and unscreened) are displayed by year in Fig. 3. High screening costs due to the high number of positive test results for prevalent adenomas and cases of CRC were involved in the first four years after the introduction of screening until 2013, when 100% implementation was achieved. During the first five years of implementation, €69.2 million were necessary on average to annually fund the screening (Fig. 3 and Additional file 2: Table S5). The savings in the BIA appear in 2023, 10 years after the complete implementation of the programme. Even though the savings from screening were small at first, they increased as the impact of the programme became apparent. Figure 3

Table 2 Sensitivity analysis for cost-effectiveness analysis of the implementation of colorectal cancer screening programme in the Basque population

		Screened population costs		Incremental costs		QALYs gained	ICER
Cost per invitation	Adenoma prevalence	Treatment cost	Total costs	Treatment cost	Total costs		
€6.06 per invitation	Base case						
	Men	1199.9	1317.0	−179.1	−81.7	37,132.5	Dominant
	Women	664.2	740.2	−77.1	−11.4	19,532.3	Dominant
	Total	1864.1	2057.2	−256.3	−93.1	56,664.8	Dominant
	Prevalence Bibliography						
	Men	1227.5	1318.9	−168.6	−97.2	36,616.9	Dominant
	Women	661.0	726.9	−77.6	−21.8	20,438.5	Dominant
	Total	1888.5	2045.7	− 246.2	−119.0	57,055.4	Dominant
€15.00 per invitation	Base case - Total	1864.1	2103.2	−256.3	−47.1	56,664.8	Dominant
€20.00 per invitation	Base case - Total	1864.1	2128.9	−256.3	−21.4	56,664.8	Dominant
€25.00 per invitation	Base case - Total	1864.1	2154.6	−256.3	4.2	56,664.8	74.1
€30.00 per invitation	Base case - Total	1864.1	2180.3	−256.3	30.0	56,664.8	529.4
€40.00 per invitation	Base case - Total	1864.1	2231.8	−256.3	81.5	56,664.8	1438.3
€50.00 per invitation	Base case - Total	1864.1	2283.2	−256.3	132.9	56,664.8	2345.4

ICER incremental cost effectiveness ratio

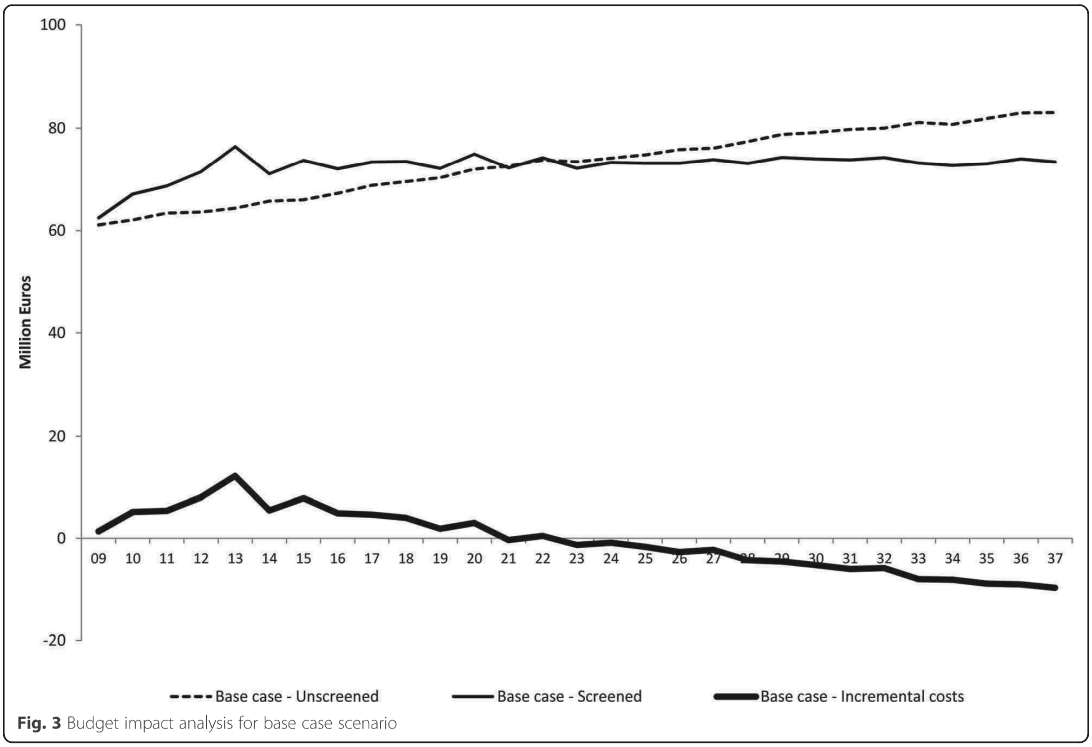

Fig. 3 Budget impact analysis for base case scenario

shows that the increase in the annual budget for the ageing unscreened population disappeared when screening was applied, and thus a stable annual budget of €73.4 million was achieved on average from year 2023 onwards.

In addition, the model predicted the number of colonoscopies during a 30-year period (Fig. 2), which reached a maximum in 2032 with 19,384. On average, the estimated annual number of colonoscopies (including diagnostic, surveillance and clinical colonoscopies) needed in the base case from 2029 through 2038 was 18,843 (52.5% surveillance colonoscopies).

Sensitivity analysis

When a scenario with lower adenoma prevalence was set, the number of colonoscopies declined to 14,167 (Additional file 1: Figure. S3) and the net cost savings amounted to €119 million in the study period (Additional file 1: Figure. S4). Similarly, when the possibility of systematic false negative test results was included in the model, it was determined that fewer colonoscopies (16,605) than estimated for the base case were necessary and involved a savings of €95.1 million compared to the no-screening scenario. Finally, when unit costs for screening invitations were increased, the model showed that the screening programme would remain cost-saving if the cost of an invitation remained ≤20€ per invitation (€21.4 million saved) (Table 2).

Discussion

This cost-effectiveness analysis featured the Basque CRC screening programme as a dominant intervention because it produced net cost savings and health benefits [9]. Budget analysis also showed a consistent savings after 10 years of its complete implementation, highlighting the affordability of the programme [16]. Both approaches to economic evaluation reveal that only a long follow-up is able to capture the late economic benefit of the screening based on the decrease in the number of cases of CRC in early and advanced stages and the consequent reduction in need for treatment. So far in Europe, no other population-based CRC screening programme has been evaluated with a comprehensive approach including both cost-effectiveness and budget impact analysis to prove the programme's efficiency and affordability. Obviously, our results support the continuity of this preventive policy for CRC. Two literature reviews confirmed this finding, emphasising that colorectal cancer screening is cost effective or dominant compared with no screening [42, 43].

Public health programmes must be reappraised periodically to confirm that they have achieved planned results [44]. Modelling can also be useful in other countries to inform the population programme planning. Our sensitivity analysis showed the impact of the actual adenoma prevalence on the need of colonoscopies. A realistic estimation for the number of colonoscopies needed could be made based on the early report produced by the COLONPREV study [20].

Different strategies for CRC screening are supported by the evidence. As the Basque programme is based on FIT, our assessment cannot avoid comparison with an alternative approach based on colonoscopy as the first test, which is the norm in the United States. To make that comparison, however, the number of colonoscopies required for effective screening must be considered. Any evaluation must assess if a health system has the capacity to absorb such increased demand for screening colonoscopies. Typically, when the demand exceeds the capacity to deliver, the implementation of the programme is obstructed. Moreover, the required number of colonoscopies is directly related to the prevalence of adenomas in the specific population [14, 19]. In our study, this indicator was especially noteworthy because the adenoma prevalence in the Basque sample of the COLONPREV study yielded a higher number than that used in the MISCAN-Colon model [20]. The consequence of this finding could jeopardize the sustainability of the programme. The higher prevalence showed that 4200 more colonoscopies annually were necessary on average than were needed in the scenario based on a low prevalence. Both numbers were lower in the scenario in which dependency of FIT results in sequential screening rounds was assumed, that is, taking into account that individuals with a false negative test result have a higher than average probability of another false negative test result at a successive screening [41]. These predicted figures highlight the sustainability of the programme in operational terms, because the number of necessary diagnostic colonoscopies stabilized at approximately 8000, which was the number already being delivered. However, the maximum capacity of the Basque Health System to carry out screening colonoscopies has been reached. Thus, any other proposal for CRC screening that led to more colonoscopies would not be feasible with the currently available resources. As colonoscopies delivery become usually a bottleneck in the process of implementing CRC screening.

To explain the long-term cost savings, we need to underline that although the screening programme and the derived colonoscopies meant a significant expense, more than 90% of the total expenditure originated with treatment costs. To reach this conclusion, future results had to be predicted. So, although the number of required colonoscopies rose with increasing prevalence of adenomas, the impact on the total cost was limited [20, 31]. The total costs in the unscreened scenario grew steadily during the analysed years because the number of CRC cases in the Basque population rose with the aging of the baby boomers. The main component of those costs was the treatment costs that were proportional to the incidence.

It is noteworthy that screening impact meant stabilization in total costs because the raw incidence was maintained and, therefore, the CRC age-adjusted rates decreased.

Decision-making on the basis of models is not without limitations. Although we used a model of high quality (MISCAN-Colon), which was adjusted to the epidemiology of the Basque population and the characteristics of the programme, model calibration was meant to force some parameters such as the classification of adenomas. The programme information system categories are risk-based, whereas the MISCAN-Colon model sorts them by size. The problem was resolved by reclassifying the adenomas found in the programme according to size. We understand that this adjustment did not involve any threat to the validity of the results, given the exhaustive process of calibration and validation. In addition, only costs related to the screening programme and CRC treatment were considered in the analysis; thus, we did not take into account the of cost of care of unrelated diseases that could appear due to increasing survival time. Including these costs could increase the final ICER and reduced the efficiency of the screening. Finally, the model did not include a probabilistic sensitivity analysis that is the norm in pharmacoeconomics, because of the difficulty of the computational burden in public health studies in which required dynamic models can include millions of individuals. However, the thorough calibration algorithm in MISCAN-Colon and the comprehensive internal and external validation warrant its robustness and, therefore, the reliability of the results.

Some of the differing results achieved in cost-effectiveness studies have been attributed to the dissimilarities in structure and parameters of the models applied to follow the entire life of the target population. The natural history of CRC as represented by the MISCAN-Colon model is shared by other CISNET partners, and its consistency has been fully proven [45, 46]. Moreover, the calibration of the MISCAN-Colon model to fit the epidemiology of CRC and adenoma prevalence in the Basque country was achieved by internal and external validation. As Patel et al. pointed out, preclinical time, screening unit costs in each setting or screening adherence, none of which is the same in all studies, can explain heterogeneous results [43]. Good intermediate indicators of programme performance, such as participation rate (64.3% in 2009–2011) and waiting time for colonoscopy (30 days), also show that the programme is on track and help to explain the final economic saving [10, 47]. Significantly, that conclusion was also valid when the unit cost of screening was doubled.

It is also important to put into context the relative costs of the screening programme, as they represented between 6% and 8% of the total cost, when we aggregated the costs of the whole follow-up. Furthermore, that percentage range will probably decrease, as treatment costs tend to grow as a consequence of the introduction of new drugs much more expensive than those currently on the market [48]. As oncology drugs become less cost effective because of rising prices over time [48], the role of preventive policies is enhanced. Thus, our results support the idea that reinforcement of screening seems a plausible future option. Consideration of inequalities in access to health care also sustains investments in screening, rather than treatment. Although differences by social class have been found in the screening programme, it is easier to provide disadvantaged groups with better access to screening services than to provide the entire population with the latest oncological drugs [49].

The BIA approach to economic evaluation is used less often than the cost-effectiveness design, but it is a complementary and useful tool to show financial streams over time. Usually the trade-offs between incurred and saved costs are shown with a short time horizon, but the BIA easily allows the application of a long follow-up to capture the full economic and health benefit of the screening programme. This is consistent with the natural history of CRC and has been underscored in the literature [5]. An extended period of time is required for the impact of polypectomies on avoided deaths and cancer treatments to manifest, and thus, the first years of the programme can be misleading because the change in natural history of CRC has not reached a steady state in terms of the population [47].

Conclusions

We would like to emphasise that this evaluation reaffirms for decision-makers that the allocated resources for maintaining the programme are a worthwhile investment. This economic evaluation showed a screening intervention with a major health gain that also produced net savings when a long follow-up was used to capture the late economic benefit. Our results support the continuity of the Basque Colorectal Cancer Screnning Programme. Due to the actual adenoma prevalence reported in the COLONPREV study a realistic estimation of the future need of colonoscopies was necessary. The number of colonoscopies required was high but remain within the capacity of the Basque Health Service. So far in Europe, no other population Colorectal Cancer screening programme has been evaluated by budget impact analysis. Budget impact analysis highlighted the affordability of the programme showing consistent savings after 10 years of complete implementation.

Additional files

Additional file 1: Model Appendix. Detailed description of the MISCAN-Colon model and the adaptation procedure. (PDF 2242 kb)

Additional file 2: Table S1. European guidelines for surveillance schedule after colonoscopy adapted to the size-dependent classification

used in the model. **Table S2.** Test characteristics by sex fitted to the positivity and detection rates of advanced neoplasia observed in the Basque programme between 2011 and 2012. **Table S3.** Generalized liner model applied to estimate annual follow-up cost in patients with metastatic colorectal cancer. **Table S4.** Disutility values used in the model for colonoscopy, its complications and four cancer states depending on cancer detection stage. **Table S5.** Budget impact analysis of the colorectal cancer programme in million euros. **Figure S1.** Number of invited and participant population: Observed data in the Basque Screening Programme Versus Simulated by MISCAN-Colon. **Figure S2.** Number of detected adenomas and cases of cancer: Observed data in the Basque Screening Programme Versus Simulated by MISCAN-Colon. **Figure S3.** Predicted number of diagnostic and total colonoscopies needed each year in base-case and low prevalence scenarios. **Figure S4.** Budget impact analysis for base case and lower adenoma prevalence scenarios. (PDF 1299 kb)

Abbreviations

BIA: Budget impact analysis; CISNET: Cancer Intervention and Screening Network; CRC: Colorectal Cancer; FIT: Faecal Immunochemical Testing; ICER: Incremental cost-effectiveness ratio; MISCAN: Microsimulation Screening Analysis; QALY: Quality adjusted life years

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Availability of data and materials

The anonymized administrative datasets used and analysed during the current study are available from the corresponding author on reasonable request. Due to the Spanish Royal Decree 1720/2007, 21st December, regulation of the Organic Law 15/1999 for Personal Data Protection the datasets are not publicly available.

Authors' contributions

Study concept and design: AA, II, JM, IP, ILV; Acquisition of data: II, IP, EAA, ILV; Model adaptation: AA, HdK, MvdM, ILV; Model validation: AA, II, JM, HdK, MvdM, IP, ILV; Cost analysis: JM, MSG, JMML, OI; Statistical analysis and interpretation of the results: AA, II, JM, MSG, IP, EAA, OI, ILV; Drafting of manuscript: AA, JM, IP, ILV; All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Basque Country's Ethics Committee (Reference number PI2014171) according to the principles expressed in the Declaration of Helsinki on 4th November 2014. Researchers affiliated to the Colorectal Cancer Screening Programme in the Basque Country obtained the correspondent administrative permission to work with anonymized institutional data in this project. Informed consent was not applicable for the use of anonymized population data required for the MISCAN model, complying with the Spanish Royal Decree 1720/2007, 21st December, regulation of the Organic Law 15/1999 for Personal Data Protection.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE Open Access

Population-based colorectal cancer screening programmes using a faecal immunochemical test: should faecal haemoglobin cut-offs differ by age and sex?

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Abstract

Background: The Basque Colorectal Cancer Screening Programme has both high participation rate and high compliance rate of colonoscopy after a positive faecal occult blood test (FIT). Although, colorectal cancer (CRC) screening with biannual (FIT) has shown to reduce CRC mortality, the ultimate effectiveness of the screening programmes depends on the accuracy of FIT and post-FIT colonoscopy, and thus, harms related to false results might not be underestimated. Current CRC screening programmes use a single faecal haemoglobin concentration (f-Hb) cut-off for colonoscopy referral for both sexes and all ages. We aimed to determine optimum f-Hb cut-offs by sex and age without compromising neoplasia detection and interval cancer proportion.

Methods: Prospective cohort study using a single-sample faecal immunochemical test (FIT) on 444,582 invited average-risk subjects aged 50–69 years. A result was considered positive at ≥20 μg Hb/g faeces. Outcome measures were analysed by sex and age for a wide range of f-Hb cut-offs.

Results: We analysed 17,387 positive participants in the programme who underwent colonoscopy. Participation rate was 66.5%. Men had a positivity rate for f-Hb of 8.3% and women 4.8% ($p < 0.0001$). The detection rate for advanced neoplasia (cancer plus advanced adenoma) was 44.0‰ for men and 15.9‰ for women ($p < 0.0001$). The number of colonoscopies required decreased in both sexes and all age groups through increasing the f-Hb cut-off. However, the loss in CRC detection increased by up to 28.1% in men and 22.9% in women. CRC missed were generally at early stages (Stage I-II: from 70.2% in men to 66.3% in women).

Conclusions: This study provides detailed outcomes in men and women of different ages at a range of f-Hb cut-offs. We found differences in positivity rates, neoplasia detection rate, number needed to screen, and interval cancers in men and women and in younger and older groups. However, there are factors other than sex and age to consider when consideration is given to setting the f-Hb cut-off.

Keywords: Adenoma, Colorectal cancer, Faecal immunochemical test, Faecal occult blood test, Interval cancers, Screening

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Background

Colorectal cancer (CRC) screening using tests for the presence of blood in faeces, commonly known as faecal occult blood tests (FOBT), has been shown to be an effective intervention for reducing CRC-related mortality in controlled studies conducted both in Europe [1–3] and in the USA [4]. The mortality reduction varied between 14 and 18%, with colonoscopy being used as the second stage investigation in those with a positive faecal test result. Thus, screening reduces the burden of CRC, which is the most common cancer in industrialized countries and has a high mortality rate of approximately 25.4 expected deaths per 100,000 in the overall population. The standardized incidence-based mortality ratio is 0.47 (95% confidence interval [CI]: 0.26–0.80) with colonoscopic polypectomy, suggesting a 53% reduction in mortality [5, 6].

FOBT has been widely implemented for CRC screening and, in 2003, the European Union (EU) published an official recommendation for its members to carry out FOBT screening for the average-risk population aged between 50 and 74 years [7]. In this regard, faecal testing has improved markedly since the aforementioned studies were carried out, with the original guaiac test (gFOBT) being superseded by faecal immunochemical tests for haemoglobin (FIT), which are potentially much better at detecting advanced adenomas (AA) and CRC and are also much better accepted by potential participants because of ease of use and the lack of a need for special dietary requirements [8, 9]. The EU guidelines recommend use of FIT in population-based programmes [10, 11] and, indeed, an impact on cancer incidence has been found in recent studies [12, 13], although further investigation is needed to assess the longer-term impact. A recent meta-analysis shows an average sensitivity of 79% and a specificity of 94% of FIT for CRC in asymptomatic subjects [14].

Current main concerns are centered on quality-assurance practices and the possible negative consequences of such programmes. Quality assurance throughout the screening process is based on criteria and indicators recommended by the European guidelines [10], whereas the negative effects concern the main side effects of CRC programmes, in particular, colonoscopy-related complications and false-negative and false-positive results. In the case of false positive results, three studies found differences between the sexes [15, 16] and noted that this situation was unsatisfactory, especially for women [17].

Some models have been designed to include faecal haemoglobin concentration (f-Hb) as a predictor for colorectal neoplasia and have suggested that adjustments must be made to take into account sex, family history or morbidities when implementing programmes [18], In this regard, the Scottish Bowel Screening Programme evaluation using FIT showed important differences in the results for men and women, with a greater participation with FIT than with gFOBT, a higher positivity rate in men than women in all groups, and a higher detection rate in men for AN and CRC. In contrast, the number of false-positive results was lower in men (49.1% versus 58.9% in women) for colonoscopies performed [19]. A similar pattern was reported by the Basque Country for lesions detected in the period 2009–2011 [20].

Adjusted incidence rates for CRC in the Basque Country have increased significantly, by 2.3% per year in men (from 60.3 per 100,000 in 2000 to 87.6 in 2011) and by 6.5% per year in women (from 56.6 in 2007 to 71.8 in 2011). The age-standardized incidence rates for 2007 (prior to implementation of the Basque Country Colorectal Cancer Screening Programme) showed a high men-to-women ratio for different locations [21].

A recent review [22] concluded that the influence of sex on the comparative performance of tests for detecting advanced colorectal neoplasia (AN) has not been investigated with sufficient power in any of the diagnostic cohort studies conducted to date. In a prospective cross-sectional study, van Turenhout et al. [23] concluded that FIT has a higher sensitivity and lower specificity for CRC in men and that different f-Hb cut-offs should be used in screening programmes. These data are consistent with those published by Fraser et al. [24], who concluded that f-Hb distributions vary by sex and age, this supporting the view that setting and using a single f-Hb cut-off in any CRC screening programme is far from ideal. Alvarez-Urturi et al. [25] have recently conclude in the ColonPrev randomized controlled trial study that FIT cut-offs could be individualized by sex and age to improve the performance of FIT in CRC screening programmes. On the other hand Kapidzic et al. [26], in a prospective cohort of invited people from the Dutch population-based screening programme, do not recommend different f-Hb cut-offs in men and women based on the consideration that positive predictive values for the sexes should be the same. Establishing different f-Hb cut-offs between men and women and between age groups could influence the effectiveness of screening. Looking ahead to achieve consistent detection rates among regions, the cut-offs could differ. However any increase in the f-Hb cut-off selected to define positivity, while increasing sensitivity for AN, can increase the rate of false positives [27].

Colonoscopy demand increases with the use of FIT when used with the widely applied low f-Hb cut-offs since the expected number of positive test results is more than three times higher than that with gFOBT, posing an economic challenge for many regions as regards the implementation of population-based screening programmes, since additional investment and resources are needed to implement them, at least in the early screening rounds. As such, an exercise to estimate the clinical outcomes

including the number needed to screen (NNS) to detect one case, and the f-Hb cut-offs to be used are a difficult dilemma for epidemiologists and decision-makers. Using quantitative FIT, the f-Hb cut-off (s) to be used becomes a crucial decision since the positivity rate determines the number of colonoscopies required. In this regard, some f-Hb cut-offs have been suggested and simulated outcomes created to answer these questions [28–30].

The main question, however, is how to determine the best f-Hb cut-off (s) for a specific target population in order to detect the true positive results without increasing the number of interval cancers (ICs), a serious consideration in any screening programme [31, 32]. In this study, we aimed to answer these questions on the basis of a high participation rate population-based screening programme and determine whether strategies using f-Hb cut-offs stratified by sex and age group may be useful.

Methods

Study population and interventions

The Basque Country CRC Screening Programme is population-based and started in 2009 as a pilot and was extended in 2010 after evaluation and optimisation of the processes involved. The main strategy was based on: A) a Coordinating Office, including clinical epidemiologists and statisticians, to plan, organize and manage the programme; B) all residents from 50 to 69 years were invited, taking into account the Health Centers and referral Hospitals, in order to adjust the positivity expected and colonoscopy capacity; C) prior to the invitation, the Coordinating Office selected the target population and linked the database to the Basque Population Cancer and Medical Procedures Registries to exclude people with a previously diagnosed CRC, terminal illness and colonoscopy reported in the last 5 years; D) training and involvement of Basque Health Service Primary Care staff; E) individualized posted invitations providing information about the programme. After 4–6 weeks from the initial invitation, the kit was sent along with instructions and an individualized bar code. This code allows the sample and person to be identified when processing the result. Samples were collected at Primary Health Centers of the Basque Public Health Service and processed in centralized public laboratories under strict total quality management systems; F) automatically the software system introduces the result in the "ad hoc" CRC database and primary care physicians review all results of their patients (reader has to bear in mind that electronic clinical records are implemented in community care in the Basque Country). Letters were posted with the results: a) if negative, the invitation will be repeated in 2 years' time if the person is younger than 70 years, or b) if positive, participants are recommended to visit their General Practitioner, who will indicate the need for a colonoscopy and c) in case of error, another kit and instructions were sent; G) colonoscopies are performed in referral public hospitals under sedation by expert specialists; H) all cases are followed-up with close coordination between Primary Care and Specialized Units; J) every case is coded by the Coordinating Office staff following standard EU guidelines and Spanish Network consensus recommendations [10, 33]. This study was approved by the Basque Country's Ethics Committee (Reference: PI2014059). All participants provide written informed consent.

Detection of ICs: prior to a subsequent invitation, all negative cases from a previous round are linked to the register of hospital discharges with ICD-9 1530–1548, in primary and secondary diagnosis, ICDO-10 C18-C21 of hospital registers and population-based Cancer registries as well as codes of Pathology. In all coinciding cases, the qualified staff from the Programme's Coordinating Centre checked the clinical history, including the cases as ICs which complied with the criteria of having a negative FIT result in the previous invitation (0–24 mo or more in case of a delay in the invitation to the screening programme). To ensure against any possible losses, this process was repeated on an annual basis.

Definitions

The FIT used from early 2009 and in early 2010 (during the pilot study) were OC-Sensor Micro (Eiken Chemical Co, Tokyo, Japan) and FOB-Gold (Sentinel CH. SpA, Milan, Italy), in both with a f-Hb cut-off of 20 μg Hb/g faeces. After comparison of the results obtained with both devices [34], OC-Sensor was selected and has been used since. OC-Sensor is a quantitative FIT, with chemistry based on human haemoglobin antibody mediated latex agglutination. Bar coded specimen collection devices were analysed for f-Hb. In the current analysis, the data are only related to this FIT. The result was considered positive when f-Hb was ≥20 μg Hb/g faeces.

The histology of all lesions detected was evaluated by expert pathologists specializing in gastrointestinal oncology according to the quality standards of the European guidelines [10]. The maximum reach of the endoscope, adequacy of bowel preparation, as well as the characteristics and location of any polyps were recorded. Adenomas ≥10 mm, adenoma with a villous component (i.e., tubulovillous or villous adenoma) or adenomas with severe/high-grade dysplasia were classified as AA [10].

AN was defined as CRC plus AA. Tumour staging was established according to the TNM classification system in agreement with the AJCC Cancer Staging Manual [35]. Finally, participants were classified and then assigned according to the most advanced lesion found.

Statistical analysis

CRC screening performance measures were assessed following the European guidelines [10]. Variables were calculated and described as percentages with 95% confidence intervals.

The number needed to screen (NNS) was calculated as the number of completed screening tests required to find one AN. All test characteristics were calculated separately for f-Hb cut-offs of 20, 25, 30, 35, 40, 50 and 60 μg Hb/g faeces, respectively.

Differences in the test characteristics between men and women and different age ranges were assessed using the chi-squared and/or Fisher's tests. Since the data on f-Hb did not follow a normal distribution, the Mann-Whitney U test was used to compare continuous variables between the groups. The normality of the distribution of continuous variables was assessed using a normal Q-Q plot. A p-value of less than 0.05 was considered to be statistically significant using a two-sided test.

A logistic regression was performed to analyze the risk of loss in the detection of AN by sex and age stratified group.

The statistical analysis was conducted using SPSS version 23.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

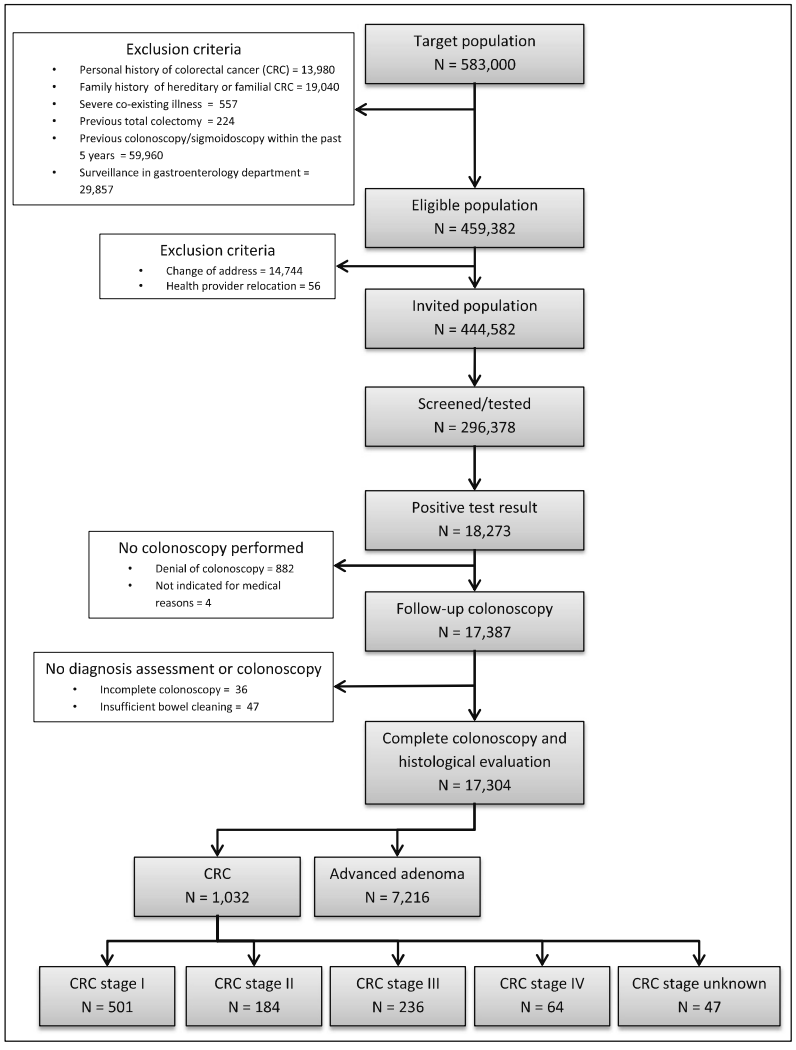

Fig. 1 Study flow diagram

Results

Between 2009 and 2012, 444,582 subjects were invited to the Basque Country CRC Screening Programme. The flow diagram is summarized in Fig. 1. The study population comprised 17,387 participants with a positive test result who underwent complete colonoscopy.

The overall participation was high (66.5%; 95% CI: 66.4–66.7), as was the colonoscopy compliance (95.1%; 95% CI: 94.8–95.5). The characteristics of the participants in the study population are summarized by sex and age group in Tables 1 and 2, respectively.

The proportion of false negative results was 7.6% (95% CI: 6.5–8.8). We identified 136 interval cancers (IC) and, in Table 3, the difference in characteristics of IC and screen-detected cancers (SD-C) are summarized divided into two groups, those cancers detected in participants attending for the first time (prevalent screening cancers) and those attending in subsequent rounds (incidence screening cancers).

Table 1 Characteristics of participants studied

	Men	Women
Participation; %	63.7	69.3
Colonoscopy compliance; %	95.0	94.2
Total number of participants[a]	10,982	7291
Colorectal cancer (CRC)	693	339
Age (years); mean (SD)	61.4 (5.1)	60.2 (5.6)
μg Hb/g faeces; median (IQR)	219.0 (74.2–694.5))	175.3 (63.8–440.8)
Location Location (proximal side/distal side/rectum)[b]; %	18.2/70.1/11.7	21.8/64.2/14.0
Stage (I-II/III-IV/missing); %	68.0/27.6/4.4	63.7/30.8/5.5
Size (cm); mean (SD)	2.7 (1.5)	2.8 (1.6)
Advanced adenomas (AA)[c]	5188	2028
Age (years); mean (SD)	60.1 (5.4)	59.8 (5.6)
μg Hb/g faeces; median (IQR)	79.2 (35.2–229.6)	71.6 (33.2–188.6)
Location Location (proximal side/distal side/rectum)[b]; %	20.1/67.4/12.5	20.1/63.7/16.2
Number polyps; median (IQR)	3.0 (2.0–5.0)	2.0 (1.0–4.0)
Higher size polyps (mm); median (IQR)	12.0 (9.0)	12.0 (8.0)
Size of AA >9 mm; %	65.1	65.1
Size of AA >19 mm; %	13.6	12.8
AA with villous component; %	36.2	36.3
AA with severe/high-grade dysplasia; %	8.6	8.7

SD Standard deviation, *IQR* Interquartile range
[a]Positives
[b]Right side includes regions up to and including the splenic flexure; left side includes descending colon and up to rectum
[c]Advanced adenomas: adenomas ≥10 mm, adenoma with a villous component (i.e., tubulovillous or villous adenoma) or adenomas with severe/high-grade dysplasia

Programme performance indicators and test characteristics

The positive predictive values (PPV) for AN, both for the study group and in each sex and age stratified groups of participants, are shown in Tables 4 and 5. Significant differences were observed at a f-Hb cut-off of 20 μg Hb/g faeces, and this patternwas maintained throughout the different f-Hb cut-offs analysed by sex. The PPV was significantly higher in men at all f-Hb cut-offs. There were also significant differences between age-specific groups in men and women, with the PPV being higher in the older population for both sexes.

The positivity rate for the range of f-Hb cut-offs assessed was also higher in men and the difference with women was also significant, with the positivity decreasing with increasing f-Hb cut-off. The positivity was lower for all age groups in both sexes as the f-Hb cut-off increased, being higher in older men and women, and with significant differences by sex (Tables 4 and 5).

The CRC detection rate (CDR) was higher in men than in women and in older subjects, with significant differences for all f-Hb cut-offs (Tables 4 and 5). In men, the CDR decreased from 5.2‰ (95% CI: 4.8–5.6) to 4.1‰ (95% CI: 3.8–4.4) and in women from 2.2‰ (95% CI: 2.0–2.4) to 1.7‰ (95% CI: 1.5–1.9). The advanced neoplasia detection rate (ANDR) was also higher in men at a f-Hb cut-off of 20 μg Hb/g faeces (44.0‰ [95% CI: 42.9–45.1]), with a significant difference with respect to women, for whom the ANDR was lower (15.9‰ [95% CI: 15.2–16.5]). This significant difference was also maintained at different f-Hb cut-offs. The ANDR was higher in older groups in both sexes, with significant differences by sex for all f-Hb cut-offs (Tables 4 and 5). In any case, the ANDR in men over 60 years remained higher than that of women.

Colonoscopy savings and the risk of losses in the detection of advanced colorectal Neoplasia

A lower NNS to detect one AN (59; 95% CI: 56–63) was seen in men at a f-Hb cut-off 20 μg Hb/g faeces compared to 92 (95% CI: 83–100) for women. On increasing the f-Hb cut-off, NNS increased to 230 for women at a f-Hb cut-off of 60 μg Hb/g faeces. The differences between men and women were significant at f-Hb cut-offs of 20 and 25 μg Hb/g faeces but not at higher cut-offs (30 and 35 μg Hb/g faeces), as shown in Fig. 2a.

A logistic regression analysis was performed to determine the risk of loss in the detection of AN by increasing the f-Hb cut-off (Fig. 2b). The risk is higher in men than in women and this risk increases significantly upon increasing the f-Hb cut-off from 1.49 (95% CI: 1.30–1.71) to 1.69 (95% CI: 1.56–1.83).

The colonoscopy saved by increasing the f-Hb cut-off in the case of women increases to 55.5% (N = 4273). As such, the savings made in terms of colonoscopies are

Table 2 Characteristics of participants stratified by sex and age

	Men < 55 years	Men 55–60 years	Men 60–65 years	Men > 65 years	Women < 55 years	Women 55–60 years	Women 60–65 years	Women > 65 years
Participation; %	59.0	63.7	67.9	66.8	65.5	70.6	72.1	69.0
Colonoscopy compliance; %	93.7	94.0	94.8	97.4	94.2	94.8	94.1	93.8
Total number of participants[a]	2415	2671	3238	2658	1775	1707	2009	1800
Colorectal cancer (CRC)	84	155	216	238	72	82	87	98
μg Hb/g faeces; median (IQR)	179.4 (56.8–536.2)	230.8 (69.6–770.4)	209.8 (70.2–682.5)	231.2 (82.4–698.7)	191.8 (77.9–542.9)	172.8 (67.6–405.3)	158 (63.2–490.4)	172.8 (54.38–443.7)
Location (proximal side/distal side/rectum)[b]; %	19.8/69.7/10.5	18.3/64.7/17.0	17.4/79.5/3.1	17.3/66.4/16.3	20.8/65.4/13.8	22.6/66.7/10.7	20.9/64.3/15.1	23.2/60.6/16.2
Stage (I-II/III-IV/missing); %	75.0/20.2/4.8	66.9/27.3/5.8	63.7/34.0/2.3	70.0/27.0/3.0	69.0/22.7/8.3	54.9/41.5/3.6	60.5/33.7/5.8	71.4/22.4/6.2
Size (cm); Mean (SD)	2.5 ± 1.6	2.5 ± 1.6	2.7 ± 1.4	2.9 ± 1.5	2.9 ± 1.5	3.0 ± 1.6	2.6 ± 1.8	2.9 ± 1.7
Advanced adenomas (AA)[c]	976	1250	1614	1348	461	498	553	516
μg Hb/g faeces; median (IQR)	78.8 (34.8–223.0)	78.8 (34.8–221.9)	84.4 (35.4–248.4)	75.8 (35.6–221.8)	71.8 (33.4–183.4)	70.2 (34.2–190.2)	71.2 (30.0–186.2)	75.6 (35.7–193.3)
Location (proximal side/distal side/rectum)[b]; %	19.4/66.2/14.4	24.3/65.1/10.6	17.3/69.4/13.3	19.3/68.9/11.8	23.5/57.8/18.7	18.4/66.5/15.1	19.1/69.2/11.7	19.5/61.2/19.3
Number polyps; median (IQR)	3.0 (1–0-4.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Higher size polyps (mm); median (IQR)	13.4 (7.5)	13.7 (7.9)	14.2 (8.5)	13.8 (10.4)	12.0 (9.7)	13.4 (8.6)	13.4 (8.4)	12.9 (7.2)
Size of AA >9 mm; %	62.4	65.2	65.3	66.4	63.4	64.2	65.2	66.1
Size of AA >19 mm; %	9.8	10.4	12.3	13.9	10.4	11.9	12.7	14.1
AA with villous component; %	35.4	36.2	35.4	37.0	34.2	36.3	35.2	36.8
AA with severe/high-grade dysplasia; %	8.0	7.8	8.5	9.0	7.4	7.8	8.2	8.9

SD Standard deviation, *IQR* Interquartile range
[a]Positives
[b]Proximal side includes regions from cecum up to and including the transverse colon; distal side includes splenic flexure, descending colon and sigmoid colon
[c]Advanced adenomas: adenomas ≥10 mm, adenoma with a villous component (i.e., tubulovillous or villous adenoma) or adenomas with severe/high-grade dysplasia

Table 3 Characteristics of interval cancers and screen-detected colorectal cancer

Total	Interval cancers[a]	Screen-detected		*p*-value
		First round	Second round	
	136 (83.3%; 1st round/ 16.2%; 2nd round)	889	143	-
Sex				
Men; n (%)	89 (65.4)	594 (66.8)	99 (69.2)	0.79
Women; n (%)	47 (34.6)	295 (33.2)	44 (30.8)	
Age (years)				
50–54; n (%)	26 (19.1)	137 (15.4)	19 (13.3)	0.06
55–59; n (%)	32 (23.5)	195 (21.9)	42 (29.4)	
60–64; n (%)	45 (33.1)	260 (29.2)	43 (30.1)	
65–69; n (%)	33 (24.3)	297 (33.4)	39 (27.3)	
μg Hb/g faeces; median (IQR)	2.9 (0.4–11.6)[b]	201.8 (74.4–589.8)[c]	638.3 (56.8–617.2)[c]	-
Location (proximal side/distal side/rectum)[c]; %	34.3 / 33.6 / 32.1	18.1 / 67.0 / 14.9	21.6 / 66.3 / 12.1	<0.001
Stage (I-II/III-IV); %	44.8 / 55.2	66.7 / 28.4	65.7 / 24.6	<0.001
Size (cm); median (IQR)	8 (6.0–12.0)	2.5 (1.5–4.0)	2.5 (1.5–3.5)	<0.001
Time to diagnosis				
Within 1 year; n (%)	64 (47.1)			-
1–2 years; n (%)	72 (52.9)			

[a]Interval cancers after a negative test result in the previous round
[b]Median μg Hb/g faeces at time of negative screening test result. **Median μ Hb/g faeces at time of positive screening test result
[c]Proximal side includes regions from cecum up to and including the transverse colon; distal side includes splenic flexure, descending colon and sigmoid colon

offset by the loss in detection of CRC and AA (Fig. 3). The loss of AA in women can be as high as 43.3% (N = 962), and 22.9% for CRC (N = 81). Around 19.1% of the colonoscopies saved upon increasing the f-Hb cut-off to 25 μg Hb/g faeces will have an AN, and this percentage rises to 24.4% on increasing the f-Hb cut-off to 60 μg Hb/g faeces It can also be seen that the CRC missed were diagnosed mostly at an early stage (Stage I-II: from 70.2% in men to 66.3% in women).

Colonoscopy savings increased in all age groups on increasing the f-Hb cut-off in both sexes. However, as can be seen from Fig. 4, there is no substantial difference in this saving by age group (from 48.6 to 51.9% in men and 54.3 to 57.0% in women). However, an analysis of the decrease in CRDR and ANDR showed a considerable difference between age groups in both sexes. Thus, in men, the AADR decreased by 24.1 and 10.9‰, in the oldest group and in the youngest groups respectively, whereas in women it decreased by 9.0‰ in the oldest group and by 4.9‰ in the youngest. A similar pattern was observed in CDR and, depending on the age group analysed, the diagnoses of early-stage CRC not detected could be as high as 86.4% in men and 80.0% in women.

Discussion

We have compared CRC screening with FIT at different f-Hb cut-offs in a large population aged between 50 and 69 years. To our knowledge, there have been few previous studies of sex and age related differences in population-based FIT screening programs.

In our study, a total of 444,582 persons were invited to participate in the Basque Country CRC Screening Programme. This large number of participants facilitated the performance of a reliable and robust statistical analysis to determine whether a simple, single f-Hb cut-off should be used for different populations without increasing the interval cancer rate, thus allowing the provision of insight for others running similar programmes.

CRC screening programmers in a number of countries have encountered higher than expected positivity [36], thus leading to overwhelming demand for scarce colonoscopy resources and a need to increase the f-Hb cut-off to lower the number of referrals. In consequence, data on the performance of FIT in men and women are of key importance due to the current widespread and growing use of FIT in population-based CRC screening programmes.

We observed a higher PPV for AN and higher detection rates for CRC and AN than other programmes, these results could be due to the high rate of compliance to colonoscopy assessment, that allowed a minimal loss of neoplasm detection As reported in recently published studies [26, 37], higher positivity was found in men at the full range of f-Hb cut-offs. This pattern is also

Table 4 Test characteristics at different faecal haemoglobin concentration cut-offs by sex

	Positive predictive value[a] (%)			Positivity rate (%)			Colorectal cancer detection rate (‰)			Advanced neoplasia detection rate (‰)		
Cut-off μg Hb/g faeces	Men	Women	*p* value	Men	Women	*p* value	Men	Women	*p* value	Men	Women	*p* value
20	52.8 (51.9–53.7)	32.9 (31.9–34.0)	< 0.0001	8.3 (8.1–8.4)	4.8 (4.7–4.9)	< 0.0001	5.2 (4.8–5.6)	2.2 (2.0–2.4)	< 0.0001	44.0 (42.9–45.1)	15.9 (15.2–16.5)	< 0.0001
25	56.0 (55.0–57.0)	36.5 (35.2–37.7)	< 0.0001	6.9 (6.8–7.1)	3.8 (3.7–3.9)	< 0.0001	4.9 (4.5–5.3)	2.1 (1.9–2.3)	< 0.0001	39.0 (38.0–40.1)	13.9 (13.3–14.5)	< 0.0001
30	57.4 (56.3–58.4)	38.3 (37.0–39.6)	< 0.0001	6.2 (6.1–6.4)	3.3 (3.2–3.4)	< 0.0001	4.7 (4.3–5.1)	2.0 (1.8–2.2)	< 0.0001	36.0 (35.0–37.0)	12.8 (12.3–13.4)	< 0.0001
35	58.6 (57.5–59.7)	39.2 (37.8–40.5)	< 0.0001	5.7 (5.6–5.8)	3.0 (2.9–3.1)	< 0.0001	4.6 (4.3–5.0)	1.9 (1.7–2.2)	< 0.0001	33.8 (32.8–34.7)	11.9 (11.3–12.4)	< 0.0001
40	59.8 (58.7–61.0)	40.6 (39.1–42.0)	< 0.0001	5.3 (5.2–5.4)	2.7 (2.6–2.8)	< 0.0001	4.5 (4.1–4.8)	1.9 (1.6–2.1)	< 0.0001	31.9 (31.0–32.8)	11.2 (10.7–11.7)	< 0.0001
50	61.5 (60.3–62.6)	42.2 (40.6–43.7)	< 0.0001	4.6 (4.5–4.7)	2.4 (2.3–2.5)	< 0.0001	4.3 (3.9–4.6)	1.7 (1.5–2.0)	< 0.0001	28.7 (27.8–29.6)	10.2 (9.7–10.7)	< 0.0001
60	62.7 (61.5–64.0)	43.3 (41.7–45.0)	< 0.0001	4.2 (4.1–4.3)	2.1 (2.0–2.2)	< 0.0001	4.1 (3.8–4.4)	1.7 (1.5–1.9)	< 0.0001	26.5 (25.7–27.4)	9.3 (8.8–9.8)	< 0.0001

[a]PPV applies for AN: defined as advanced adenoma (AA) plus colorectal cancer (CRC). Advanced adenomas: adenomas ≥10 mm, ≥3 adenoma, adenoma with a villous component (i.e., tubulovillous or villous adenoma) or adenomas with severe/high-grade dysplasia

Table 5 Test characteristics at different faecal haemoglobin concentration by sex and age group

	Positive predictive value[a] [%(95% CI)]											
Cut-off μg Hb/g faeces	Women <55 years	Men <55 years	*p* value	Women 55–60 years	Men 55–60 years	*p* value	Women 60–65 years	Men 60–65 years	*p* value	Women >65 years	Men >65 years	*p* value
20	30.6 (28.5–32.7)	44.0 (42.0–45.9)	< 0.0001	34.2 (32.0–36.4)	51.9 (50.1–53.8)	< 0.0001	32.0 (30.0–34.0)	56.4 (54.7–58.0)	< 0.0001	35.2 (33.0–37.3)	57.4 (55.6–59.2)	< 0.0001
25	34.5 (32.1–36.9)	47.7 (45.5–49.9)	< 0.0001	38.2 (35.6–40.7)	55.2 (50.1–53.8)	< 0.0001	34.6 (32.3–36.9)	59.5 (57.7–61.3)	< 0.0001	38.9 (36.5–41.4)	60.2 (58.2–62.1)	< 0.0001
30	35.7 (33.1–38.3)	49.1 (46.8–51.4)	< 0.0001	40.8 (38.1–43.6)	55.2 (53.1–57.2)	< 0.0001	36.3 (33.8–38.8)	60.4 (58.5–62.3)	< 0.0001	40.2 (37.6–42.8)	61.7 (59.6–63.7)	< 0.0001
35	36.4 (33.7–39.1)	49.9 (47.5–52.2)	< 0.0001	41.6 (38.8–44.5)	56.4 (54.3–58.5)	< 0.0001	37.8 (35.1–40.4)	52.8 (50.8–54.8)	< 0.0001	41.3 (38.5–44.0)	63.3 (61.2–65.4)	< 0.0001
40	38.0 (35.1–40.9)	50.9 (48.4–53.4)	< 0.0001	42.9 (39.8–45.9)	58.0 (55.8–60.2)	< 0.0001	38.8 (36.1–41.6)	62.7 (60.7–64.7)	< 0.0001	42.8 (40.0–45.7)	64.3 (62.1–66.5)	< 0.0001
50	39.9 (36.8–43.0)	52.5 (49.9–55.2)	< 0.0001	43.6 (40.4–46.8)	60.9 (58.5–63.4)	< 0.0001	42.0 (39.0–45.0)	64.2 (62.1–66.3)	< 0.0001	44.4 (41.3–47.5)	66.0 (63.7–68.3)	< 0.0001
60	40.8 (37.5–44.2)	54.2 (51.4–57.0)	< 0.0001	45.1 (41.7–48.6)	62.3 (59.8–64.9)	< 0.0001	42.3 (39.1–45.5)	65.6 (63.4–67.8)	< 0.0001	45.4 (42.1–48.7)	67.3 (64.9–69.7)	< 0.0001
Positivity rate [%(95% CI)]												
20	3.9 (3.8–4.1)	6.1 (5.9–6.3)	< 0.0001	4.4 (4.2–4.6)	7.9 (7.7–8.2)	< 0.0001	5.3 (5.1–5.5)	9.5 (9.2–9.8)	< 0.0001	6.2 (6.0–6.5)	10.7 (10.3–11.0)	< 0.0001
25	3.1 (3.0–3.3)	5.0 (4.8–5.2)	< 0.0001	3.4 (3.3–3.6)	6.6 (6.4–6.9)	< 0.0001	4.1 (4.0–4.3)	8.1 (7.8–8.3)	< 0.0001	5.0 (4.8–5.3)	9.0 (8.7–9.4)	< 0.0001
30	2.8 (2.6–2.9)	4.5 (4.3–4.7)	< 0.0001	3.0 (2.8–3.2)	6.0 (5.7–6.2)	< 0.0001	3.6 (3.0–3.4)	7.3 (7.0–7.5)	< 0.0001	4.5 (4.3–4.7)	8.1 (7.8–8.5)	< 0.0001
35	2.5 (2.4–2.6)	4.1 (3.9–4.3)	< 0.0001	2.7 (2.6–2.9)	5.4 (5.2–5.7)	< 0.0001	3.2 (3.0–3.4)	6.7 (6.5–7.0)	< 0.0001	4.1 (3.8–4.3)	7.5 (7.2–7.8)	< 0.0001
40	2.3 (2.1–2.4)	3.7 (3.6–3.9)	< 0.0001	2.5 (2.3–2.6)	5.0 (4.8–5.3)	< 0.0001	2.9 (2.8–3.1)	6.2 (6.0–6.5)	< 0.0001	3.7 (3.5–4.0)	6.9 (6.6–7.2)	< 0.0001
50	2.0 (1.9–2.1)	3.3 (3.1–3.4)	< 0.0001	2.2 (2.1–2.4)	4.4 (4.2–4.6)	< 0.0001	2.5 (2.4–2.7)	5.5 (5.2–5.7)	< 0.0001	3.3 (3.1–3.5)	6.1 (5.8–6.4)	< 0.0001
60	1.8 (1.6–1.9)	2.9 (2.8–3.1)	< 0.0001	2.0 (1.8–2.1)	3.9 (3.7–4.1)	< 0.0001	2.3 (2.1–2.4)	5.0 (4.8–5.2)	< 0.0001	2.8 (2.7–3.0)	5.5 (5.2–5.8)	< 0.0001
Colorectal Cancer (CRC) Detection Rate [‰ (95% CI)]												
20	1.6 (1.2–2.0)	2.2 (1.7–2.6)	0.053	2.1 (1.7–2.6)	4.5 (3.8–5.2)	< 0.0001	2.3 (1.8–2.7)	6.4 (5.6–7.3)	< 0.0001	3.5 (2.8–4.1)	9.3 (8.1–10.4)	< 0.0001
25	1.5 (1.2–1.9)	2.0 (1.6–2.4)	0.107	2.0 (1.6–2.4)	4.3 (3.6–5.0)	< 0.0001	2.1 (1.7–2.6)	6.1 (5.3–6.9)	< 0.0001	3.2 (2.6–3.9)	8.7 (7.6–9.8)	< 0.0001
30	1.5 (1.1–1.8)	1.9 (1.5–2.3)	0.127	2.0 (1.5–2.4)	4.1 (3.4–4.8)	< 0.0001	2.1 (1.6–2.5)	5.9 (5.1–6.7)	< 0.0001	3.0 (2.4–3.6)	8.4 (7.3–9.5)	< 0.0001
35	1.5 (1.1–1.8)	1.9 (1.5–2.3)	0.127	1.9 (1.5–2.3)	4.0 (3.3–4.7)	< 0.0001	2.0 (1.6–2.5)	5.8 (5.0–6.6)	< 0.0001	2.9 (2.3–3.5)	8.3 (7.2–9.4)	< 0.0001
40	1.4 (1.1–1.8)	1.8 (1.5–2.3)	0.150	1.8 (1.4–2.2)	3.9 (3.3–4.6)	< 0.0001	2.0 (1.5–2.4)	5.5 (4.8–6.3)	< 0.0001	2.8 (2.2–3.4)	8.0 (7.0–9.1)	< 0.0001
50	1.4 (1.0–1.7)	1.7 (1.3–2.1)	0.241	1.7 (1.3–2.1)	3.7 (3.1–4.4)	< 0.0001	1.8 (1.4–2.2)	5.3 (4.5–6.0)	< 0.0001	2.6 (2.0–3.2)	7.8 (6.8–8.9)	< 0.0001
60	1.3 (1.0–1.6)	1.6 (1.2–1.9)	0.328	1.7 (1.3–2.0)	3.6 (3.0–4.2)	< 0.0001	1.7 (1.3–2.1)	5.0 (4.3–5.8)	< 0.0001	2.5 (2.0–3.1)	7.6 (6.5–8.6)	< 0.0001
Advanced Neoplasia (AN) Detection Rate [‰ (95% CI)]												
20	12.1 (11.1–13.0)	26.9 (15.3–28.5)	< 0.0001	15.0 (13.8–16.2)	41.3 (39.2–43.4)	< 0.0001	16.9 (15.6–18.2)	53.6 (51.2–55.9)	< 0.0001	21.9 (20.3–23.6)	61.2 (58.3–64.1)	< 0.0001
25	10.8 (9.9–11.8)	23.9 (22.5–25.4)	< 0.0001	13.1 (12.0–14.2)	36.5 (34.6–38.5)	< 0.0001	14.4 (13.2–15.5)	47.9 (45.7–50.2)	< 0.0001	19.6 (18.0–21.2)	54.2 (51.5–56.9)	< 0.0001
30	9.9 (9.0–10.7)	21.9 (20.5–23.3)	< 0.0001	12.3 (11.2–13.3)	33.6 (31.7–35.4)	< 0.0001	13.0 (11.9–14.1)	44.0 (41.9–46.1)	< 0.0001	18.0 (16.5–19.5)	50.1 (47.5–52.8)	< 0.0001
35	9.1 (8.2–9.9)	20.3 (19.0–21.7)	< 0.0001	11.4 (10.4–12.4)	31.5 (29.6–33.3)	< 0.0001	12.1 (11.1–13.2)	35.6 (33.7–37.5)	< 0.0001	16.8 (15.4–18.2)	47.6 (45.0–50.1)	< 0.0001
40	8.6 (7.8–9.4)	19.1 (17.8–20.4)	< 0.0001	10.7 (9.7–11.7)	30.0 (28.2–31.8)	< 0.0001	11.4 (10.4–12.4)	39.0 (37.0–47.1)	< 0.0001	16.0 (14.6–17.5)	44.6 (42.1–47.1)	< 0.0001
50	7.9 (7.1–8.7)	17.2 (15.9–18.4)	< 0.0001	9.7 (8.8–10.7)	26.7 (25.1–28.4)	< 0.0001	10.7 (9.7–11.7)	35.2 (33.3–37.1)	< 0.0001	14.5 (13.1–15.8)	40.4 (38.1–42.8)	< 0.0001
60	7.2 (6.5–8.0)	16.0 (14.8–17.2)	< 0.0001	8.9 (8.0–9.8)	24.5 (22.9–26.1)	< 0.0001	9.7 (8.7–10.7)	32.8 (30.9–34.7)	< 0.0001	12.9 (11.7–14.2)	37.1 (34.9–39.4)	< 0.0001

[a]PPV applies for AN: defined as advanced adenoma (AA) plus colorectal cancer (CRC). Advanced adenomas: adenomas ≥10 mm, ≥3 adenoma, adenoma with a villous component (i.e., tubulovillous or villous adenoma) or adenomas with severe/high-grade dysplasia

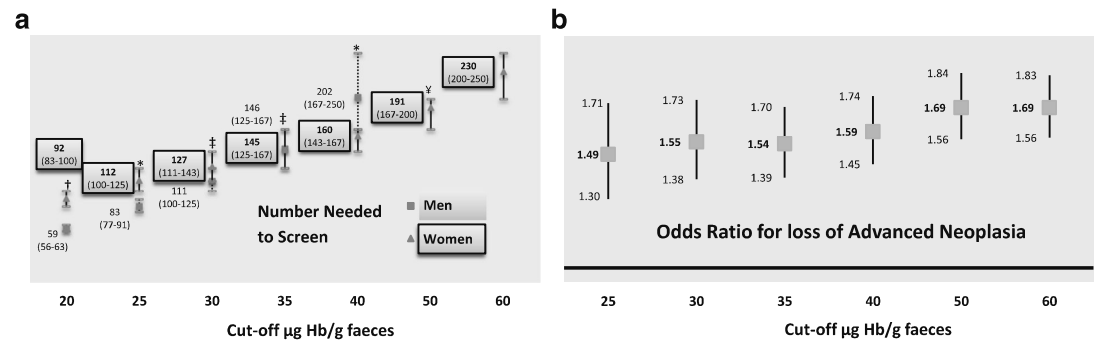

Fig. 2 Number Needed to Screen to detect Advanced Neoplasia (AN) (**a**) and the Odds Ratio for the loss in detection of AN (**b**) Men versus women through increasing the faecal haemoglobin cut-off. (*$p < 0.001$; †$p < 0.05$; ‡no significance). (¥Cut-off 50 µg Hb/g faeces in men = 509 [95% CI: 333–1000])

consistent when comparing older men and women against younger ones, with these variables being higher in older groups. A decision on whether to adjust the age at which screening begins also requires taking into consideration whether the recommended age for men should be younger or the recommended age for women older. In this regard, Sung et al. [38], in the Asia Pacific consensus recommendations for CRC screening, suggested that women may start screening at later ages due to the relatively low incidence of CRC at 50–55 years. Similarly, Brenner suggested that the optimal age for screening initiation should be five years younger for men than for women. Despite this, European guidelines recommend that screening programs for CRC should start at age 50 years for both men and women of average risk [10]. However, the question of using different f-Hb cut-offs for men and women and/or younger and older participants remains unsolved. Differences in the epidemiological pattern of CRC among sexes have been identified during the last years [39]. Hence, it is a matter of discussion if the screening must be implemented on the basis of same sex, age and f-Hb cut-off.

Recent studies [22, 27] have concluded that FIT has a higher sensitivity and a lower specificity for CRC in men than in women and therefore that equal test characteristics can be achieved by allowing different f-Hb cut-offs for the sexes. However, Kapidzic et al. [26], observed that there were no significant differences between men

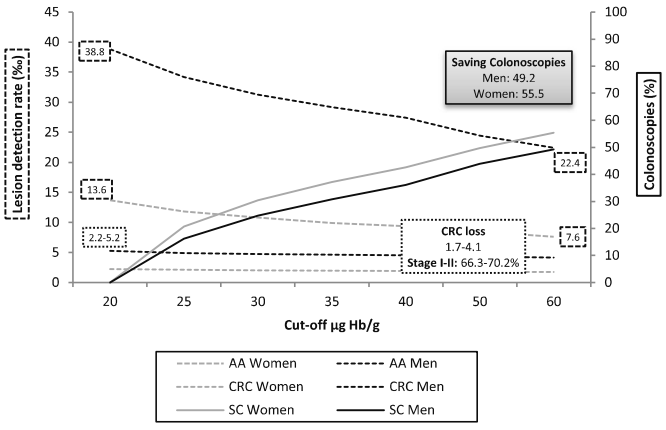

Fig. 3 Relation between saving colonoscopies (SC) and lesion loss upon increasing the faecal haemoglobin concentration cut-off by sex. Dotted lines represent lesion detection rates (for colorectal cancer (CRC) and advanced adenoma (AA)) and solid lines saved colonoscopies. The left Y axis represents lesion detection rate and the right Y axis the percentage of colonoscopies saved. Saving Colonoscopies: the percentage of colonoscopies that will not be performed in the programme by increasing the f-Hb cut-off, due to the reduction of positivity rate

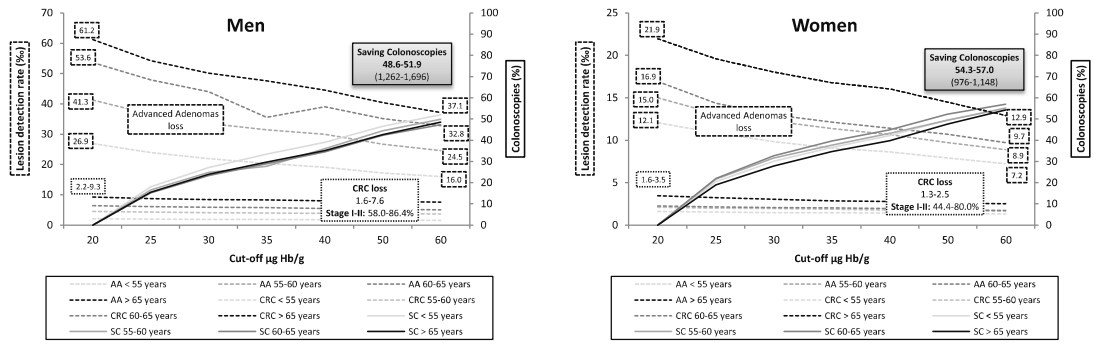

Fig. 4 Relation between saving colonoscopies (SC) and lesion losses upon increasing the cut-off level of the FIT by sex and age group. Dotted lines express lesion detection rates (colorectal cancer (CRC) and advanced adenoma (AA)) and solid lines saved colonoscopies. The left Y-axis represents lesion detection rate and the right axis the percentage of colonoscopies saved. Saving Colonoscopies: the percentage of colonoscopies that will not be performed in the programme by increasing the f-Hb cut-off, due to the reduction of positive rate

and women in PPV at a f-Hb cut-off of 10 μg Hb/g faeces, thus meaning that the chance that a colonoscopy is unnecessary after a positive test result is the same. It was suggested that, if the same differences were to persist between men and women in a larger sample, the differences in PPV would become significant, and this is exactly what we have observed in our study, in which the differences between men and women have remained statistically significant. However, can we therefore argue that it would be better to increase the f-Hb cut-off for women? According to the results of Kapidzic et al. [26], the PPV could be improved using a higher f-Hb cut-off in women; however, this would be at the expense of increasing the NNS as this increases at higher f-Hb cut-offs.

It may take approximately 10 years from the appearance of the first lesion with abnormal histopathology to develop a possible malignant lesion. In 2007, Brenner et al. [39] showed that the risk of transition from AA to CRC was similar for men and women, but increased with age. Some studies [40, 41] have reported significantly higher detection rates for AN and CRC with colonoscopy for men than for women in all age groups, thus suggesting that male sex constitutes an independent risk factor for colorectal neoplasia. Such studies recommended sex-specific ages for screening. These differences are similar to those observed in our study.

Colonoscopy resource can be key to defining the strategies and characteristics adopted in screening programmes. Indeed, the additional number of colonoscopies that need to be performed may become an important factor when deciding whether to establish any such programme. We observed that the saving in colonoscopies increased consistently in both sexes and in all age groups as the f-Hb cut-off was increased. It might seem appropriate to increase the f-Hb cut-off since this would a lower the number of colonoscopies required. However, when increasing the f-Hb cut-off, the risk of lowering the ANDR increases significantly in both sexes and in all age groups. The proportion of IC could be higher in men than in women and in older groups. Thus, an increase in the f-Hb cut-off could increase the loss from 7.9 to 28.1% in men and from 5.1 to 22.9% CRC in women. This loss in the detection of CRC is consistent over all age groups. Moreover, taking into account that most of those with CRC would be diagnosed in their early stages, this would go against the principles of preventive screening programmes. These results are consistent with those published recently by Digby et al. [42], who concluded that CRC screening programmes would benefit from using low f-Hb cut-off to gain lower IC proportions as well as higher sensitivity and detection of earlier stage disease, but at the cost of increased demand for colonoscopy.

Recent studies suggested the potential benefits of using a risk prediction model including f-Hb in CRC screening [18, 29, 31, 43] to improve the effectiveness of screening strategies. Future studies performed should therefore be designed to evaluate the benefits of implementing models according to the different risks of different groups according to sex and age. Some studies have suggested that other factors could be used to determine the optimal cut-off values for men and women, and that the combination of these data with microsimulation models could improve the implementation of screening programmes [28, 44].

One of the main strengths of the current study was the large number of participants evaluated, all of whom were recruited in an organized, population-based screening programme, coordinated and systematically evaluated at a single centre. The lack of studies published to date with real data from such a FIT-based programme and with a participation rate of more than

65% (the level recommended in the European guidelines [10]) is also worth noting.

However, several limitations have to be acknowledged. The study included assessment of the effects of sex and age but no other possible confounding factors, such as socio-economic status which has been shown to affect f-Hb [36, 45], though they could be retrospectively explored on the basis of a case/control nested analysis. Furthermore, Brenner [38] suggested that appropriate differentiation of age at initiation of CRC screening by sex might be equally or more relevant from a public health point of view than the widely used differentiation by family history.

Conclusions

In conclusion, this population-based study provides relevant information on the performance of a realistic FIT-based colorectal screening programme in men and women at different f-Hb cut-offs. Men have higher PPV, CDR and ANDR, which results in a lower NNS when compared to women, and this pattern is consistent when comparing younger and older groups. However, given the assessed loss in detection of AN and CRC, most of them in their early stages, it may be that the f-Hb cut-off that is going to be implemented should not be change only by sex or age, at least initially, in accordance with the recommendations of the European guidelines, in order not to increase the ratio of interval cancers, which is another important variable to examine.

Abbreviations

AA: Advanced adenoma; AN: Advanced colorectal neoplasia; ANDR: Advanced neoplasia detection rate; CDR: Cancer detection rate; CRC: Colorectal cancer; f-Hb: Faecal haemoglobin concentration; FIT: Faecal immunochemical test; FOBT: Faecal occult blood test; Hb: Haemoglobin; IC: Interval cancers; NNS: Number needed to screen to detect one case; PPV: Positive predictive value; SD-C: Screen-detected cancers

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Availability for data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

EAA, BU, RP, II, IPV and IIR conceived the idea for this analysis. The data used for this analysis stem from a study that was designed and conducted by EAA and IGI collaborated on the data analysis. EAA, IGI and IPV drafted the manuscript. CGF critically reviewed the manuscript and gave important intellectual input. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Basque Country's Ethics Committee.

Consent for publication

Not applicable.

Competing interests

CGF has undertaken paid consultancy with Immunostics Inc. and Kyowa-Medex Co., Ltd., and received funding for attendance at meetings from Alpha Labs Ltd. Other authors have none to declare.

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RESEARCH ARTICLE Open Access

Evaluation of the colorectal cancer screening Programme in the Basque Country (Spain) and its effectiveness based on the Miscan-colon model

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Abstract: The population-based Basque Colorectal Cancer (CRC) Screening Programme started in 2009 with a biennial immunochemical quantitative test (FIT) biennial and colonoscopy under sedation in positive cases. The population target of 586,700 residents was from 50 to 69 years old and the total coverage was reached at the beginning of 2014. The aim of our study was to determine possible scenarios in terms of incidence, mortality and reduction of Life-years-Lost (L-y-L) in the medium and long term of CRC.

Methods: Invitations were sent out by the Programme from 2009 to 2014, with combined organizational strategies. Simulation was done by MISCAN-colon (Microsimulation Screening Analysis) over 30 years comparing the results of screening vs no-screening, taking the population-based Cancer Registry into account. Lifetime population and real data from the Programme were used from 2008 to 2012. The model was run differentially for men and women.

Results: 924,416 invitations were sent out from 2009 to 2014. The average participation rate was 68.4%, CRC detection rate was 3.4% and the Advanced Adenoma detection rate was 24.0‰, with differences observed in sex and age. Future scenarios showed a higher decrease of incidence (17.2% vs 14.7%), mortality (28.1% vs 22.4%) and L-y-L (22.6% vs 18.4%) in men than women in 2030.

Conclusions: The Basque Country CRC Programme results are aligned to its strategy and comparable to other programmes. MISCAN model was found to be a useful tool to predict the benefits of the programme in the future. The effectiveness of the Programme has not been formally established as case control studies are required to determine long term benefits from the screening strategy.

Keywords: Colorectal cancer, Early detection of cancer, Incidence, Mortality, Life year lost, Effectiveness, Programme evaluation

Background

Colorectal cancer (CRC) is the third leading cancer-related cause of death in developed countries. The European Union (EU) has the highest incident rate and ranks second in mortality of both sexs, with 446,000 newly-diagnosed cases each year and a mortality rate estimated in 214,000 cases annually [1].

In the Basque Country, one of the 17 autonomous regions of Spain, it is also the most frequent type of cancer. In 2008, 642 new cases and 286 deaths in women and 1227 new cases and 504 deaths in men were registered [2].

Different screening strategies have been proposed to reduce the CRC incidence and mortality, by means of different diagnostic tests. Previously, evidence of the reduction in mortality using the guaiac test (gFOBT) for population-based screening, showed a reduction in mortality of 10–16% [3–5].

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Although there are few studies demonstrating the impact on mortality of a CRC screening programme using immunochemical quantitative tests (FIT), several clinical trials show that these tests achieve a higher neoplasia detection rate and higher positive predictive values (PPV) than the gFOBT [6–8]. In fact, the European guidelines of screening for CRC (2010) [9] recommended these tests for population-based screening programmes.

A recent study published by Zorzi et al. [10] established that the screening programmes based on FIT were associated with a reduction of up to 22% in CRC mortality.

In accordance with the European recommendation (2003) [11] and the National Health System's strategy against cancer (NHS) [12, 13], in 2008 the Basque Government approved the implementation of a regional population-based screening programme for CRC. The programme was aimed at men and women between 50 and 69 years old, using one sample biennially of FIT and a colonoscopy under sedation as a diagnostic confirmation in positive cases. The programme started in 2009, reaching almost the whole target population (approximately 586,700 people) at the beginning of 2014. The main results found in the first period showed a high participation rate, as well as high adenoma and CRC detection rates [14, 15].

In order to measure the effectiveness of the Programme and its current strategy in comparison to no-screening, the MISCAN-colon tool [16], widely and internationally validated, was chosen.

The objectives of this study were to predict future scenarios and outcomes for the Basque population and to determine the epidemiological benefits of the screening programme in terms of incidence, mortality and years of life lost (L-y-L).

This kind of evaluation could be useful to those countries rolling out screening programmes in order to implement actions and guarantee their continuation.

Methods

The Basque Country CRC Screening Programme is population-based and its main strategy was based on: A) a coordinating office, including clinical epidemiologists and statisticians, to plan, organize, manage and evaluate the Programme; B) all residents from 50 to 69 years were invited biennially, taking into account the health centers and referral hospitals, in order to adjust the positivity expected and colonoscopy capacity; C) prior to the invitation, the coordinating office selected the target population and linked the database to the Basque population cancer and medical procedures registries to exclude individuals with a previously-diagnosed CRC, terminal illness and reported colonoscopy in the past five years; D) training and involvement of the primary care staff; E) individualized posted invitations providing information about the Programme. After 4–6 weeks from the initial invitation, the kit (FIT) was sent along with instructions and individualized bar code. This bar code allowed the sample and person to be identified when processing the result. Samples were collected at primary health centers and processed in centralized public laboratories under strict and total quality management systems; F) all results were reviewed by primary care physicians and introduced in "ad hoc" CRC prevention software. Letters were posted with results. In positive cases, participants were recommended to visit their general gractitioner, who referred them to the hospital for colonoscopy. G) Colonoscopies (diagnostic and therapeutic if needed) were performed in public hospitals under deep sedation by specialists. H) All cases were followed-up with close coordination between primary care and specialized units; I) every case was coded by the coordinating office staff following standard EU guidelines and Spanish network consensus [17]; J) interval cancer and complications were identified and monitored by registries linkage before invitation and after colonoscopy performance. The programme is identified in (Fig. 1).

This study was approved by the Basque Country's Ethics Committee.

The FIT used was OC-Sensor Micro (Eiken Chemical Co. Ltd., Toyo, Japan) (from 2009 until now) and FOB-Gold (Sentinel CH. SpA, Milan, Italy) 2009–2010 in 15,000 invitations). The faecal-Haemoglobin (f-Hb) cut-off was 20 μg Hb/g faeces for both sexs. The decision to use one single sample of FIT and the biennial period between invitations followed the recommendations of Levis and van Rossum [18, 19], in order to reach the highest participation rate with the best balance between sensitivity and specificity.

A satisfactory colonoscopy was considered if the caecum was reached and the quality of colonic cleansing was coded higher than 6 in all segments measured by the Boston Bowel Preparation Scale (BBPS). The American Association's classification was used for CRC and stages [20]. Accordingly, the results of the colonoscopy were coded and follow-up recommendations assigned to each one as: 1) Normal/No adenomatous pathology and will be invited to perform a screening test within 10 years; 2) Hyperplastic polyps and will be invited to perform a screening test within 10 years; 3) Low risk adenomas and will be invited to perform a test within 5 years 4) Intermediate risk adenomas and remain on colonoscopy surveillance within 3 years; 5) High risk adenomas and remain on colonoscopy surveillance within 1 year; 7) Cancer, neoplasia which infiltrates the submucosa layer ≥pT1) followed by the hospital specialists.

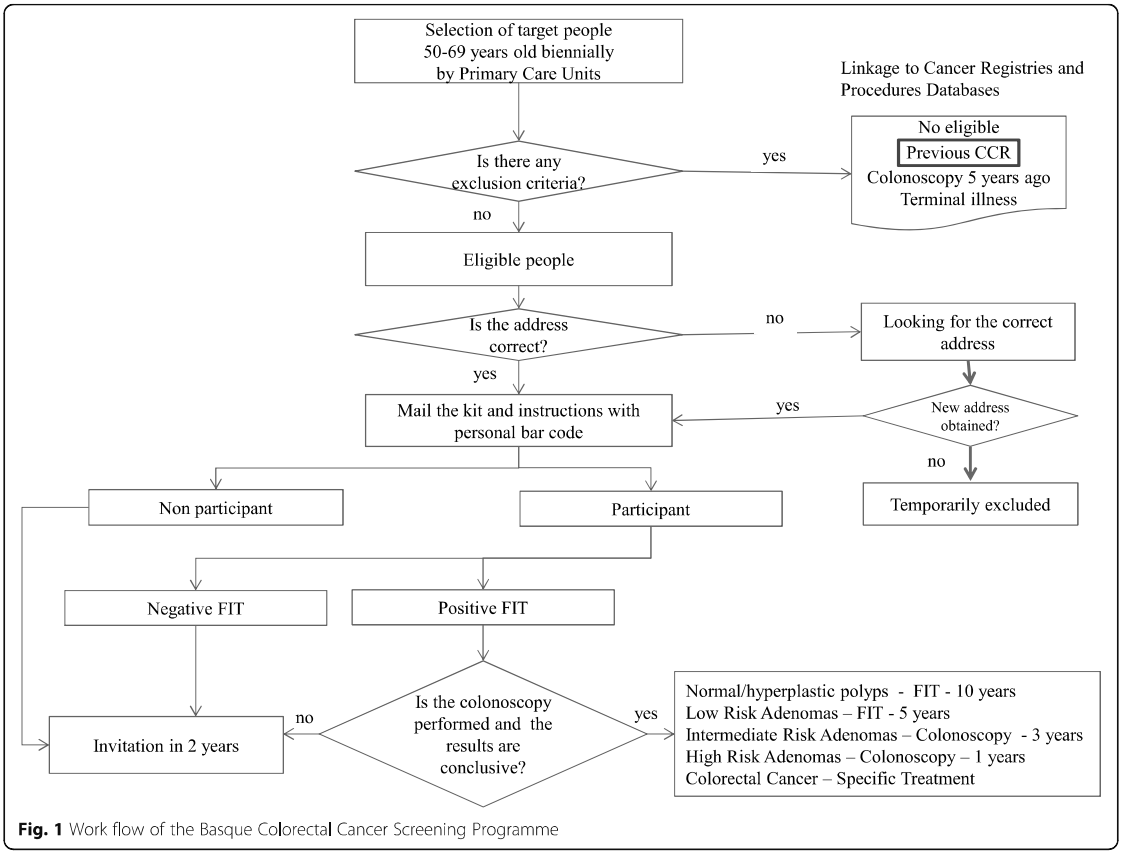

Fig. 1 Work flow of the Basque Colorectal Cancer Screening Programme

The main results from 2009 to 2014 were used in order to describe the main benefits of the Programme. For the simulation model, the result of the period of 2009–2012 was used for the Basque Country's inhabitants, and the results obtained from the invitation during 2013–2014 were used to check and contrast the results obtained by the simulation on the MISCAN-colon.

MISCAN model adaptation

The MISCAN-colon was used to estimate the results of the screening strategy of biennial FIT from 50 to 69 year-olds in the Basque Country. The MISCAN model and the parameter's sources were fully explained in previous publications [15, 21] and in the standardized model profile of the Cancer Intervention and Screening Network (CISNET) [22]. This model simulates the relevant life histories of a large population of individuals from birth to death. CRC arises in this population in accordance with the adenoma-carcinoma sequence [23].

MISCAN simulated the Basque population in 2008 with its age-structure divided into different strata depending on the age at which they were invited to the Programme for the first time (or never invited if they were over 70 in 2008). Given the significant differences in the epidemiology of CRC between men and women, MISCAN model was run separately for each sex. The validation took into account the stage and localization of CRC in the period of 2005–2008 and the adenoma prevalence calculated for the Basque population using a sample of the COLONPREV study [24].

After reproducing the natural history without screening, the model reproduced the behavior of CRC in a screening scenario by considering the impact of removing adenomas and anticipating CRC stage at diagnosis. Those consequences were translated into quality-adjusted life years gained and treatment costs avoided [25].

In this analysis, the MISCAN-colon model was adjusted to represent the situation of the Basque Country: birth and lifetables and CRC risk and survival from the Cancer Population Register and the Basque Institute of Statistics (EUSTAT) [26]. For the Basque Country, the MISCAN-colon modelling has been adapted to regard the findings of adenomatous lesions, in adenomas

smaller and bigger than 10 mm. The projection has been done for 30 years from the implementation of the screening programme. For the prevalence of adenomas, the COLONPREV study and other studies were considered [22, 27, 28].

Results

Outcomes of the population-based Basque CRC screening Programme

924,416 individuals were invited (2009–2014), with an average participation rate of 68.4% representing an incremental increase over the study period (58.1% - 70.3%). Trends of participation increased 2.2% yearly (95% CI 2.0–2.4; $p < 0.001$) with 91.8% being regular participants in the second round and 95.8% in the third round. The adherence to colonoscopy after FIT positive result has been higher than 92% in all years of the study. The Advanced Adenoma (AA) detection rate was 23.9‰ and CRC detection rate was 3.4‰. In he 66.4% of CRC cases, the detection was registered in Stage I-II. Indicators by round and sex are detailed in Table 1.

Comparing the results obtained on the actual screening scenario with the observed data for invitations, participation rate, positive screen tests and detection rates, we can conclude that the model reproduced well the observed data (Fig. 2).

In Table 2, the future projections were predicted for men and women regarding future invitations, participation, diagnostic/surveillance colonoscopies and detected lesions in different years, the last projection being done in 2038. Observed differences between men and women were noticed in participation, as well as in detected lesions. A trend towards stabilization was observed in all parameters of the projection for 2020 and onwards, but the surveillance colonoscopies seemed to stabilize ten years later.

In Fig. 3, a decrease in the CRC incidence was shown after 30 years of screening, greater in men (17.2%) than in women (14.7%). In both sexs, ten years after the Programme started, a decrease was found in the number of cases of CRC. Considering both sexs, the average decrease found was 16.3%.

Regarding the reduction in mortality for this same projection, the decrease for men was 28.1% and 22.4% for women, with an upward trend from the beginning of the Programme, the average decrease being 26.1% (Fig. 4).

The reduction of Life-years-Lost was also greater in men than in women (22.6% vs 18.4%) with an upward trend from the beginning of the Programme and an average for both sexs of 21% (Fig. 5).

Discussion

The strategy of the CRC Screening Programme in the Basque Country has been implemented according to the recommendations of the EU [9], taking into account the target group and professionals when considering its implementation.

The main results of the Programme showed a high participation rate in both sexs in the three rounds from 2009 to 2014, possibly related to the implemented strategy, according to McGregor et al. [29], who demonstrated a relation to participation in both sexs (men OR 5.0; 95% CI 2.9 to 8.3 and women OR 3.8; 95% CI 2.3 to 6.5). Tinmouth et al. [30] also showed the importance of the family physician when providing information about the programme's role after Programme invitation. However, Van Roosbroeck et al. [31] demonstrated a higher participation rate related to the type of invitation, higher in shipping kits to a participant's home than when delivered by the rimary care physician (OR 2.96 95% CI 2.78 to 3.14). Combined strategies could be efficient to achieve a higher participation rate. Also, quality assurance plays an important role (Von Karsa et al., 2013) [32].

The f-Hb cut-off point chosen in FIT has generated a lot of discussion in terms of the number of colonoscopies to be performed, which was an initial limitation to the total extension of the Programme. However, it has not been modified in terms of cut-off age to deal with the management of positive cases, but that should be taken into account in successive rounds, according to van Rossum 2009 [33].

The lesion detection rate analysis reported a high trend in the first round with a significant decrease in successive rounds, following the same pattern as the positive FIT test. The largest decline occurred primarily in men and in AA. Denters et al. [34] found a significant decrease in PPV for AN (Advanced Neoplasia) between the first and the second round of 55% (132/239) to 44% (112/252), ($p = 0.017$). The PPV for CRC was 8% (20/239) in the first round vs 4% (9/252) in the second round ($p = 0.024$).

CRC detected by screening were in early stages (I-II) in 66.4%, contrasting with previous data (45.8%) (Departamento de Sanidad y Consumo et al., 2010) [2].

In the Basque Country Programme, considering its rapid extension and its high participation rate and lesions detected, a positive medium-to -term impact could be expected. This impact was suggested by Zorzi et al. [10] who found a better impact related to geographic locality and the implementation of screening, with higher reductions in mortality in women (RR=0.64; 95% CI = 0.51–0.80) than in men (RR 0.87 95% CI 0.73–1.04), but with significant results in all cases.

The choice of the MISCAN-colon model to simulate the impact of the Programme, both mid and long term, has given us the opportunity to establish a future scenario based on real data, regarding the incidence and

Table 1 Main results of the Programme by sex and rounds 2009–2014

	FIRST ROUND				SECOND ROUND				THIRD ROUND				TOTAL				TOTAL	
	WOMEN		MEN		WOMEN		MEN		WOMEN		MEN		WOMEN		MEN			
Eligible People	298,896	%	286,054	%	154,183	%	143,960	%	41,770	%	36,670	%	494,849	%	466,684	%	961,533	%
Invited People	288,775	96.6	273,317	95.5	149,234	96.8	137,705	95.7	40,397	96.7	34,988	95.4	478,406	96.7	446,010	95.6	924,416	96.1
Participants	200,422	69.4	174,968	64	108,776	72.9	93,368	67.8	30,095	74.5	24,427	69.8	339,293	70.9	292,763	65.6	632,056	68.4
Positive test	10,421	5.2	15,671	9	4659	4.3	6422	6.9	1245	4.1	1717	7.0	16,325	4.8	23,810	8.1	40,135	6.3
PPV		%		%		%		%		%		%		%		%		%
Advanced Adenoma		29.4		47.8		23.5		39.0		24.1		40.5		27.3		44.9		37.7
Advanced Neoplasia		34.4		54.5		27.0		43.5		27.5		44.5		31.7		50.8		43.0
CRC		5.0		6.7		3.5		4.5		3.4		3.9		4.4		5.9		5.3
Diagnostic colonoscopy	9720	93.3	14,678	93.7	4282	91.9	5842	91.0	1176	94.4	1595	92.8	15,178	93.0	22,115	92.9	37,293	92.9
Detected Lesions		‰		‰		‰		‰		‰		‰		‰		‰		‰
Advanced Adenoma	3063	15.3	7487	42.8	1094	10.1	2504	26.8	300	9.9	696	28.5	4457	13.1	10,687	36.5	15,144	24.0
Advanced Neoplasia	3583	17.9	8533	48.8	1257	11.6	2796	29.9	342	11.4	764	31.3	5182	15.3	12,093	41.3	17,275	27.3
CRC	520	2.6	1046	6.0	163	1.5	292	3.1	42	1.4	68	2.8	725	2.1	1406	4.8	2131	3.4
CRC Stage		%		%		%		%		%		%		%		%		
I-II	320	61.5	716	68.5	112	68.7	206	70.5	22	52.4	38	55.9	454	62.6	960	68.3	1414	66.4
III-IV	157	30.2	279	26.7	45	27.6	76	26.0	20	47.6	25	36.7	222	30.6	380	27.0	602	28.2
Unknown	43	8.3	51	4.9	6	3.7	10	3.4	0	0	5	7.4	49	6.8	66	4.7	115	5.4

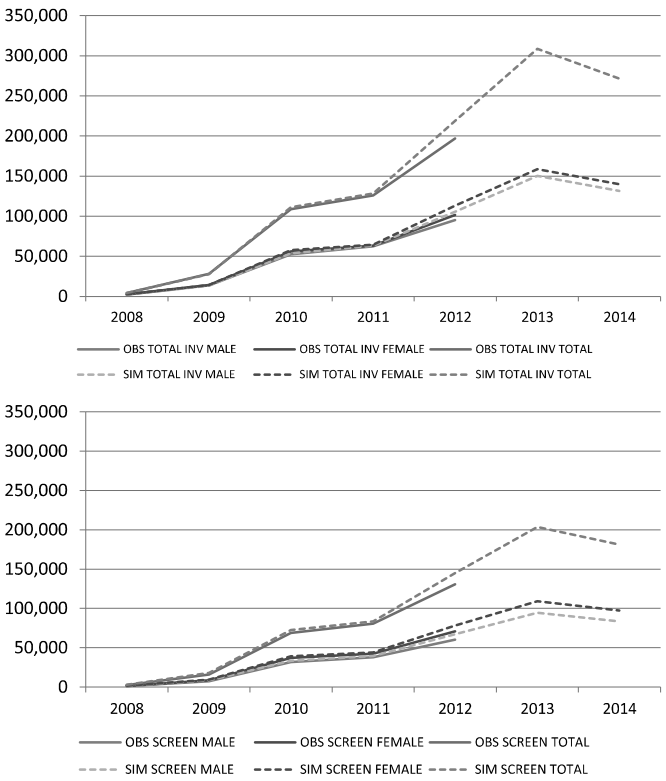

Fig. 2 Observed and simulated invitations and participants by sex 2009–2014

mortality before screening as well as the Programme's results after its start in 2009. One outstanding feature of this method was being able to count on internationally-renowned cancer registers, which make the study of the effectiveness in screening feasible (Anttila et al., 2015) [35].

In this respect, the incidence and mortality rates in the Basque Country are different than in other European regions [36]. When compared with European Population Registers, the Basque Country showed a higher incidence rate in men and an average rate in women compared to the Netherlands, Italy, and Scotland and North Thames in the UK. The mortality rate in men was also higher. However, these incidence and mortality rates showed an intermediate position for women [37].

The simulation applied to sexs offered a wider vision of CRC, which was not reflected in a majority of research, and which was, however, important to calculate the impact of screening programmes. In the current study, the impact of dealing with different population groups was evident, not only regarding the incidence and mortality of CRC, but also how both sexs behaved in participation, positive test rates and the rate of detected lesions. Hence, the programme's impact was shown to be greater in men than in women, but unfortunately men participated less than women.

After a 30-year projection, and with participation rates adjusted to the results of the Programme, the decrease in incidence and mortality found seems compatible with what is reflected in current literature, although it is difficult to compare results, due to the dissimilarities in context, including simulations of 100% participation and short or indeterminate follow-up periods. However, the quality of simulation and the adaptation of parameters proved successful according to the real data provided by the Programme.

The reduction in incidence would start in the first ten years of the Programme's implementation with significant increases over time. As other authors have stated, CRC screening not only decreases mortality, but it prevents new cases Ventura et al. [38], which contributes to minimizing the burden of the disease in the future. On the basis of higher incidence rates, the mid-to-long term impact could represent an important reduction in both

Table 2 Future projections by sex: invitations, participants and lesions detected

	INVITATIONS AND PARTICIPANTS								
	Men population			Women population			Total population		
Year	Invitations	Participants	%	Invitations	Participants	%	Invitations	Participants	%
2012	93,822	58,994	62.9	99,099	68,045	68.7	192,921	127,039	65.9
2015	130,983	85,337	65.2	139,006	98,553	70.9	269,989	183,889	68.1
2020	137,436	91,543	66.6	144,522	104,610	72.4	281,958	196,153	69.6
2025	132,995	88,238	66.3	137,473	99,219	72.2	270,468	187,457	69.3
2030	133,678	88,969	66.6	137,485	99,935	72.7	271,164	188,904	69.7
2035	123,789	83,234	67.2	127,178	93,397	73.4	250,966	176,630	70.4
2038	114,699	77,577	67.6	118,248	87,204	73.7	232,947	164,781	70.7
	DIGANOSTIC COLONOSCOPIES AND LESIONS DETECTED								
	Men population			Women population			Total population		
Year	Colonos copies	Adenomas Detected	CRC Detected	Colonos-copies	Adenomas Detected	CRC Detected	Colonoscopies	Adenomas Detected	CRC Detected
2012	4070	2658	295	2786	1231	142	6856	3888	437
2015	5580	3620	347	3973	1730	185	9553	5350	532
2020	5764	3638	348	4120	1745	159	9884	5384	508
2025	5397	3372	304	3839	1597	148	9236	4969	452
2030	5394	3354	310	3839	1587	148	9233	4941	458
2035	5073	3199	288	3627	1505	140	8700	4704	428
2038	4766	3041	289	3406	1427	134	8172	4468	424
	SURVEILLANCE COLONOSCOPIES AND LESIONS DETECTED								
	Men population			Women population			Total population		
Year	Colonos copies	Adenomas Detected	CRC Detected	Colonos copies	Adenomas Detected	CRC Detected	Colonos copies	Adenomas Detected	CRC Detected
2012	941	259	2	380	101	1	1321	360	3
2015	1971	459	7	900	185	3	2871	644	10
2020	3801	787	16	1832	338	4	5634	1115	20
2025	5190	1172	25	2511	523	9	7701	1695	34
2030	5757	1310	27	2743	571	8	8500	1881	35
2035	5666	1278	25	2706	551	10	8371	1829	35
2038	5523	1233	31	2638	544	9	7561	1777	40

Table 2 Future projections by sex: invitations, participants and lesions detected *(Continued)*

	TOTAL COLONOSCOPIES (Diagnostic and Surveillance) AND LESIONS DETECTED								
	Men population			Women population			Total population		
year	Colonos copies	Adenomas Detected	CRC Detected	Colonos copies	Adenomas Detected	CRC Detected	Colonos copies	Adenomas Detected	CRC Detected
2012	5011	2917	297	3166	1332	143	8177	4248	440
2015	7551	4079	354	4872	1915	188	12,424	5994	542
2020	9566	4425	364	5952	2083	163	15,517	6499	528
2025	10,586	4544	328	6350	2120	157	16,937	6664	485
2030	11,151	4664	337	6582	2158	156	17,733	6822	493
2035	10,738	4477	313	6333	2056	150	17,071	6533	463
2038	10,289	4274	320	6044	1971	143	15,734	6245	463

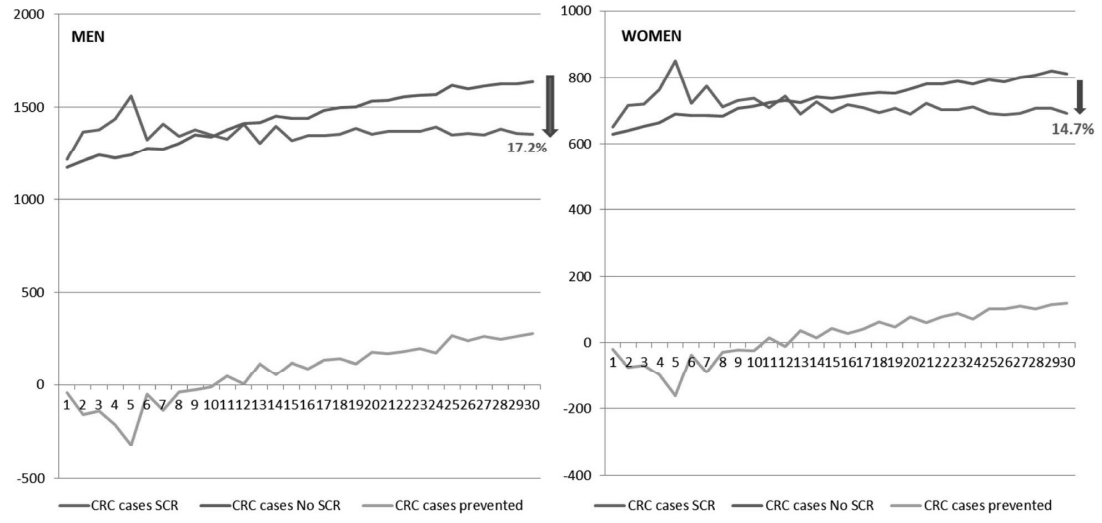

Fig. 3 Incidence decreasing for men and women in 30 years

the number of cases and death, according to Parente et al. [39] who found a significantly lower mortality rate in screening in 5 years compared to non-screening or pre-screening colorectal cancer patients (19% vs 37% and 41%; $p < 0.001$).

In this sense, the L-y-L for both sexs is very high and provided an important tool for regional and national authorities, as well as policy makers, to invest and support these types of programmes, taking into account organization and quality indicators. That recommendation was suggested by van Hees et al., [40] from the Netherlands.

Comparisons between programmes are difficult, as was suggested by Klabunde et al. [41], who found a range of invitation coverage from 30 to 100% and coverage by the screening Programme from 7 to 67.7%,

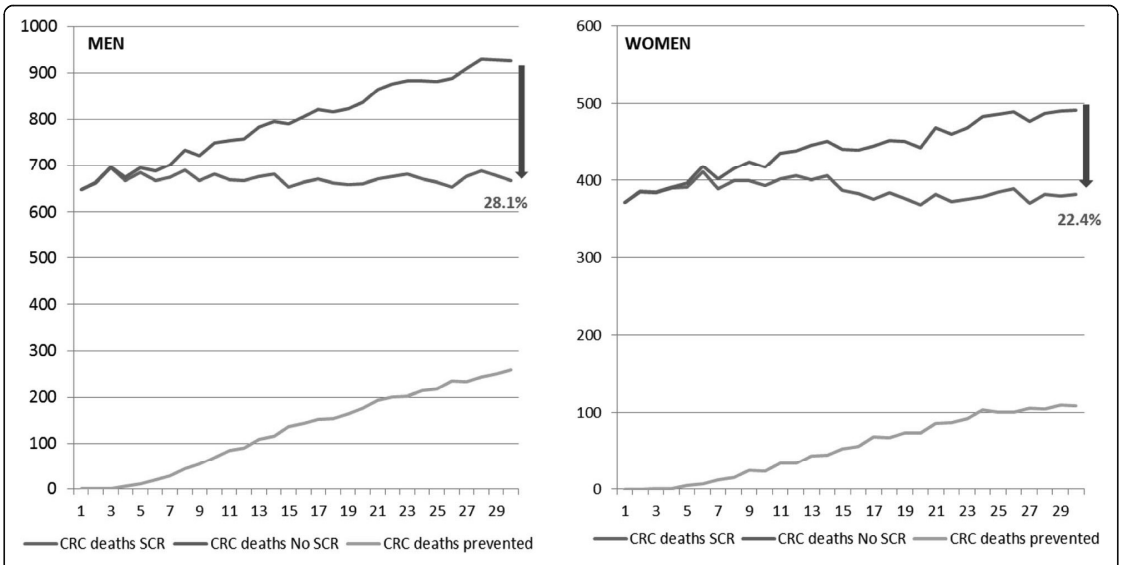

Fig. 4 Mortality decreasing by sex in 30 years

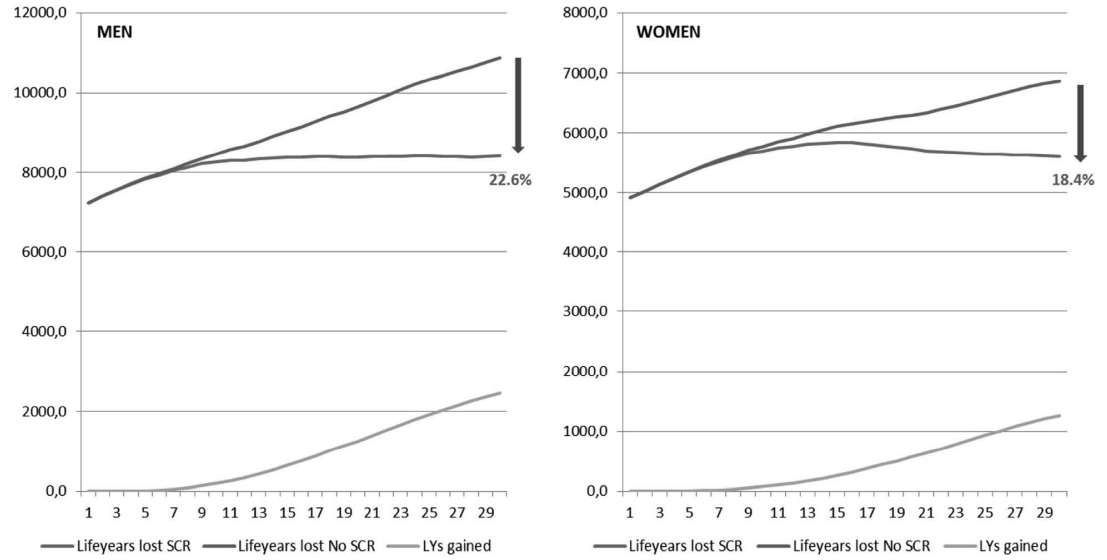

Fig. 5 Decreasing in Life years lost by sex in 30 years

overall participation rate from 7 to 67.7%, and first invitation participation from 7 to 64.3%. These differences could be minimized by implementing different measures to increase coverage and catchment in order to maximize the equality of access and the impact on public health recommended by Senore et al. [42]. One of the limitations of this study is that the classification of the risk of those with removed adenoma, due to the use of MISCAN model, had to be done based only on the size of the lesion, so those identified with other characteristics such as number of adenomas or the grade of dysplasia, had to be proportionally distributed [43].

Another limitation is the uncertainty in estimated adenoma prevalence, which was considerably higher than previously observed in other studies included, to build the MISCAN-colon model. This is, however, consistent with the fact that the study programme has a high participation rate that has been maintained throughout the study period and has not declined in new participants. Based on the robustness of the model, this maintained rate supports the prediction.

An important strength of our study is a well validated model based on several years of data from a high participation-rate population-based programme, directly reported by The Basque Country data and the concordant results observed.

In the future, some findings in FIT performance characteristics, with respect to repeating screening rounds, would be taken into account in order to increase efficiency (van der Meulen et al., 2016) [44]. NowaCurrently, we still have difficulty comparing data from different models, relatedd to a lack of randomized control trials on the effectiveness of FIT, and a lack of data on participation in surveillance and uncertainty in adenoma prevalence. Consequently, there is a need to carry out prospective cohort studies to evaluate the impact of the effectiveness of these programmes within the context of implementation and considering all the possible parameters and their influence.

The results obtained within this research are in line with previously published studies on cost-effectiveness analysis [45].

Nevertheless, the results of the projections offer a rather modest reduction of the main parameters measured. These projections indicate a need to consider how to improve the efficiency of currently implemented strategies. This incudes analyzing the possibility of implementing complementary or improved strategies such as the introduction of algorithms of risks, differentiating among men and women, familiar susceptibility (detected lesions subgroup analysis) or adjusting the cut off levels of the current test. Primary care physicians and authorities are key in maintaining the programme as it is described here. Primary care physicians are central to informing the population about the benefits of being screened and, thus, maintaining the high participation rates. Authorities are important in ensuring the level of investment in order to guarantee that no delays in the subsequent diagnostics and managing processes are generated. The latter is crucial not just from the perspective of the programme itself and its intermediate results

(detected lesions as early as possible), but to improve the final outcomes on life expectancy and quality of life.

Conclusions

The Basque Country CRC Programme results are aligned to its strategy and comparable to other programmes. MISCAN model was found to be a useful tool to predict the benefits of the programme in the future. According to the parameters of simulation of MISCAN-colon and by means of the early obtained data of the Programme, the screening seems to be an effective strategy in order to reduce the incidence, mortality and L-y-L. These results provide further evidence on the efficiency of population-based CRC programmes. These data support the continuity of the programme and show the need for further improvements in the selected strategy to increase its efficiency.

Abbreviations

AA: Advanced Adenoma; AN: Advanced Neoplasia; BBPS: Boston Bowel Preparation Scale; CISNET: Cancer Intervention and Screening Network; CRC: Colorectal Cancer; EU: The European Union; f-Hb: faecal-Haemoglobin; FIT: Immunochemical quantitative test L-y-L: Life-years-Lost; gFOBT: the guaiac faecal occult blood test; MISCAN-colon: Microsimulation Screening Analysis; PPV: Positive predictive values

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the Spanish Royal Decree 1720/2007, 21st December, regulation for development of the Organic Law 15/1999 for Personal Data Protection, but are available from the corresponding author on reasonable request.

Authors' contributions

II, AA, IP and EAA conceived the idea for this analysis. The data used for this analysis come from a study that was designed and conducted by II, IP, AA, MS, RL, LMI and JM who collaborated on the data analysis. II, IP and EAA drafted the manuscript. HK, IL and MM critically reviewed the manuscript and gave important intellectual input and expertise in the MISCAN-colon simulation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Basque Country's Ethics Committee. Complying with the Spanish Royal Decree 1720/2007, 21st December, regulation for development of the Organic Law 15/1999 for Personal Data Protection for the use of anonymized population data, required for the MISCAN model, no informed consent was requested. For the collection of data from participants with screening lesions or complications of the colonoscopy written informed consent was collected.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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ORIGINAL ARTICLE

Retrospective Study

Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain)

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Author contributions: All authors have contributed as qualified researchers in the article: Portillo I in the design and writing of the paper with Arana-Arri E, who also wrote the discussion with Gutierrez-Ibarluzea I and the statistical methodology in coordination with Martínez-Indart L, who analyzed the data and drew up the results; Idigoras I and Bilbao I registered every cancer case and reviewed all items related to quality control; Bujanda L reviewed all clinical features and contrasted the data against published articles; Gutierrez-Ibarluzea I offered feedback on all drafts in order to include an appropriate bibliography and analyze the relevance of the results to health systems to write the discussion.

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Institutional review board statement: This study was approved by Carlos III Health Institute, Spanish Government.

Informed consent statement: Participants gave their consent to participate when they accepted the invitation for Colorectal Cancer Screening.

Conflict-of-interest statement: No conflicts of interest.

Data sharing statement: All data published have been previously anonymized, as is required by the Ethics Committee and authorities in the Basque Country (See attached pdf of Basque Ethics principles). Technical appendix, statistical code, and dataset available from the corresponding author at mariaisabel.portillovillares@osakidetza.eus. Participants gave informed consent for data.

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Abstract

AIM

To assess proportions, related conditions and survival of interval cancer (IC).

METHODS

The programme has a linkage with different clinical databases and cancer registers to allow suitable evaluation. This evaluation involves the detection of ICs after a negative faecal inmunochemical test (FIT), interval cancer FIT (IC-FIT) prior to a subsequent invitation, and the detection of ICs after a positive FIT and confirmatory diagnosis without colorectal cancer (CRC) detected and before the following recommended colonoscopy, IC-colonoscopy. We conducted a retrospective observational study analyzing from January 2009 to December 2015 1193602 invited people onto the Programme (participation rate of 68.6%).

RESULTS

Two thousand five hundred and eighteen cancers were diagnosed through the programme, 18 cases of IC-colonoscopy were found before the recommended follow-up (43542 colonoscopies performed) and 186 IC-FIT were identified before the following invitation of the 769200 negative FITs. There was no statistically significant relation between the predictor variables of ICs with sex, age and deprivation index, but there was relation between location and stage. Additionally, it was observed that there was less risk when the location was distal rather than proximal (OR = 0.28, 95%CI: 0.20-0.40, $P < 0.0001$), with no statistical significance when the location was in the rectum as opposed to proximal. When comparing the screen-detected cancers (SCs) with ICs, significant differences in survival were found ($P < 0.001$); being the 5-years survival for SCs 91.6% and IC-FIT 77.8%.

CONCLUSION

These findings in a Population Based CRC Screening Programme indicate the need of population-based studies that continue analyzing related factors to improve their detection and reducing harm.

Key words: Colorectal cancer; Population Screening Programme; Interval cancer; Faecal immunochemical test; Colonoscopy; Diagnosis; Mortality; Survival

Core tip: Population based screening programmes are implemented when benefits are superior to harms and risks are acceptable to healthy population. However, programmes should continuously improve their quality and efficiency. This study shows by means of a well-accepted screening strategy that there is room for improvement and those programmes could be personalized or at least, stratified. Main results show that instead of a reduction in the cut-off points of faecal inmunochemical test, other strategies such as different follow up periods for sex, stage and previous location could be more effective and minimize risks at the same time that they increase benefits.

Portillo I, Arana-Arri E, Idigoras I, Bilbao I, Martínez-Indart L, Bujanda L, Gutierrez-Ibarluzea I. Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain). *World J Gastroenterol* 2017; 23(15): 2731-2742 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i15/2731.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i15.2731

INTRODUCTION

The Basque Country is one of the 17 autonomous regions of Spain and has a population of approximately 2200000 inhabitants. Colorectal cancer (CRC) is the most common type of cancer when taking both sexes into account and is the most frequent in men[1]. The number of cases has increased since 1990 and there has been certain stability in mortality rate. In 2008, the year before the screening programme was implemented, there were 1869 new cases and 798 deaths were registered due to this type of cancer[2].

Following the 2003 European Guidelines[3] and the National Strategy against Cancer of 2006, validated in 2009[4,5], population based screening of CRC was approved by the Basque Autonomous Government and implemented in 2009. The screening is based on the detection of occult blood in faeces (FOB) using a biennial quantitative faecal immunochemical test (FIT), targeting women and men between 50 and 69 years of age (approximately 586700 inhabitants) and a colonoscopy under sedation for FIT positive cases. With the first invitation, almost 100% of the target population was reached at the beginning of 2014; by the end of 2015, 85% of the population had been invited at least twice and 56% a third time.

The characteristics of the programme and the main results of the first invitation were published in 2013, obtaining an average participation rate of (64.3%, 95%CI: 64.1%-64.5%) higher in women[6], finding significant differences in the rate of detection of Advanced Adenomas (AA) between women and men (OR = 0.45, 95%CI: 0.41-0.49) and CRC (OR = 0.80, 95%CI: 0.66-0.96), more frequent in men as well as the positive predictive value (PPV) for any type of adenoma which was significantly higher in men (72.4%, 95%CI: 71.2%-73.5%) than in women (48.8; 95%CI: 47.2%-50.5%), with differences depending on the age group and type of adenoma[7]. Likewise, there were differences in participation and detection of lesions according to the index of deprivation: men on the most deprived index, having a lower participation rate (60.2%) although a higher rate in the

identification of lesions (55.7/1000) compared to the least deprived (41.0/1000)[8].

The characteristics of CRC detected by the programme in the first and second rounds after a negative result were observed by Bujanda *et al*[9]; significant differences being found in location, most frequently in the second round in the right-sided colon and in a less advanced stage.

Participation and the detection rate of advanced lesions and CRC were found to be within the parameters defined by the European Guidelines of Quality (2010)[10], which recommend 65% participation and an Adenoma detection rate between 13.3‰-22.3‰ and of CRC between 1.8‰-9.5‰. However, one aspect to bear in mind is the possible losses of the programme, which are interval cancers (ICs), and which are one of the biggest concerns of the screening programme as not only the capacity for detection is measured, but also the quality of the confirmatory diagnostic test, in this case a colonoscopy. As was pointed out by Robinson *et al*[11], in the Randomized Controlled Trial in Nottingham, both the positive effects (reduction of mortality because of screening) as well as the negative effects (false negatives among others) should be monitored and taken into account.

In fact, for a correct detection, it is necessary to have an organized Screening Programme and the possibility of individualized linkage with clinical databases (diagnostic procedures, pathological confirmation, hospital discharges and cancer registers), in such a way as to allow a suitable evaluation of the impact of the programmes[12].

A standardized methodology like the proposal for GISCoR 2013[13] is also required.

The aim of this study is to compare CRC detected by the Programme or screened cancers (SCs) and ICs detected from 2009-2015 both after a negative FIT and before the following invitation (IC-FIT), such as post-confirmatory colonoscopy cancers following a positive FIT and before a follow-up colonoscopy, depending on the lesion found (IC-colonoscopy).

MATERIALS AND METHODS

The Basque Country's Population Based Screening Programme has the support of a Coordinating Centre which plans, organizes, monitors and evaluates the individualized invitation process as well as the test results and follow-up of all positive cases. This is possible thanks to the interaction of software, specially designed for the programme, with clinical databases and cancer registries. The software contains a system of encryption and access in accordance with the current data protection laws as it is all systematically anonymized for analysis and subsequent publication. Participants in the programme are informed and consent to the use of their data. The FIT tests used were FOB Gold in 2009 and 2010 (Sentinel Diagnosis SpA, Milan Italy) and OC-Sensor from 2010 onwards (Eiken Chemical Co. Tokyo, Japan). Only one sample was collected, as the haemoglobin concentration cut-off (f-Hb) 100 ng Hb/mL of buffer, which is equivalent to 17 μg Hb/g faeces in Sentinel and to 20 μg Hb/g faeces in OC-Sensor, as the comparison of both tests showed[14].

The screening is based on the detection of occult blood in faeces (FOB) using a biennial quantitative FIT, targeting women and men between 50 and 69 years of age (approximately 586700 inhabitants) and a colonoscopy under sedation for FIT positive cases.

The tests were analyzed in the laboratories of the publicly-funded hospital system under strict internal and external quality control. The colonoscopies were also performed in publicly-funded hospitals by qualified and trained specialists in the digestive system; sedation was also provided by the same endoscopy team, although 20% included the presence of an anaesthetist. The recommendations of the European Guidelines (2010) and Spanish Guide for Quality Control (2011)[15] were followed in all cases. The resected polyps and CRC with biopsy and/or endoscopic or surgical resection were analyzed in laboratories of Pathological Anatomy by staff skilled in histopathology of gastrointestinal disease with specific emphasis on CRC. CRC was diagnosed when the neoplastic cells pass through the muscularis mucosae, invading the submucosae (≥ pT1). All CRCs were registered according to the criteria of the American Joint Committee on Cancer (AJCC)[16].

Methodology of interval cancer detection

Detection of ICs after a negative FIT (IC-FIT): prior to a subsequent invitation, all negative cases from a previous round are linked to the register of hospital discharges with ICD-9 1530-1548, in primary and secondary diagnosis, ICDO-10 C18-C21 of hospital registers and population-based Cancer registries as well as codes of Pathology. In all coinciding cases, the qualified staff from the Programme's Coordinating Centre checked the clinical history, including the cases as ICs which complied with the criteria of having a negative FIT result in the previous invitation (0-24 mo or more in case of a delay in the invitation to the screening programme). To ensure against any possible losses, this process was repeated on an annual basis with all negative FITs from the previous 24 mo.

Detection of ICs after a positive FIT and confirmatory diagnosis without CRC detected and before the following recommended colonoscopy (IC-colonoscopy): these data were annually cross-referenced with all the colonoscopies with a different result to detected CRC by the Programme or Screen-detected Colonoscopies (SCs), following the same methodology as the previous section. It was considered to be IC if a CRC was detected prior to the scheduled follow-up: 10 years with an invitation for a FIT in the case of a normal result/non-neoplastic polyps; 5 years with an invitation for a FIT in the case of a Low-Risk Adenoma (1-2 tubular

adenomas and/or ⩽ 10 mm and/or without high grade dysplasia); a colonoscopy after 3 years in the case of an Intermediate Risk Adenoma (3-4 adenomas and/or ⩾ 10 mm and < 20 mm and/or a vellous component and/or a high grade dysplasia; colonoscopy in < 1 year in the case of a detected High-Risk Adenoma (⩾ 5 adenomas and/or ⩾ 20 mm). Given that the follow-up period is longer, cases detected up to May 2016 were taken into consideration, which means that the number could increase in the next five years.

In all the cases of SCs and ICs, the following variables were taken into account when analyzing: (1) type of participant (first invitation, regular - participated in the last two invitations, irregular - participated in at least one previous invitation), ICs were not considered in the case of not participating or refusing a colonoscopy after a positive FIT; (2) round of invitations; (3) sex and age; (4) deprivation index assigned to each patient - socioeconomic deprivation index (DI) of their area of residence, using the methodology of the MEDEA project[17]; (5) quantitative result of the test in μg Hemoglobin/g of faeces in invitations prior to a negative FIT; result of a confirmatory colonoscopy and date; diagnostic method in ICs and date; (6) details of CRC: location, size, morphology, TNM, degree of differentiation, state and type of first treatment; and (7) survival with a link to the Population Death Register until 1st December 2016.

For the description of qualitative variables frequency tables and percentages were used, for quantitative variables means and standard deviation or median and interquartile range (IQR). For comparison between two groups contrast of exploratory hypotheses have been made using exact test of Fisher or χ^2 for categorical variables. To compare quantitative variables and categorical variables with 2 categories *t*-test or the non-parametric Mann Whitney *U* test was used. Logistic regression analysis was performed with interval *vs* screening detected CRC as the outcome variable. Overall survival after CRC diagnosis for the patients with interval CRC was compared, by Kaplan-Meier estimation, long-rank test and Cox proportional hazard ratios. The survival time was measured from the date of CRC diagnosis to date of death or censoring resulting from the end of the study period (December 1, 2016). Significance was set at the 5% level. The analysis was performed by a biomedical statistician using IBM SPSS Statistics 23.0.

RESULTS

From January 2009 to December 2015, 1193602 people were invited to the CRC Screening Programme, with a participation rate of 68.6%. Of the participants, 49687 obtained a positive result, with 2518 cancers diagnosed, with a 92.7% acceptance rate for screening colonoscopies. The global adenoma detection rate by the Programme for the period studied was 57.25‰.

Seven point five percent (204/2722) of the diagnosed cancers were IC. Of the colonoscopies performed, 18 cases of IC-colonoscopy were found before the recommended follow-up and of the 769200 negative FITs, 186 IC-FIT were identified before the following invitation. Table 1 shows the characteristics associated with the three types of cancers analyzed in this study. Significant statistical differences were observed by age, round of invitations and characteristics of the tumour such as: location, stage, morphology, degree of differentiation and size of the tumour.

Table 2 shows the medians of f-Hb and their corresponding IQR in the invitation, just before the diagnosis of IC. No differences between the variables analyzed were observed: sex, age, deprivation index, time to diagnosis; neither was there differences found in the characteristics of the tumour: location, state, morphology, degree of differentiation and size. What was observed in both the analysis of variables as well as in the global (Median: 2.8 μg Hb/faeces; IQR: 0.4-9.9) was that the values of the f-Hb of the FIT with a negative result prior to the diagnosis of IC-FIT were found to be very distant from the cut-off point established as positive (20 μg Hb/g faeces). Patients diagnosed after two rounds with a negative result, also presented low values in the first round (Median: 0.8 μg Hb/g faeces; IQR: 0.0-4.5).

In Table 3 the characteristics of negative colonoscopies are shown for CRC prior to the diagnosis of an interval cancer (IC-colonoscopy) and after a positive FIT result. More than a third of the diagnosed cancers were seen to be in the sigma location and 27.8% in the caecum. In 55.5% of colonoscopy cases prior to screening, polyps were detected and removed, although in two cases their removal was in the same location as the diagnosed cancer, in sigma. In 83.3% of the colonoscopies, the caecum was reached and the rate of colonic preparation was adequate in the majority of cases (66.7%). It should be clarified that out of the 18 IC-colonoscopies, 12 had an adequate preparation, 2 had a bad quality of colonic cleansing and 4 were not described in the report.

On the other hand, consultations were made about 85% of these interval cancers for suspected symptomology - rectal bleeding (30.1%) and abdominal pain (29.6%) being the most frequent causes, respectively. On the other hand, in those cases where there were no symptoms, anaemia was the diagnostic sign in 5.4% of the cases.

Figure 1 shows the distribution of the different types of colorectal cancer by stages at the time of diagnosis and its link to their location. A larger proportion of advanced stages were observed, firstly in the rectum and then in the proximal colon, in both the IC-FIT and IC-colonoscopy.

Table 4 shows that there was no statistically significant relation between the possible predictor variables of interval cancer by sex, age and deprivation index, but there was a relation between location and stage. However, it was observed that there was less risk

Table 1 Characteristic of interval cancers and screen-detected colorectal cancers *n* (%)

	Interval cancers		Screen-detected (SCs)	*P* value
	FIT	Post-colonoscopy		
Total	186 (6.8)	18 (0.7)	2518 (92.5)	-
Patient characteristics				
Sex				
Male	125 (67.2)	10 (55.6)	1651 (65.6)	0.601
Female	61 (32.8)	8 (44.4)	867 (34.4)	
Age (yr)				
Mean (SC)	60.2 (4.9)	62.0 (3.5)	61.7 (3.4)	0.042
50-54	28 (15.1)	0 (0)	375 (14.9)	
55-59	53 (28.5)	5 (27.8)	539 (21.4)	0.001
60-64	61 (32.8)	10 (55.6)	709 (28.2)	
65-69	44 (23.7)	3 (16.7)	895 (35.5)	
Round of invitation				0.001
1	143 (76.9)	16 (88.9)	1615 (64.1)	
2	40 (21.5)	2 (11.1)	680 (27.0)	
3	3 (1.6)	0 (0)	223 (8.9)	
Type participation				0.086
Initial	149 (80.1)	17 (94.4)	1863 (74.0)	
Regular	35 (18.8)	1 (5.6)	639 (25.4)	
Irregular	2 (1.1)	0 (0)	16 (0.6)	
Deprivation Index				0.192
1 (least deprived)	42 (23.9)	3 (16.7)	521 (21.4)	
2	43 (24.4)	1 (5.5)	503 (20.6)	
3	29 (16.5)	6 (33.4)	539 (22.1)	
4	38 (21.6)	2 (11.1)	461 (18.9)	
5 (most deprived)	24 (13.6)	5 (27.8)	414 (17.0)	
Unknown	0 (0)	1 (5.5)	0 (0)	
Time to diagnosis (months)			-	< 0.0001
Median (IQR)	13.5 (8.5-18.9)	28.1 (16.5-40.1)		
Range	1.5-39.4	5.6-61.2		
Cancer characteristics				
Location				< 0.0001
Proximal[1]	68 (36.6)	7 (38.9)	478 (19.0)	
Distal[2]	58 (31.2)	9 (50.0)	1529 (60.7)	
Rectum	58 (31.2)	2 (11.1)	404 (16.0)	
Unknown	2 (1.1)	0 (0)	107 (4.2)	
Stage				< 0.0001
Ⅰ	43 (23.1)	4 (22.2)	1376 (54.6)	
Ⅱ	36 (19.4)	2 (11.1)	408 (16.2)	
Ⅲ	57 (30.6)	7 (38.9)	566 (22.5)	
Ⅳ	50 (26.9)	5 (27.8)	152 (6.0)	
Unknown	0 (0)	0 (0)	16 (0.6)	
Morphology				0.002
ADC, NOS	139 (74.7)	15 (83.3)	1823 (72.4)	
ADC in adenomatous polyp	4 (2.2)	0 (0)	121 (4.8)	
Carcinoid tumor	0 (0)	0 (0)	7 (0.3)	
ADC in villous adenoma	6 (3.2)	0 (0)	154 (6.1)	
ADC in tubulovillous adenoma	10 (5.4)	0 (0)	174 (6.9)	
Mucinous ADC	5 (2.7)	2 (11.1)	42 (1.7)	
Mucin-producing ADC	3 (1.6)	0 (0)	23 (0.9)	
Signet ring cell carcinoma	0 (0)	0 (0)	4 (0.2)	
Other	15 (8.1)	0 (0)	64 (2.5)	
Unknown	4 (2.2)	1 (5.6)	106 (4.2)	
Degree of differentiation				< 0.0001
Well differentiated	76 (41.1)	7 (38.9)	988 (39.2)	
Moderately differentiated	59 (31.9)	7 (38.9)	1061 (42.2)	
Poorly differentiated	14 (7.6)	1 (5.5)	86 (3.4)	
Undifferentiated/anaplastic	33 (17.8)	2 (11.1)	320 (12.7)	
Unknown	3 (1.6)	1 (5.5)	63 (2.5)	
Size (mm)				0.022
Median (IQR)	20 (8.0-40.0)	38.0 (30.0-60.0)	26.0 (19.7-40.0)	
Range	2.0-90.0	9.0-80.0	2.0-95.0	

Treatment				< 0.0001
Endoscopic resection	5 (2.7)	0 (0)	733 (29.1)	
Surgery	56 (30.1)	9 (50.0)	182 (7.2)	
Surgery and neoadjuvant therapy	106 (57.0)	7 (38.9)	1332 (52.9)	
Palliative procedure	18 (9.7)	2 (11.1)	164 (6.6)	
Unknown	1 (0.5)	0 (0)	107 (4.2)	

[1]Cecum, Ascending, Hepatic Flexure, and Transverse; [2]Splenic Flexure, Descending, Sigmoid. ADC: Adenocarcinoma; FIT: Faecal inmunochemical test.

Table 2 f-Hb values of previous negative screening test in interval cancer cases

	Median f-Hb (μg Hb/g faeces)	IQR	*P* value
All	2.8	0.4-9.9	-
Sex			
Male	3.4	0.2-10.0	0.409
Female	1.9	0.4-9.8	
Age (yr)			0.380
50-54	1.9	0.2-6.9	
55-59	3.0	0.6-13.0	
60-64	2.8	0.2-8.6	
65-69	4.0	0.4-12.5	
Deprivation Index			0.887
1 (least deprived)	3.0	0.6-11.9	
2	2.6	0.0-10.2	
3	4.2	1.1-12.4	
4	4.0	0.4-11.2	
5 (most deprived)	2.6	0.0-8.7	
Time to diagnosis (mo)			0.795
Within 1 yr	3.4	0.2-10.6	
1-2 yr	2.5	0.5-9.6	
Location			0.171
Proximal[1]	1.9	0.0-9.3	
Distal[2]	3.8	0.3-13.7	
Rectum	3.9	0.7-9.1	
Unknown	1.0	0.0-…	
Stage			0.927
Ⅰ	2.0	0.0-9.7	
Ⅱ	2.6	0.2-10.6	
Ⅲ	3.2	0.7-9.8	
Ⅳ	4.0	0.2-9.9	
Unknown			
Morphology			0.550
ADC, NOS	3.0	0.6-10.0	
ADC in adenomatous polyp	10.0	2.0-17.2	
ADC in villous adenoma	0.5	0.0-9.8	
ADC in tubulovillous adenoma	2.4	0.0-9.3	
Mucinous ADC	0.4	0.0-12.5	
Mucin-producing ADC	14.0	0.0-…	
Other	1.7	0.0-6.0	
Unknown	1.0	0.0-6.9	
Degree of differentiation			0.600
Well differentiated	2.8	1.0-9.0	
Moderately differentiated	4.4	0.6-13.0	
Poorly differentiated	0.6	0.0-5.6	
Undifferentiated/anaplastic	4.0	0.0-9.4	
Unknown	2.0	0.0-…	
Size (mm)			
< 10	1.4	0.4-12.4	0.586
10-19.99	1.0	0.0-7.9	
≥ 20	2.9		

[1]Caecum, ascending, hepatic flexure, transverse; [2]Splenic flexure, descending. ADC: Adenocarcinoma; IQR: Interquartile range.

when the location was distal rather than proximal (OR = 0.28, 95%CI: 0.20-0.40, $P < 0.001$), with no statistical significance when the location was in the rectum as opposed to proximal. The risk of having an advanced stage at the time of diagnosis was significantly higher in relation to the stage of the cancers detected out the programme said relation in Stage Ⅱ: 2.73 (1.75-4.24); in Stage Ⅲ 3.31 (2.24-4.88) and in Stage Ⅳ: 10.6

Table 3 Characteristics of post colonoscopy colorectal cancers at the time of diagnosis

	n (%)
Interval CRC tumor site	
Appendix and caecum	5 (27.8)
Ascending	0 (0)
Hepatic flexure	1 (5.6)
Transverse	1 (5.6)
Splenic flexure	0 (0)
Descending	2 (11.1)
Sigmoid	7 (38.8)
Rectum	2 (11.1)
Unknown	0 (0)
Polyp found on the Screening colonoscopy	
Yes	10 (61.1)
No	8 (38.9)
Polyp frequency	
Median (IQR)	2.0 (1.0-3.5)
Range	1-6
Previous resection in the same location	
Yes	2 (11.0)
No	16 (89.0)
Report of incomplete Screening colonoscopy	
Yes[2]	3 (16.7)
No	15 (83.3)
Polyp size on the Screening colonoscopy ⩾ 10 mm	
Yes	2 (11.1)
No	16 (88.9)
Polyp histology (*n* = 10)	
Hyperplastic polyp	0 (0)
LRA	6 (60.0)
AA	4 (40.0)
Bowel preparation	
Inadequate	2 (11.1)
Adequate[1]	12 (66.7)
Unknown	4 (22.2)
Diverticulosis	
Yes	5 (27.8)
No	13 (72.2)

[1]Boston scale ⩾ 7; [2]Complementary radiological test (Barium Enema or Computerized Tomography) was performed after colonoscopy. AA: Advanced adenoma; LRA: Low risk adenoma; CRC: Colorectal cancer; IQR: Interquartile range.

Table 4 Multivariate analysis of patients and tumors predictors of interval cancers compared with screen-detected cancers

	% with CI	OR (95%CI)	*P* value
Sex			
Female	69 (33.8)	1 (ref.)	
Male	135 (66.2)	1.03 (0.76-1.39)	0.860
Age (yr)			
50-54	28 (13.7)	1 (ref.)	
55-59	58 (28.4)	1.44 (0.90-2.31)	0.127
60-64	71 (34.8)	1.34 (0.84-2.11)	0.206
65-69	47 (23.0)	0.70 (0.43-1.14)	0.153
Deprivation			
1 (least deprived)	45 (23.3)	1 (ref.)	
2	44 (22.8)	1.01 (0.66-1.56)	0.954
3	35 (18.1)	0.75 (0.48-1.19)	0.222
4	40 (20.7)	1.00 (0.64-1.57)	0.984
5 (most deprived)	29 (15.0)	0.81 (0.50-1.32)	0.396
Location			
Proximal[1]	74 (36.8)	1 (ref.)	
Distal[2]	67 (33.3)	0.28 (0.20-0.40)	< 0.0001
Rectum	60 (29.9)	0.96 (0.67-1.38)	0.824
Stage			
Ⅰ	47 (23.0)	1 (ref.)	
Ⅱ	38 (18.6)	2.73 (1.75-4.24)	< 0.0001
Ⅲ	64 (31.4)	3.31 (2.24-4.88)	< 0.0001
Ⅳ	55 (27.0)	10.59 (6.93-16.18)	< 0.0001

[1]Caecum, ascending, hepatic flexure, transverse; [2]Splenic flexure, descending.

(6.93-16.18), respectively.

With regard to the analysis of survival rate, an average follow-up time was 3.6 ± 1.6 years (Range: 0.46-7.7 years). Significant differences in survival were found between groups ($P < 0.0001$), when comparing the screening-detected group (SCs) with the ICs. Figure 2 shows the survival graph and the percentages for groups at 1, 3 and 5 years, SCs having a better prognosis. It was also observed that for women, a distal rather than a rectal location, stages Ⅰ-Ⅱ has a significantly better survival prognosis as do SCs, as the risk of death is 3 times lower in relation to interval cancers (ICs).

DISCUSSION

Screening programmes are implemented into health systems to detect early and cure or improve the prognosis of the pathologies which they are aiming to address. There are two main aims in the case of early detection of cancer programmes: detecting the cancer at early stages to be able to cure it and, in the later stages, to begin the treatment to improve the chances of survival and the quality of life of the individuals concerned. There are a series of factors which determine the value and quality of the programmes. On the one hand, the cases which are not identified (false negatives) and the cases which are "wrongly identified" (false positives) and, on the other hand, the time periods in which there is no diagnosis and new premalignant or malignant lesions may occur. There are various screening methods and it is necessary to determine which is the most effective and which are the periods or typology of lesion (location, size...) to guarantee the best result for them to be effective and efficient. This study on the basis of the Population Based CCR screening Programme in the Basque Country, following a rigorous methodology in the diagnosis of both SCs and ICs, presents relevant data regarding both the methodology used as well as results of interest. The validity of these results is based on a programme with a high participation rate and acceptance of the diagnostic tests including colonoscopy, an effective cross-referencing between databases and adequate follow up in a public health system with universal coverage.

Various limitations can be found in the study's findings. One of these is that when comparing FIT ICs to post-colonoscopy Interval Cancers, the latter are

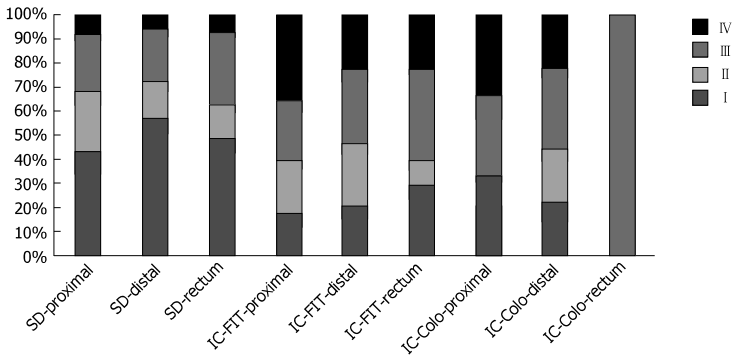
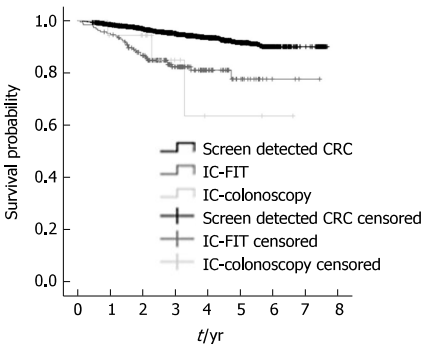


Figure 1 Distribution of colorectal cancer stages by location and type.



	1-yr survival	3-yr survival	5-yr survival
Screen detected CRC	98.5%	95.0%	91.6%
IC FIT	95.2%	82.4%	77.8%
IC colonoscopy	94.4%	85.0%	63.8%

Figure 2 Kaplan-Meyer survival curve by different colorectal cancer types.

underestimated as they require a longer follow-up time and therefore the number of cases could increase in the next few years, hence the figures for post-colonoscopy ICs should be considered with caution. The same is not true regarding the data related to each individual case and their characteristics which justify the importance of this study.

Another limitation of this study is not having taken other risk factors of patient-related ICs into account, such as habits or other biochemical or genetic markers in order to provide a more detailed analysis. These factors are to be explored in prospective future studies. Advanced Adenomas were not analyzed either, as they were in the study by Stegeman *et al*[18]. In the FIT arm (OC Sensor) of the clinical trial, with a cut off of 50 ng/100 mL, defined a person with an advanced neoplasia (AA + CRC) found in a colonoscopy as a false negative. In Stegeman *et al*[18] study, of 1112 participants, 65 (64%) had a false negative result, age (OR = 1.04 per additional year) and smoking (OR = 2.02) were found to be risk factors and sensitivity in women was lower. However, these results coincide with our programme's regarding age and sex. The classification and definition used by Sanduleanu *et al*[19] was also employed our this study, using a modified Delphi methodology defining Interval Cancer as a "colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam" (Table 5). Classification was established based on the systematic revision from January 2004 to January 2014, checking the time of diagnosis, location, stage and histology as well as the etiology (missed, incompletely resected polyps or biological factors associated with a more rapid progression). In the afore-mentioned revision, people with hereditary CRC syndromes or inflammatory bowel diseases were excluded. This classification used in our study will allow a more standardized comparison of the results, which has not happened in previous studies.

Our results show similarities to those found by Zorzi *et al*[20] in Italian CRC screening programmes. In these studies, ICs which had had a negative result with only a FIT (OC-Sensor in 4 programmes and FOB Gold in one of them with a cut-off of 100 ng/100 mL) were analyzed. The follow-up period was from 2002-2007 in 267789 invitations *via* linkage with hospital discharges and an active search in clinical histories and pathological anatomy reports. Of the 126 ICs identified, compared with the expected 572 cases, 15.3% and 31.0% were found in the first and second period (interval-years), respectively. Of the total number of cases identified, in 86 cases with known stages, 21.2% were stage Ⅰ, 22.3% stage Ⅱ and 56.5% stages Ⅲ/Ⅳ. The most advanced stage was found in the proximal colon (76.6% as opposed to 46.8% in the distal colon above the splenic flexure). The sensitivity for the proximal colon was 68.3% (95%IC: 57.7%-76.8%). Even though cases of those not invited and not participants were not analyzed, the most frequent cases in men with ICs and in the left-sided colon (distal colon and rectum) coincided exactly with those shown by Gill *et al*[21] in their comparative study of SCs (322 cases), ICs (192 cases), controls

Table 5 Hazard ratios and 95%CI for interval cancer *vs* screen-detected cancers

	Hazard ratio	95% CI	*P* value
Sex			
Female (ref)			
Male	1.39	1.01-1.93	0.049
Age (yr)			
50-54 (ref)			0.451
55-59	1.37	0.79-2.36	0.258
60-64	1.22	0.72-2.07	0.463
65-69	1.47	0.89-2.44	0.137
Deprivation Index			
1 (least deprived) (ref)			0.839
2	0.89	0.54-1.46	0.639
3	1.01	0.63-1.62	0.956
4	0.90	0.54-1.51	0.696
5 (most deprived)	1.16	0.72-1.88	0.537
Location			
Rectum (ref)			< 0.001
Proximal[1]	1.17	0.78-1.77	0.456
Distal[2]	0.56	0.39-0.82	0.003
Stage			
Ⅰ (ref)			< 0.001
Ⅱ	1.99	1.11-3.54	0.020
Ⅲ	3.67	2.31-5.83	< 0.001
Ⅳ	26.54	17.37-40.56	< 0.001
CRC type			
Screen detected CRC (ref)			< 0.0001
IC FIT	3.31	2.25-4.85	< 0.0001
IC colonoscopy	3.49	1.11-10.97	0.032

[1]Caecum, ascending, hepatic flexure, transverse; [2]Splenic flexure, descending.

never invited (511) and non-participants (311) in the National Health Service. Although these were done with gFOBT, in which ICs were found to be more frequent in men (60.4%, $P = 0.003$), in the left-sided colon (66.7%, $P = 0.003$). However, the study undertaken by Steel *et al*[22], points out that where location is concerned, screening cancers are diagnosed in earlier stages than interval cancers in the colon (Ⅰ-Ⅱ: 62.2% *vs* 21.5%) but not in the rectum (Ⅰ/Ⅱ: 54.3% *vs* 49.9%); unlike in our study in which all screening cancers were diagnosed in earlier stages than those of interval cancers.

There was a significant reduction in the detection rate of SCs in subsequent rounds, which was also seen in ICs. When comparing the three rounds of screening with gFOBT of 48500 invitations with an average participation rate of 61.8%, 57.0% and 58.7% respectively, Moss *et al*[23] found a sensitivity of 71% and 50% in men and women, respectively, in the first round and 65% and 51%, respectively, in the second round, observing the same pattern of reduction. In our study, the detection rates of ICs were found to have the same trend, which points to the fact that screening is a protective factor, corroborated in our study by the high participation rate. In this sense, no significant differences were found regarding participation in SCs and ICs, unlike those found by Steele *et al*[24], who categorized the cancers detected in Scotland with the gFOBT Programme according to the pattern of participation, finding that of the 1927 CRC detected, 405 were SCs, 529 were ICs and 993 CRC in people who had not participated in over 2 years, and of which 658 had never participated. The stage was similar in those who had participated one, two or three times, indicating that it was not likely that the prognosis of SCs would be worse if it had not been detected in the first invitation. Similarly, differences were found between SCs and ICs in the pattern of participation.

Regarding the study by Garcia *et al*[25], differences were found in the detection rate of ICs in rounds. An increase was observed, even though different tests were used in four invitations with gFOBT and FIT, and a shorter follow-up period than in our case, 30 mo of monitoring (30480 tests carried out), finding 97 SCs, 74 ICs after a negative test result, 17 after an inconclusive result and 2 in post-colonoscopy follow-up. The rate of ICs increased in the rounds (32.4%-46.0%). In their study, they also found that the ICs were found predominantly in the rectum (OR = 3.66, 95%CI: 1.51-8.88), as opposed to our study in which they were more commonly found in a proximal location in the case of IC-FIT and distal in IC-colonoscopy. However, very similar data were found regarding the most advanced stages of ICs ($P = 0.025$) and there were no significant differences regarding sex or location.

Many studies published over the last few years have tried to study the impact of ICs in screening programmes as well as the factors associated with its appearance. Robertson *et al*[26] study, which monitored 9167 patients who had had a colonoscopy with adenomas diagnosed after a follow-up of an average of 47.2 mo, identified 58 ICs, 0.6%, similar to our findings of IC-colonoscopy (0.7%). Fifty-two percent of the CRC were classified as possible missed lesions, 24% as probable new lesions and 19% possibly related to a previous and incomplete resection of polyp. One of the risk factors associated with an IC-colonoscopy could therefore be an incomplete resection, which was shown in 11% of the cases in our study, which is an important fact in the quality of the programme and its possible consequences. le Clercq *et al*[27], in their follow-up of people diagnosed with CRC (5107 patients) five years after an index colonoscopy, where 147 ICs were identified or postcolonoscopy CRCs (PCCRCs) found that 8.8% were seen to have had an incomplete resection in the previous colonoscopy. Location could also be another risk factor to be taken into account. In this study as well as others which have been published in recent years [Brenner *et al*[28], Samadder *et al*[29] and Richter *et al*[30], a proximal location or right-sided colon seem to be a risk factor when developing an IC; similar to our study in which a proximal location was significantly more frequent than distal]. These locations would benefit from further

targeted research.

Moreover, the study by Samadder *et al*[29], carried out on 26851 patients who had had a colonoscopy, found 159 ICs which developed between 6-60 mo after the colonoscopy. In 57.2% of the cases, previous adenomas had been identified, which is a similar percentage to our study (61.1%). As in other studies, another factor associated with IC is the stage. In the study by Samadder *et al*[29], as well as that by Brenner *et al*[28], ICs are diagnosed in more advanced stages than screening cancers, which also coincides with our study.

Neither sex nor age seem to play an important part in the diagnosis of an IC. Samadder *et al*[29], like our study, did not find any relation between these two factors. On the other hand, Richter *et al*[30] identify being over the age of 60 as a risk factor. These differences could be due to the context of implementation of the programmes, but new studies should corroborate or reject this hypothesis.

Another key point in screening programmes is the f-Hb cut-off. In a study carried out by Digby *et al*[31] with FIT analyzing interval cancers, they concluded that the average value of f-Hb just before the round prior to the diagnosis of interval cancer (2.8 μgr f-Hb/g faeces) is much lower than the cut-off used most frequently in screening programmes (20 μgr f-Hb/g Faeces). In this study, by reducing the cut-off to 10 μgr f-Hb/g Faeces, the rate of positives would increase from 2.4% to 9.4%, with an important increase in the need for colonoscopies (increasing the number of false positives), which would increase the proportion of interval cancers by 38.3%. In this study, a similar average of f-Hb to this study was observed, so interval cancers do not seem to have f-Hb levels close to positive in previous rounds. This fact could reduce both cut-off and sensitivity without an important increase in the number of colonoscopies needed. Moreover, it is considered that an increase in false negatives would affect the balance risks/benefits of the programmes, increasing the risk for healthy people unnecessarily and reducing the number needed to harm (NNH).

In our study, a survival pattern was seen to be greater in SCs and also in women, even though significant differences were not found in the deprivation index. These data are in keeping with those analyzed by Gill *et al*[32], although a different classification of the stage was used in our study. In their study, 322 SCs were compared with 192 ICs with gFOBT, according to their stage, and differences were found in survival in stages Dukes C and D, higher in SCs than in ICs (P = 0.014 and P = 0.04, respectively). In fact, Cox's proportional hazards regression showed that Dukes' stage, location of tumour and diagnostic group (HR = 0.45, 95%CI: 0.29-0.69, P < 0.0001) as SCs were all found to have a significant impact on patients' survival.

These data also coincide with the study carried out by Morris *et al*[33], in which a better prognosis is estimated, with earlier stages in screening cancers (95.9% one-year survival rate) and interval cancers (78.4% one-year survival rate), which is the greatest difference when compared to our study. Patients with screening cancers were offered a higher percentage of treatments with curative intent than those with interval cancers, which is the same as in our study.

On the basis of our results, there are a wealth of options, among which a comparison of CRCs in people who were not invited (in fact, total coverage was not achieved until the beginning of 2014), people who have not participated in any of the rounds of the programme, people who refused a colonoscopy after a positive test and CRC detected during the scheduled follow-up stand out. These comparisons would help us to know the programme's outcomes and quality? more precisely and the impact of early detection by screening as opposed to other strategies, as developed by Morris *et al*[33].

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COMMENTS

Background

Colorectal cancer (CRC) is one of the main leading causes of death in the world. There is a consensus that population based screening programmes help improving life expectancy and quality of life of those suffering from CRC by early detecting CRCs and early management of patients. Interval Cancers in CRC screening programmes could be seen as failures of detection and they are due to the inexistence of diagnostic tools that ensure 100% sensitivity without harming healthy people (false positives).

Research frontiers

Except for those well-known genetic disorders that are directly linked to CRC (5% of the CRC) to whom personalised strategies are proposed, the rest of the population are managed equally in CRC population based CRC screening programmes. In this sense, there is a need to know the characteristics of interval cancer (ICs), in order to achieve a better understanding of CRC development and thus, propose context and patients' tailored strategies that could improve the efficiency of CRC screening programmes while innovators are trying to find more accurate diagnostic tools.

Innovations and breakthroughs

This research has studied the differences among ICs and Screening-detected cancers (SCs) on the basis of a high rate participation and population based screening programme (100% coverage and more than 70% participation rate). When studying ICs and SCs we have found that the survival rate of SCs is higher than ICs. Furthermore, we observed relation between ICs, lesion location and stage.

Applications

These findings help designing more efficient and tailored strategies that reduce

unnecessary harm and improve current achievements regarding quality of life and overall life expectancy. Under current diagnostic paradigm, these findings can define a less harmful and more efficient alternative to those that propose an increase of diagnostic cut-off points to improve detection while increasing harms (false positives) and costs (increasing number of unnecessary colonoscopies).

Terminology

Interval cancer refers to lesions that are detected within the periods in which no diagnostic strategies are performed. Interval Cancers FIT (IC-FIT) refers to interval cancers that are detected after a negative FIT and before the following invitation inside a CRC screening programme. In the case, the period among invitations is two years. Interval cancers colonoscopy (IC-colonoscopy) refers to interval cancers that are post-confirmatory colonoscopy cancers following a positive FIT and before a follow-up colonoscopy. SCs refer to lesions that have been detected within the programme in each round.

Peer-review

It's an interesting and informative manuscript, although the manuscript has a little complicated design to understand, especially in terms of data presentation.

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PROYECTO CRIBEA: LESIONES DETECTADAS EN SEIS PROGRAMAS POBLACIONALES DE CRIBADO DE CÁNCER COLORRECTAL EN ESPAÑA

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RESUMEN

Fundamentos: En este estudio se presentan los resultados de seis programas poblacionales de cribado de cáncer colorrectal desde 2005 a 2012 (Cataluña, Valencia, Murcia, Cantabria, País Vasco y Canarias) que utilizan diferentes tipos de test de cribado de sangre oculta en heces (SOH) bienal. El objetivo fue describir y comparar los resultados en cuanto a lesiones detectadas tanto por programa, participación, sexo, edad, tipo de test y comunidad autónoma.

Metodos: Estudio de cohorte retrospectivo de las personas participantes en al menos una ronda completa cuya edad estaba comprendida entre los 50 y los 74 años. Lesiones consideradas: adenomas avanzados (AA), cáncer aolorrectal invasivo (CCR) y la suma de ambos, neoplasia avanzada (NA). Se realizó un nálisis de regresión logística y estudio de tendencias temporales.

Resultados: Se obtuvieron 1.995.719 participaciones, lo que supuso el 46,7% de las invitaciones a participar. Se detectaron 21.228 neoplasias avanzadas (2.813 CCR y 18.415 AA). Se observaron diferencias en la detección de neoplasia avanzada (NA) entre los programas variando entre 15,1‰ y 35,8‰ participantes. La participación se relacionó con las tasas de detección (OR: 1,25 en 40-60% de participación). El test inmunoquímico cualitativo obtuvo una OR de 4,79 y el cuantitativo de 7,30 sobre guayaco. Los hombres tuvieron una OR de 2,73 sobre las mujeres, observándose en el 2012 una tasa de detección de neoplasia avanzada en hombres y mujeres de 33,1 y 14,2 x 1.000 respectivamente.

Conclusiones: El tipo de test resultó el factor más determinante en la detección de lesiones. Las tendencias temporales mostraron un aumento de la tasa de detección por el cambio de test a partir del 2010.

Palabras clave: Cribado de cáncer, Cáncer colorrectal, Adenoma, Detección precoz de cáncer, Test de cribado de cáncer, Programas nacionales de salud.

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ABSTRACT

CRIBEA Project: Lesions Detected in Six Spanish Colorectal Cancer Screening Population Based Programmes

Background: In this study, the results of six Colorectal Cancer Screening Population Programmes are shown (Catalonia, Valence, Murcia, Cantabria, the Basque Country and the Canary Islands collected between 2005 and 2012. These programmes use the faeces occult blood test (FOBt) biennial. Objective: To determine and compare the results of lesions detected by the programmes, participation, sex, age and test used.

Methods: Retrospective cohort study based on people invited, aged between 50-74 years, in at least a complete round. Lesions considered: Advanced Adenomas (AA), Colorectal Invasive Cancer (CRC) and both of them, known as Advanced Neoplasia (AN). Logistic Regression and time trends are used.

Results: 1,995,719 of invitations registered, with an average participation-rate of 46.7%. 21,228 Advanced Neoplasias (2,813 CRC and 18,415 AA). Differences in detection rates observed between programmes (varying from 15.1‰ to 35.8‰ between participants). Participation rates were related to lesions' detection rates (OR 1.25 in 40-60% of participation). . Inmunochemical qualitative test showed an OR of 4.79 and quantitative test an OR of 7.30 over the guaiac test. Men showed an OR of 2.73 with respect to women. In 2012 the Advanced Neoplasia rate for women and men was 33.1 and 14.2 by 1,000 participants.

Conclusions: The test used was the most important factor for detecting lesions. Time trends showed an increase in detected lesions caused by the change of the type of test in 2010.

Keywords: Cancer screening, Colorectal cancer, Adenoma, Early detection of cancer, Cancer screening test, National Health Programs

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INTRODUCCIÓN

El cáncer colorrectal (CCR) es la tercera neoplasia maligna más frecuentes en el mundo y la cuarta en mortalidad si consideramos ambos sexos. En hombres es el segundo tumor con 746.298 (10,0%) del total, al igual que en las mujeres con 614.304 (9,2%) casos encontrándose diferencias geográficas y por sexos en cuanto a incidencia y mortalidad, siendo más frecuente en regiones desarrolladas y en hombres. España ocupa una situación intermedia dentro de la región europea, con 19.261 nuevos casos en hombres (43,9 ASRi) y 12.979 en mujeres (24,1 ASRi) estimados para el 2012. En mortalidad, para el mismo periodo, se estimaron 8.742 casos en hombres (37 tasa de incidencia estandarizada por edad ó ASRi) y 5.958 en mujeres (8,4 ASRi). Para los próximos 5 o 10 años se ha estimado un incremento tanto de incidencia como de mortalidad por esta causa[1].

El cribado de CCR ha demostrado ser una estrategia coste-efectiva para reducir la mortalidad y la incidencia a largo plazo independientemente del método utilizado, sangre oculta en heces (SOH), colonoscopia o sigmoidoscopia[2,3]. En el caso del cribado con SOH la evidencia disponible muestra una reducción de la mortalidad por esta causa de hasta el 14%[4,5,6,7] siendo el método más extendido a pesar de demostrarse disminuciones mayores con la colonoscopia y sigmoidoscopia[8,9] según refleja una revisión global de métodos de cribado publicada en recientemente[10].

En España el método utilizado desde el comienzo de los programas de cribado es la detección de SOH, siguiendo las recomendaciones europeas incorporadas en la Estrategia Nacional del Cáncer, ratificada en 2009[12]. Los programas son poblacionales y están integrados en una Red de Cribados que permiten la estandarización y las evaluaciones según criterios establecidos[13] y acordes con la Guía Europea[14]. En 2014, el Ministerio de Sanidad incorporó en la Cartera Básica de Servicios el cribado poblacional de CCR dirigido a mujeres y hombres de 50 a 69 años de edad, que no presentan riesgo genético o familiar detectado, mediante la detección de SOH bienal y colonoscopia como prueba de confirmación diagnóstica, teniendo como objetivo cubrir a toda la población diana estatal en 2025[15].

Algunos programas empezaron utilizando como test de cribado la detección de SOH basada en resina de guayaco (SOHg). Estos programas se cambiaron al test inmunoquímico (FIT) al evidenciarse una mayor aceptación de la población y mejora en las tasas de detección[16,17]. Recientemente un metaanálisis mostró también mayores tasas de sensibilidad y especificidad para el FIT[18].

La participación en los programas es un factor clave para determinar su impacto a medio y largo plazo[19,20]. Existe evidencia de que factores como la edad, el sexo y las desigualdades socioeconómicas influyen en la participación y la detección de lesiones[21].

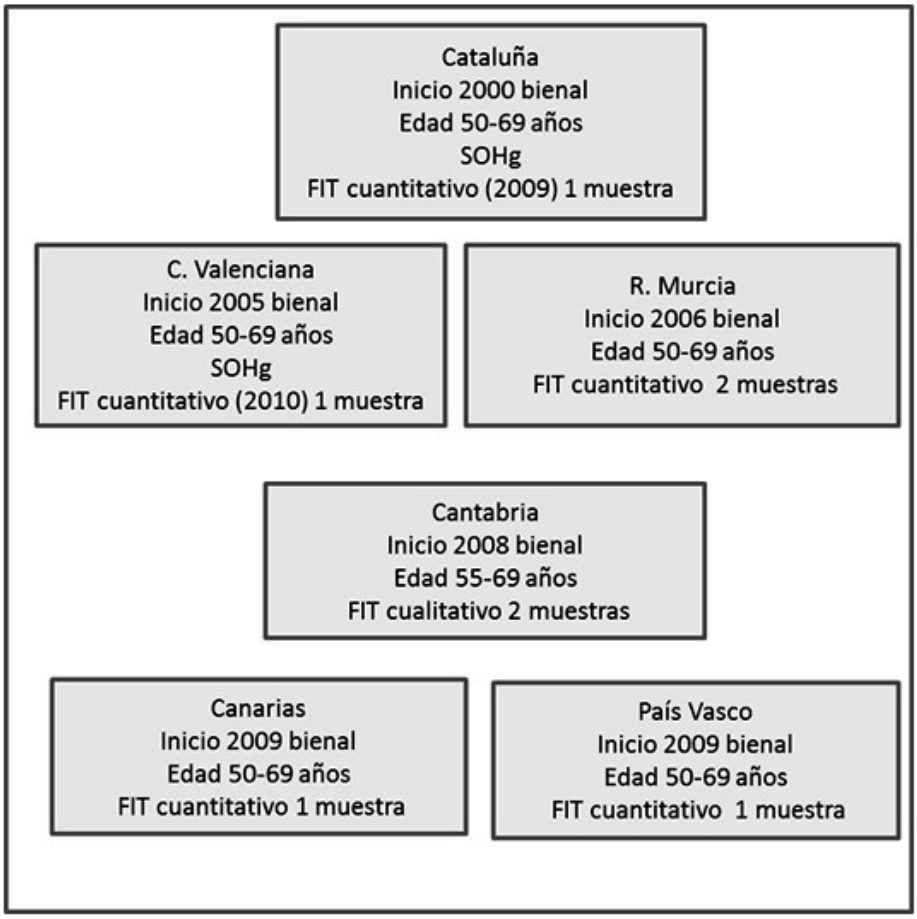
El objetivo del estudio fue describir y comparar los resultados de seis programas en cuanto a lesiones detectadas tanto por programa, participación, sexo, edad,tipo de test y comunidad autónoma.

SUJETOS Y MÉTODOS

Diseño. Este estudio forma parte del proyecto CRIBEA. Se trata de un estudio retrospectivo de una cohorte de hombres y mujeres de 50 a 74 años invitados a participar en alguno de los 6 Programas de Cribado de España: Comunidad Valenciana, Murcia, Cataluña, Cantabria, País Vasco y Canarias. Se tuvieron en cuenta las características de todos los programas y los test utilizados (figura 1).

Periodo de estudio. Las invitaciones a participar se cursaron entre 2005 y 2012. Todos los participantes completaron al menos una ronda de cribado. No se incluyeron datos del período 2000 a 2004 por dificultades para realizar la recogida y estandarizar las variables.

Figura 1
Características de los Programas de Cribado incluidos en CRIBEA



Se elaboró un protocolo conjunto de variables sobre características personales, características organizativas y de resultados. Las fuentes utilizadas fueron los datos propios de los programas y búsqueda activa en resultados no disponibles. Para obtener una base de datos común se vincularon los datos de todos los programas. La información para el estudio fue anonimizada, siendo aprobado el proyecto por los comités de ética regionales.

Variables. Comunidad autónoma, año de invitación, sexo y edad en el momento de la invitación, tipo de invitación (primera invitación/sucesiva), participación (inicial primera invitación/inicial sucesiva invitación/sucesivo), tipo de test utilizado (SOHg), FIT cualitativo y FIT cuantitativo, resultado del test utilizado (positivo/negativo), colonoscopia realizada en cribado positivo, número de adenomas avanzados (AA) detectados (≥3 adenomas y/o al menos 1≥10mm y/o componente velloso y/o displasia de alto grado) y cánceres colorectales invasivos detectados (CCR) (≥pT1). Se consideró neoplasia avanzada a la suma de AA y CCR (NA).

En el momento de la invitación se excluyó a personas con CCR previo al cribado, colonoscopia previa en los últimos 5 años y personas con enfermedades graves. Se consideraron invitaciones válidas las que no habían sido devueltas por correo por dirección desconocida y participantes a las personas que, teniendo una invitación válida, habían realizado la prueba de cribado con resultado válido (negativo/positivo).

No se incluyó como variable la estrategia específica de invitación de cada programa.

Se definió participación en la colonoscopia la tasa de colonoscopias realizadas en los casos positivos y con un resultado definitivo en cuanto a detección de lesiones. En todos los casos se registró la lesión más severa.

Las tasas de detección se expresaron en personas con AA/CCR/NA x 1.000 participantes.

No se analizaron los estadíos del CCR por haberse utilizado diferentes nomenclaturas y clasificaciones en los programas. Se excluyó el análisis de las complicaciones de las colonoscopias por ser objeto de otro estudio.

No se analizaron otras características individuales, como el nivel socioeconómico, al no disponerse de asignación de quintiles de privación en todas las regiones.

Los resultados se agruparon en tres frupos de edad: menores de 55 años, entre 55 y 64 y mayores de 65 años). Se construyó un índice de participación para establecer comparaciones (<40%; 40-60% y >60%).

En el análisis univariado se compararon las tasas de detección de lesiones (AA, CCR y NA) con la tasa y el tipo de participación, sexo, grupo de edad y tipo de test de cribado. En el análisis de regresión logística se calcularon las odds ratio (OR) de la detección de cada tipo de lesión para cada categoría del resto de variables y ajustando por todas ellas. Se analizaron las tendencias temporales por sexo y grupos de edad de ≤60 y >60 años.

Se utilizó el programa SPSS vs 22 y R para Windows.

RESULTADOS

En la tabla 1 figuran los principales indicadores por comunidades autónomas, correspondiendo la tasa más alta de participación al País Vasco (66,6%) seguido de Murcia (52,5%). Se observaron también diferencias en la tasa de detección de neoplasia avanzada y cáncer, correspondiendo a Murcia la más alta de adenoma avanzado por mil participantes (33,6‰) y la más baja a Cantabria (16,3‰). En la tabla 2 se presentan los resultados de la variabilidad encontrada en cuanto a tasas de detección que resultaron ser superiores en tasas de participación superiores al 60% en AA y CCR (25,4‰; IC 95% 24,9-25,9) y 3,6‰; IC 95% 3,4-3,8) respectivamente. La tasa de detección también fue superior en Inicial Primera invitación para ambas lesiones (22,2‰ IC95%: 21,9-22,6 y 3,3‰ IC95% 3,2-3,4). Se observó en hombres una tasa para NA del 34,6‰ (IC95%:34,1-35,0) y en mujeres de 12,9‰ (IC95%: 12,6-13,2), así como mayor tasa de detección de NA en personas de más de 65 años (28,7‰; IC95%:22,5-23,1).

El test cuantitativo detectó el 23,8‰ (IC 95% 23,5-24,1) de AA y cáncer sobre SOHg y el FIT cualitativo el 3,4‰ (IC95%: 3,2-3,5).

En el análisis multivariante ajustado por edad y sexo (tabla 3) se observó cómo la participación de 40-60% aumentaba en OR: 1,33 (IC95%: 1,28-1,38) la tasa de detección de AA, disminuyendo la de CCR (OR:0,86;IC95%: 0,78-0,95) a diferencia de la participación superior al 60% tuvo una OR:1,02;IC95%:0,92-1,12).

El tipo de kit resultó ser el factor que más determinó la probabilidad de detectar AA, con un OR:6,44;IC95% 5,69-7,29 al utilizar

Tabla 1
Indicadores por Programas de cribado 2005-2012

Comunidad autónoma	Invitaciones válidas	Participantes	Participación	Positivos	Positividad (%)	Colonoscopias	Cumplimentación colonoscopias %	TD AA (‰)	TD CCR (‰)	TD NA (‰)
Canarias	105.347	40.824	38,8	2.339	5,7	2.233	95,5	18,6	5,2	23,8
Cantabria	129.045	45.964	35,6	3.220	7,0	2.016	62,6	16,3	3,1	19,4
Catalunya	614.758	221.215	36,0	10.769	4,9	9.477	88,0	15,6	2,7	18,3
Valencia	540.590	242.302	44,8	10.158	4,2	8.830	86,9	12,7	2,4	15,1
Murcia	156.526	82.237	52,5	8.800	10,7	7.844	89,1	33,6	2,3	35,8
País Vasco	449.453	299.377	66,6	19.632	6,6	18.330	93,4	25,4	3,6	29,0
Total	1.995.719	931.919	46,7	54.918	5,9	48.730	88,7	19,8	3,0	22,8

*Invitaciones válidas: personas invitadas cuya carta no ha sido devuelta por domicilio desconocido. **TD AA: tasa detección adenomas avanzados x 1000 participantes; TD CCR: tasa detección cáncer colorrectal x 1000 participantes; TD NA: tasa detección neoplasia avanzada x 1000 participantes.

Tabla 2
Variabilidad de las tasas de detección de lesiones según participación, sexo, edad y tipo de test

		TD* AA	IC95%	TD* CCR	IC95%	TD* NA	IC95%
Tasa de aprticipación	<40%	16,1	15,7-16,6	3,1	2,9-3,3	19,2	18,8-19,7
	40-60%	18,1	17,7-18,6	2,4	2,2-2,6	20,4	19,9-20,8
	>60%	25,4	24,9-25,9	3,6	3,4-3,8	29,0	28,5-29,6
Número de participación	Inicial primera	22,2	21,9-22,6	3,3	3,2-3,4	25,5	25,2-25,9
	Inicial no primera	19,2	18,3-20,2	4,1	3,6-4,6	23,3	22,2-24,4
	Sucesiva	13,9	13,5-14,4	2,1	1,9-2,3	16,0	15,6-16,5
Sexo	Mujer	11,0	10,7-11,3	1,9	1,7-2,0	12,9	12,6-13,2
	Hombre	30,2	29,7-30,7	4,4	4,2-4,6	34,6	34,1-35,0
Grupo de edad	<54 años	15,2	14,7-15,6	1,6	1,5-1,8	16,8	16,3-17,3
	55-64 años	20,3	19,9-20,7	3,1	2,9-3,2	23,4	23,0-23,8
	>65 años	24,0	23,4-24,6	4,6	4,4-4,9	28,7	28,0-29,3
Tipo test SOH	Guayaco	2,6	2,4-2,9	1,4	1,2-1,6	4,0	3,7-4,3
	Inmunoquímico cualitativo	16,3	15,2-17,4	3,1	2,6-3,6	19,4	18,3-20,7
	Inmunoquímico cuantitativo	23,8	23,5-24,1	3,4	3,2-3,5	27,2	26,9-27,6

*TD AA: tasa detección adenomas avanzados x 1000 participantes; TD CCR: tasa detección cáncer colorrectal x 1000 participantes; TD NA: tasa detección neoplasia avanzada x 1000 participantes

FIT cualitativo y una OR:9,86;IC95% 8,94-10,87 con FIT cuantitativo sobre SOHg.

En la tabla 3 y la figura 2 se observa que en todos los periodos los hombres presentaron tasas de detección de NA del 27,3‰ (IC95%: 21,3-33,2) en 2009 y del 33‰ (IC95%: 32,0-34,1) en 2012, respecto a mujeres que presentaron para el mismo periodo el 6,1‰ (IC 95% 2,3-9,9) en 2009 y el 14,2‰ (IC 95% 13,6-14,9) en 2012. En ambos casos se observaron incrementos significativos y tendencias superiores a partir del uso de FIT en 2010.

En el caso de la edad (figura 3) se observó que las personas mayores de 60 años presentaron también una probabilidad de tener NA del 21,9‰ (IC95%: 20,6-23,2) y del14,1‰

Tabla 3
Análisis multivariante para determinar factores relacionados con las tasas de detección

Variable			OR*	OR IC95%	p	Curva ROC	IC 95% curva ROC
Detección de adenomas avanzados	Tasa de participación	<40% (referencia)	1		< 0,001	0,712	0,709-0,716
		40-60%	1,33	1,28-1,38	< 0,001		
		> 60%	1,22	1,17-1,27	< 0,001		
	Sexo	Mujeres (referencia)	1				
		Hombres	2,78	2,69-2,87	< 0,001		
	Edad	< 55 años (referencia)	1		< 0,001		
		55-64 años	1,55	1,49-1,61	< 0,001		
		≥65 años	1,93	1,85-2,02	< 0,001		
	Tipo de test	Guayaco (ref.)	1		< 0,001		
		Cualitativo	6,44	5,69-7,29	< 0,001		
		Cuantitativo	9,86	8,94-10,87	< 0,001		
	Tipo de participación	Inicial 1ª ref.			< 0,001		
		Inicial no 1ª	0,95	0,90-1,01	0,118		
		Sucesiva	0,59	0,57-0,61	< 0,001		
Detección de cancer colorrectal	Tasa de participación	<40% (referencia)	1		0,002	0,685	0,675-0,694
		40-60%	0,86	0,78-0,95	0,003		
		> 60%	1,02	0,92-1,12	0,740		
	Sexo	Mujeres (referencia)	1				
		Hombres	2,34	2,16-2,53	< 0,001		
	Edad	< 55 años (referencia)	1		< 0,001		
		55-64 años	2,09	1,87-2,34	< 0,001		
		≥65 años	3,32	2,95-3,74	< 0,001		
	Tipo de test	Guayaco (referencia)	1		< 0,001		
		Cualitativo	1,67	1,49-2,34	< 0,001		
		Cuantitativo	2,41	2,09-2,78	< 0,001		
	Tipo de participación	Inicial 1ª ref.	1		< 0,001		
		Inicial no 1ª	1,24	1,08-1,41	0,002		
		Sucesiva	0,60	0,55-0,67	< 0,001		
Detección de neoplasia avanzada	Tasa de participación	<40% (referencia)	1		< 0,001	0,707	0,704-0,710
		40-60%	1,25	1,21-1,30	0,001		
		> 60%	1,19	1,14-1,23	< 0,001		
	Sexo	Mujeres (referencia)	1				
		Hombres	2,73	2,65-2,81	< 0,001		
	Edad	< 55 años (referencia)	1		< 0,001		
		55-64 años	1,60	1,55-1,66	< 0,001		
		≥65 años	2,08	1,99,16	< 0,001		
	Tipo de test	Guayaco (referencia)	1		< 0,001		
		Cualitativo	4,79	4.,31-5,32	< 0,001		
		Cuantitativo	7,30	6,74-7,90	< 0,001		
	Tipo de participación	Inicial 1ª (referencia)	1		< 0,001		
		Inicial no 1ª	0,99	0,94-1,05	0,001		
		Sucesiva	0,59	0,57-0,61	< 0,001		

*OR=Odds Ratio; IC= Intervalo de Confianza; ROC: Característica Operativa del Receptor

Figura 2
Tasas de detección de Neoplasia Avanzada por sexo

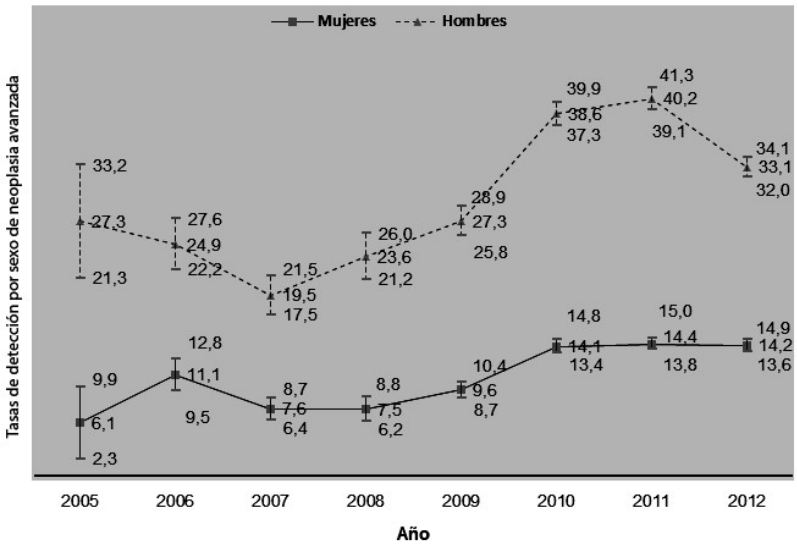
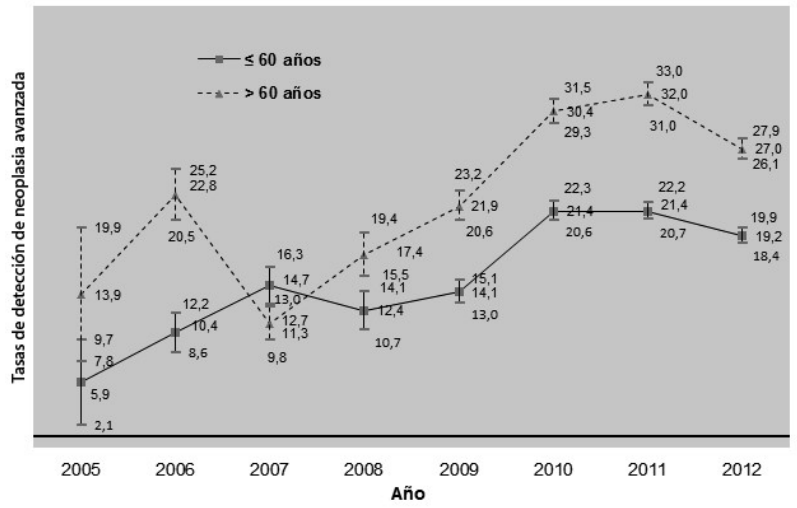


Figura 3
Tasas de detección de Neoplasia Avanzada por grupos de edad



(IC95%: 13,0-15,1) en 2009 que se mantuvo en todos los periodos, si bien en el 2007 se observó una disminución puntual. Las tendencias resultaron también significativas.

DISCUSIÓN

La tasa de participación mostró una relación positiva en el caso de la detección de NA, aunque no parece que un aumento a partir de 60% influya de forma significativa en las tasas de detección. Este efecto puede ser debido a que la mayor participación se produce también con el test inmunoquímico, que detecta mayor número de adenomas avanzados. No obstante, el impacto en la reducción de la morbimortalidad a nivel poblacional pareció estar relacionado con una mayor participación, por lo que es necesario seguir impulsando la participación tanto inicial como en sucesivas rondas garantizando la adherencia a los programas de cribado[11].

Las diferencias en la detección de lesiones de más del doble en hombres que en mujeres tanto en AA como en CCR se correspondió con lo encontrado en la mayoría de los programas[22,23]. Otro factor determinante de la detección de lesiones fue la edad, encontrándose mayor porcentaje de lesiones avanzadas según aumentaba[24]. Estos resultados fueron especialmente relevantes en las primeras rondas, cuyas tasas de detección resultaron mayores y disminuyeron en las sucesivas debido a la detección y extirpación precoz de adenomas avanzados.

Tal cómo se observó en otros programas poblacionales, existió variabilidad en la utilización de las pruebas de cribado, que fueron progresivamente cambiando a FIT cuantitativo, siendo el test utilizado más frecuentemente, acorde con la evidencia disponible de mayor tasa de detección de NA y la posibilidad de elegir el punto de corte, adecuándolo a la capacidad de realizar las colonoscopias de confirmación[10]. En nuestro contexto se utilizan puntos de corte diferentes en el caso del test inmunoquímico cuantitativo, debido a que si bien las marcas proponen 100ng Hb/ml buffer, lo que no resulta equivalente en los test, tal como se demostró en el estudio realizado en el País Vasco que comparaba los test utilizados en España[25].

Tampoco la edad de cribado fue homogénea en el tiempo, si bien la cartera básica de servicios define que esté entre los 50 y 69 años.

Sería importante unificar las unidades de medida y el número de muestras para poder comparar de forma pormenorizada los resultados en los casos de FIT, dado que se apreciaron diferencias estadísticamente significativas en las tasas de detección que podrían corresponder a concentraciones diferentes de hemoglobina por el uso de diferentes marcas comerciales[26]. Este factor ha sido estudiado por la red de programas de cribado con el fin de mejorar la comparabilidad de los resultados.

En nuestro estudio se mostró una tasa de detección de AA prácticamente 10 veces superior con FIT cuantitativo que con guayaco, si bien la tasa de CCR es el doble, ocupando una posición intermedia el uso del FIT cualitativo. La migración a FIT, adoptada por los programas pioneros (Cataluña y Valencia) y el comienzo de los demás con FIT está de acuerdo a la revisión realizada por Tinmouth et al.[27], que recomiendan su uso en programas por su mayor impacto. Hay que tener en cuenta que uno de los programas (Murcia) utiliza FIT cuantitativo con 2 muestras, obteniendo una tasa mayor de detección de lesiones.

De acuerdo al estudio de Zorzi et al[28] en Italia, a medio plazo el uso de FIT podría reducir la mortalidad específica por CCR en hasta un 22% con una sola muestra, punto de corte 20μg/g heces de forma bienal. Así mismo, tanto con FIT como con guayaco se evidencia una probable disminución de la incidencia a largo plazo debido a la extirpación de lesiones precancerosas (AA)[29,30].

En nuestro estudio se registró una tasa de detección de lesiones avanzadas inferior en participantes sucesivos tanto en AA como en

CCR, que mostraría el efecto "protector" de los cribados anteriores en cuanto a especificidad de la prueba[31].

Es decir, no solamente el test de cribado es un factor determinante en la detección de lesiones, sino el seguir participando en el cribado y realizarse la colonoscopia en caso de resultado positivo, ya que las lesiones evolucionan en un periodo largo de tiempo, lo que permite extirpar las avanzadas para impedir su progresión y CCR en estadios precoces.

La principal fortaleza de este estudio es la capacidad de analizar los datos de seis programas poblacionales en España, con diferencias metodológías y tasa de participación. Ello permite comparar el efecto de estas diferencias en la detección de lesiones. Además se han sentado las bases de colaboración y comparación, lo que permite establecer recomendaciones para mejorar la cobertura, la participación y la calidad del proceso y los resultados. Esto puede servir de guía para los programas que se están implantando.

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Implementation of colorectal cancer screening in Spain: main results 2006–2011

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The Spanish Cancer Screening Network involves the participation of all regional programmes and has been working for over 20 years to co-ordinate strategies and implement quality assurance in current and new regional programmes. In colorectal cancer, the target population is the group aged 50–69 years, who are offered biennial testing using the faecal occult blood test in all programmes, with follow-up colonoscopy if the faecal occult blood test is positive. This article presents the main trends, indicators and differences by sex. The main indicators from 2006 to 2011 were analysed: coverage, participation rate, positivity rate, colonoscopy uptake and lesions detected. Annual trends were adjusted by sex and region. In 2011, coverage was 9.74% of the Spanish target population. A total of 1 001 669 first invitations were registered from 2006 to 2011 and 596 649 individuals participated in the programmes (43.83% participation rate). Results were positive in 30 544 individuals (5.47%), with the lowest positivity rate occurring in 2007 (3.06%) and the highest in 2011 (6.30%) ($P<0.001$). In all, 27 568 colonoscopies were registered, with a high compliance rate (90.00% in 2011 and 95.59% in 2007) ($P=0.381$). The adenoma and colorectal cancer detection rates increased over the period, reaching 32.25/1000 and 3.42/1000 participants in 2011, respectively ($P<0.001$ and $P=0.001$). Comparison of differences by sex showed that detection rates were significantly higher in men than in women ($P<0.001$). Participation increased over time and has now reached an acceptable rate. Men show low participation but higher detection rates, indicating the need for further intervention. The Spanish Cancer Screening Network provides common evaluation, performance and organizational benchmarking. ***European Journal of Cancer Prevention*** **26:17–26**

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common in women worldwide. In Spain, it is the first incidental cancer in both sexes. In 2012, 32 240 new cases and 14 708 deaths were estimated and trends for 2020 show a clear increase, similar to other European regions and countries (Ferlay *et al.*, 2012). In Spain, 30 628 new cases of CRC were diagnosed in 2006 and there were 12 877 deaths from this cause. In 2012, these figures increased to 47 874 new cases and 13 204 deaths (Sánchez *et al.*, 2010).

Several systematic reviews have provided evidence that CRC screening decreases mortality rates (Holme *et al.*, 2013; Brenner *et al.*, 2014). To reduce the burden of CRC in the European Union and on the basis of the evidence of screening strategies, in 2003, the European Commission recommended that all states perform population-based screening programmes in individuals aged 50–74 years using the faecal occult blood test (FOBT) (Unión Europea, 2003).

Spain is divided into 17 autonomous regions with a high level of selfgovernment in different issues, such as health service organization and provision. Consequently, healthcare delivery is not necessarily identical, but there is an InterRegional Coordination Board managed by the Spanish Health Ministry that shares and approves

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common strategies and actions in public health and services provision. In 2005, the National Health Cancer Strategy adopted the European CRC Screening recommendation to carry out pilot studies in Spain (Ministerio de Sanidad y Consumo, 2006). This recommendation was ratified in 2009, including the objectives to initiate and continue established programmes with a view to achieving 50% coverage of the target population (average risk population aged 50–69 years) in 2015 (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2010). In the past year, the Ministry of Health has included screening as a basic health service in the National Health Catalogue (España. Orden SSI/2065, 2014).

All regional programmes take part in the Spanish Cancer Screening Network (SCSN). This network has been working for over 20 years to coordinate regional screening programmes, holding annual meetings, launching common research projects and taking part in the European network and related projects. Through the SCSN, quality criteria and assessment indicators are shared and agreed upon among all regional programmes. All documents are available on the web site *http://www.cribadocancer.com*.

In Spain, all regions offer breast cancer screening as a population-based programme and coverage is now 100% for women aged 50–69 years (Ascunce *et al.*, 2013). In addition, cervical cancer screening is offered in all regions, mainly as an opportunistic programme. The CRC screening programme was introduced more recently. Catalonia was the first region to start CRC screening in Spain in 2000, followed by Valencia (2005) and Murcia (2006). The experience of these pilot projects was essential to the development of other programmes in other regions of Spain (Peris *et al.*, 2007; Ascunce *et al.*, 2010; Málaga López *et al.*, 2010; Portillo *et al.*, 2013a).

The present study aimed to analyse the main trends in the implementation of CRC screening programmes in Spain as well the methodology and the main results for the period 2006–2011.

Methods

In 2011, CRC screening programmes (with partial coverage) were implemented in nine Spanish regions and pilot programmes were implemented in another region. For all regions, the common target population consisted of men and women aged 50–69 years. However, some regions implemented their programmes by temporarily inviting a different age bracket.

All programmes are population based and send an individual written invitation to each member of the target population. Programme organization differs among regions.

In general, the screening kit is sent by mail or individuals are referred to their primary healthcare centres to collect the kit, in some cases to a neighbourhood pharmacy.

Testing is performed using the FOBT, guaiac (gFOBT) or faecal immunochemical test (FIT) every 2 years. Not all programmes used the same test brand. One program used HEMOTEST from 2008 to 2014 and two programmes used the guaiac chemical test (gFOBT) from 2000 to 2010.

The Valencia Region used the 'Cenogenics TRI-SLIDE' guaiac test from 2006 to 2010 and the immunoquantitative test from 2010. Catalonia used the 'HEMA-SCREEN' guaiac test until 2009 and then switched to the immunoquantitative test. Therefore, both tests were used during this period (Table 1). Nowadays, all programmes use FIT OC-Sensor and FOB-Gold.

Kits are returned to primary healthcare centres or the pharmacy. The gFOBT and qualitative test were analysed in each health centre. All FIT quantitative immunochemical tests were analysed in public hospitals under quality control measures.

If the test was positive, a colonoscopy was recommended.

The managers of CRC screening (Valencia Region) collected and analysed the methods and results from the all the regional programmes every year. They also presented general trends and comparisons in relation to the main indicators previously discussed and agreed upon at the annual meetings.

Data sources

One of the most important challenges was to standardize data collection and to establish the basis of a detailed working definition of the main indicators according to the Guidelines (Edge *et al.*, 2010; Segnan *et al.*, 2010). All data were collated by sex and age groups considering the test used (gFOBT, FIT quantitative and qualitative) and the cutoff for a positive test used in the quantitative tests.

An important issue was to establish common criteria to exclude individuals from the screening programme: individuals previously diagnosed with CRC (permanently excluded), those with a colonoscopy performed 5 years earlier (temporarily excluded) and those with a familial history of CRC who were followed up by a specific protocol (permanently excluded).

The collated data needed to calculate the indicators were obtained from each regional programme in Excel format.

Main indicators

Indicators were analysed by screening type: initial screening (the initial invitation irrespective of the organizational screening round plus successive invitations for previous never responders) and successive screening (successive invitations for those screened previously).

The main indicators calculated to compare the results were as follows.

Table 1 Characteristics of colorectal cancer screening programmes in Spain, 2011

Autonomous region	Year programme started	Target population total programme[a]	Number of individuals invited for initial screening in each programme[b]	Coverage by invitation (%)[a]	Age group (years)	Programme or pilot	Interval (years)	FOBT	Number of samples	FOBT brand	FOBT change (years)	Cut-off[c]	FIT brand
Canary Islands	2009	446 363	63 475	14.22	50–69	Programme	2	FIT	1	No	No	100 ng/ml	OC-sensor
Cantabria	2008	141 638	77 168	54.48	55–69	Programme	2	FIT	2	No	No	20 μg Hb/g	HEMOTEST
Castile–Leon	2010	612 676	1934	0.32	50–69	Programme	2	FIT	1	No	No	100 ng/ml	OC-sensor
Catalonia	2000	1 651 586	200 809	12.16	50–69	Programme	2	FIT	1	HEMA-SCREEN (gFBOT)	2009	100 ng/ml	OC-sensor
Valencian community	2005	1 143 667	307 427	26.88	50–69	Programme	2	FIT	1	CENOGENICS TRI-SLIDE (gFBOT)	2010	100 ng/ml	OC-sensor
Extremadura	2011	237 063	5595	2.36	50–69	Pilot	2	FIT	2	No	No	100 ng/ml	OC-sensor
Murcia	2006	276 476	94 973	34.35	50–69	Programme	2	FIT	2	No	No	117 ng/ml	FOD-Gold
Basque Country	2009	501 000	235 219	46.95	50–69	Programme	2	FIT	1	No	No	100 ng/ml	OC-sensor
La Rioja	2010	71 347	15 069	21.12	50–69	Programme	2	FIT	1	No	No	100 ng/ml	OC-sensor
Total of regions		10 283 772	1 001 669	9.74									

FIT, faecal immunochemical testing; FOBT, faecal occult blood test; gFBOT, guaiac faecal occult blood test.
[a]By December 2011.
[b]During the entire period 2006–2011.
[c]Cutoffs of the Sentinel and OC-Sensor marks correspond to the cutoff of the HEMOTEST mark (20 μg Hb/g).

Coverage (%): number of individuals invited during 2006–2011 divided by eligible population. Participation rate (%): individuals invited and screened divided by individuals invited. Positive FOBT rate (%): individuals with a positive FOBT result divided by individuals adequately screened. Colonoscopy compliance rate (%): individuals having attended a colonoscopy examination divided by positive cases. Colonoscopy completion rate: individuals with a complete first colonoscopy divided by colonoscopies performed. Advanced adenoma detection rate (‰): individuals with at least one advanced adenoma (detection of intermediate-risk or high-risk adenoma) divided by individuals adequately tested. Adenoma detection rate (‰): individuals with detection of any adenoma (low-risk, intermediate-risk or high-risk adenoma) divided by individuals adequately tested. CRC detection rate (‰): individuals with detection of CRC divided by individuals adequately tested. Positive predictive value (PPV) for advanced adenoma: individuals with detection of advanced adenoma divided by individuals with a performed colonoscopy. PPV for any adenoma: individuals with detection of adenoma (low-risk, intermediate-risk and high-risk adenoma) divided by individuals with a performed colonoscopy. PPV for CRC: individuals with detection of CRC divided by individuals with a performed colonoscopy.

Statistical analysis

Cumulative rates between 2006 and 2011 are shown by type of screening (initial/successive) and by sex and age groups. For each group, Poisson regression models were used to compare indicators by sex and age, adjusted for year and region. A Poisson regression model was also used to compare each indicator with type of screening (initial and successive), adjusted by sex and age groups, year and region.

Time trends in the main indicators are shown by year, from 2006 to 2011. Poisson regression models were used to compare indicators by year of screening, adjusted by sex and region and type of screening.

Time trends per year for men and women are shown in graphs. The χ^2-test was used to compare indicators by sex. Poisson regression models were used for each sex, one model for each indicator, and all models were adjusted by region.

All statistical analyses were carried out using Excel for Windows and R Project for Statistical Computing (Free Software Foundation's GNU General Public License) version 2.14.2.

Results

Table 1 provides details of the programmes in each region, including the target population, screening interval, type of FOBT, number of samples and cutoff value in the case of the immunochemical test. CRC screening

programmes in Spain from 2006 to 2011 included 1 001 669 individuals between the ages of 50 and 69 years, representing 9.74% of the Spanish population in that age group (10 283 772 individuals).

Table 2 shows the results obtained throughout the period, from the start of the programmes to 2011, for initial or successive screening, by age and sex groups. Participation in initial screening was 47.36%. The rates were highest among women and lowest among men aged 50–59 years (43.52%). The positive test rate was highest in initial screening, especially among men aged older than 60 years (8.75%), and lowest in successive screening in women aged 50–59 years.

Colonoscopy compliance rates and colonoscopy completion rates were very similar between different age and sex groups both in initial screening and in successive screening.

The adenoma and advanced adenoma detection rates were higher in initial screening than in successive screening. The highest rates were observed in men older than 60 years of age. The same was true for CRC detection, with the highest rate also being found in initial screening in men older than 60 years of age (6.42/1000). The PPV for advanced adenoma was higher in initial screening (41.06%) than in successive screening (35.73%); similarly, in the case of any adenoma, the PPV was 58.97% as opposed to 56.89%, with the highest values being found in the group of men older than 60 years of age at the initial screening (68.99%). For the PPV for cancer, these differences were also observed, with 6.14% in initial screening and 4.66% in successive screening, and values were highest among men older than 60 years of age at the initial screening.

Table 3 shows trends in the main indicators from 2006–2011. A total of 1 361 286 valid invitations were registered and 596 649 individuals participated in the programmes (43.83% participation rate). The lowest participation rate was found in 2007 (33.28%) and the highest in 2010 (46.97%) ($P < 0.001$ adjusted for sex and region). The initial participation rate was between 30.15% in 2007 and 47.46% in 2010 ($P < 0.001$), whereas for successive screening, participation reached 84.09% in 2008 and 89.28% in 2007 ($P < 0.001$).

The positivity rate in this period was 5.47%. The lowest positivity rate was found in 2007 (3.06%) and the highest in 2011 (6.30%) ($P < 0.001$). Among the total number of colonoscopies indicated, the colonoscopy performance rate was 90.79%. The colonoscopy completion rate was higher than 90% for all years.

The advanced adenoma detection rate (‰) was 18.58/1000 participants and was the highest in 2011 (22.72/1000, $P < 0.001$). The detection rate for any adenoma was 27.09/1000, the highest being in 2011 (32.25/1000, $P < 0.001$). The detection rate for CRC varied widely from 2.17 in 2007 to 3.42 in 2011 ($P < 0.001$).

The PPV for advanced adenoma reached 40.22% and no significant differences were found by year ($P = 0.421$). The PPV for adenoma was 58.64% ($P = 0.593$). Nevertheless, the average PPV for CRC was 5.91%, with a wide variation from 4.98% in 2009 to 6.97% in 2007 ($P < 0.001$).

Figure 1 shows the main trends in the participation rate, positive FOBT rate, colonoscopy compliance and complete colonoscopy rate separately for women and men. As shown by the data, the participation rate increased from 2007 to 2010 ($P < 0.001$). The participation rate was four points higher in women (45.96%) than in men (41.55); in contrast, the positive FOBT rate was three points higher in men (7.01%) than in women (4.16%). The positive FOBT rate also increased in both sexes from 2007 to 2011 ($P < 0.001$).

The colonoscopy compliance and complete colonoscopy rates were above 90% in both sexes for the entire period.

Figure 2 shows the detection rates and PPV in men and women. The advanced adenoma and any adenoma detection rates increased from 2007 in men from 15.95 to 32.96/1000 participants ($P < 0.001$) for advanced adenomas and from 23.58 to 44.91/1000 ($P < 0.001$) for any adenoma. In women, detection of advanced adenomas also increased from 6.67/1000 in 2007 to 11.35/1000 in 2011 ($P < 0.001$) and that of any adenoma increased from 11.51 to 17.72/1000 ($P < 0.001$).

For the CRC detection rate, an increment was reached at the end of the period in men in 2011 [4.66/1000 ($P = 0.003$)]. However, in women, the highest result was found in 2011 (1.96) and the lowest in 2007 (0.99) ($P = 0.053$).

The PPV for advanced adenoma for women ranged between 25.71 and 33.99% ($P = 0.043$) and the PPV for any adenoma ranged between 44.74 and 53.77% ($P = 0.149$). For CRC, the PPV ranged from 4.51% in 2007 to 4.95 in 2008 and 2011 ($P = 0.012$). Similarly, in men, the PPV ranged from 42.57 to 51.73% ($P = 0.686$) for advanced adenomas, from 65.95 to 70.79% ($P = 0.983$) for any adenoma and from 5.19 to 8.91% ($P < 0.001$) for CRC.

All detection rates for advanced adenomas, any adenoma and CRC were higher in men than in women over the study period ($P < 0.001$). A similar pattern was observed for PPV.

Discussion

CRC screening programmes have been implemented since 2000 in Spain and coverage in 2011 was 9.74% (a target population of 10 283 772 and 1 001 669 included in CRC screening programmes). All programmes were

Table 2 Performance indicators of colorectal cancer screening by initial and successive screening and by age and sex

	Initial screening (years)					Successive screening (years)						
Performance indicators[a]	Women 50–59	Men 50–59	Women > 60	Men > 60	Total	Women 50–59	Men 50–59	Women > 60	Men > 60	Total	*P* value[b]	Total
Number of individuals invited (first invitation)	279 937	270 891	232 808	212 438	996 074	33 482	27 309	48 951	38 897	148 639		1 144 713
Number of individuals screened	137 850	117 884	116 019	99 955	471 708	28 405	23 157	41 246	32 133	124 941		596 649
Participation rate (%)	49.24	43.52	49.83	47.05	47.36	84.84	84.80	84.26	82.61	84.06	< 0.001	52.12
P value	< 0.001	< 0.001	< 0.001	Reference		0.001	< 0.001	0.008	Reference			
Number of individuals adequately tested	129 232	108 977	111 902	96 319	446 430	24 679	20 146	37 543	30 070	112 438		558 868
Number of individuals with a positive FOBT result	4784	6914	5709	8426	25 833	825	967	1315	1604	4711		30 544
Positive FOBT rate (%)	3.70	6.34	5.10	8.75	5.79	3.34	4.80	3.50	5.33	4.19	< 0.001	5.47
P value[a]	< 0.001	< 0.001	< 0.001	Reference		< 0.001	< 0.001	< 0.001	Reference			
Number of individuals referred for colonoscopy	4749	6898	5675	8382	25 704	818	961	1296	1585	4660		30 364
Number of individuals having attended a colonoscopy examination	4316	6248	5052	7575	23 191	779	903	1209	1486	4377		27 568
Colonoscopy compliance rate (%)	90.88	90.58	89.02	90.37	90.22	95.23	93.96	93.29	93.75	93.93	0.013	90.79
P value[a]	0.882	0.896	0.438	Reference		0.976	0.768	0.867	Reference			
Number of individuals attending a colonoscopy examination	4316	6248	5052	7575	23 191	779	903	1209	1486	4377		27 568
Number of individuals attending a colonoscopy completion examination	4127	6003	4727	7236	22 093	725	858	1135	1410	4128		26 221
Colonoscopy completion rate (%)	95.62	96.08	93.57	95.52	95.27	93.07	95.02	93.88	94.89	94.31	0.866	95.11
P value[a]	0.575	0.759	0.316	Reference		0.988	0.647	0.791	Reference			
Number of individuals with at least one detected advanced adenoma	1187	2873	1555	3908	9523	187	369	317	691	1564		11 087
Advanced adenoma detection rate (%)	8.61	24.37	13.40	39.10	20.19	6.58	15.93	7.69	21.50	12.52	< 0.001	18.58
P value[a]	< 0.001	< 0.001	< 0.001	Reference		< 0.001	< 0.001	< 0.001	Reference			
Number of individuals with at least one detected adenoma	1872	4099	2478	5226	13 675	348	597	552	993	2490		16 165
Adenoma detection rate (%)	13.58	34.77	21.36	52.28	28.99	12.25	25.78	13.38	30.90	19.93	< 0.001	27.09
P value[a]	< 0.001	< 0.001	< 0.001	Reference		< 0.001	< 0.001	< 0.001	Reference			
Number of individuals with at least one detected cancer	189	305	288	642	1424	23	45	46	90	204		1628
Cancer detection rate (%)	1.37	2.59	2.48	6.42	3.02	0.81	1.94	1.12	2.80	1.63	< 0.001	2.73
P value[a]	< 0.001	< 0.001	< 0.001	Reference		0.022	< 0.001	< 0.001	Reference			
PPV for advanced adenoma (%)	27.50	45.98	30.78	51.59	41.06	24.01	40.86	26.22	46.50	35.73	< 0.001	40.22
P value[a]	< 0.001	< 0.001	< 0.001	Reference		< 0.001	0.071	< 0.001	Reference			
PPV for adenoma (%)	43.37	65.60	49.05	68.99	58.97	44.67	66.11	45.66	66.82	56.89	0.028	58.64
P value[a]	0.005	< 0.001	< 0.001	Reference		< 0.001	0.598	< 0.001	Reference			
PPV for cancer (%)	4.38	4.88	5.70	8.48	6.14	2.95	4.98	3.80	6.06	4.66	0.054	5.91
P value[a]	< 0.001	< 0.001	< 0.001	Reference		0.011	0.626	0.021	Reference			

FOBT, faecal occult blood test; PPV, positive predictive value.

[a]Poisson model results, *P* value associated with age and sex group variable, reference category male > 60 years old, also adjusted for region and year.

[b]Poisson model results, *P* value associated with type of screening variable, initial reference category, also adjusted by age and sex groups, region and year.

Table 3 Time trends of performance indicators of the colorectal cancer screening programmes in Spain, 2006–2011

Early performance indicators[a]	2006	2007	2008	2009	2010	2011	*P* values[b]	2006–11
Number of individuals invited (first invitation)	57 703	116 693	77 115	207 538	359 666	542 571		1 361 286
Number of individuals screened	24 466	38 840	30 294	87 086	168 927	247 036		596 649
Initial participation rate (%)	42.40	30.15	33.42	43.01	47.46	43.92	<0.001	38.90
Successive participation rate (%)	–	89,28	84,09	85,73	84,47	85,05	<0,001	84,06
Participation rate (%)	42,40	33,28	39,28	41,96	46,97	45,53	<0,001	43,83
Number of individuals adequately screened	18 892	36 452	28 681	78 500	165 103	231 240		558 868
Number of individuals adequately screened (first screening)	18 892	30 744	17 421	47 566	150 819	180 988		446 430
Total adequate screening (first screening) (%)	100.00	84.34	60.7	60.59	91.35	78.27		79.88
Number of individuals adequately screened (successive screening)	–	5708	11 260	30 934	14 284	50 252		112 438
Total adequate screening (successive screening) (%)	–	15,66	39,3	39,41	8,65	21,73		20,12
Number of individuals with a positive FOBT result	868	1114	1037	3404	9561	14 560		30 544
Positive FOBT rate (%)	4.59	3.06	3.62	4.34	5.79	6.30	<0.001	5.47
Number of individuals referred for colonoscopy	861	1110	1036	3415	9484	14 458		30 364
Number of individuals attending a colonoscopy examination	810	1061	969	3094	8622	13 012		27 568
Colonoscopy compliance rate (%)	94,08	95,59	93,53	90,60	90,91	90,00	0,202	90,79
Number of individuals attending a colonoscopy examination	810	1061	969	3094	8622	13 012		27 568
Number of individuals attending a colonoscopy completion examination	757	999	896	2972	8227	12 370		26 221
Colonoscopy completion rate (%)	93.46	94.16	92.47	96.06	95.42	95.07	0.757	95.11
Number of individuals with at least one detected advanced adenoma	343	422	346	1201	3522	5253		11 087
Advanced adenoma detection rate (%)	18.16	10.87	12.06	15.30	21.33	22.72	<0.001	18.58
Number of individuals with at least one detected adenoma	495	659	604	1845	5104	7458		16 165
Adenoma detection rate (%)	26.20	16.97	19.94	23.50	30.91	32.25	<0.001	27.09
Number of individuals with at least one detected cancer	53	74	59	154	498	790		1628
Cancer detection rate (%)	2.17	1.91	2.06	1.96	3.02	3.42	<0.001	2.73
PPV for advanced adenoma (%)	42,35	39,77	35,71	38,71	40,85	41,39	0,421	40,22
PPV for adenoma (%)	61,11	62,11	62,33	59,63	59,20	57,32	0,593	58,64
PPV for cancer (%)	6.54	6.97	6.09	4.98	5.78	6.07	<0.001	5.91

FOBT, faecal occult blood test; PPV, positive predictive value.
[a]Regions that provided data: Valencian Community (2006–2011), Murcia (2006–2011), Catalonia (2007–2011), Basque Country, Cantabria and Canary Islands (2009–2011), La Rioja and Castile-León (2011). Percentages by FOBT type: 2006 (29% i-quantitative-2 samples-FOBT and 71% gFOBT), 2007 (16% i-quantitative-2 samples-FOBT and 84% gFOBT), 2008 (19% i-quantitative-2 samples-FOBT and 71% gFOBT), 2009 (16% i-quantitative-2 samples-FOBT, 55% gFOBT, 27% i-quantitative-1 sample-FOBT and 2% i-qualitative-FOBT), 2010 (7% i-quantitative-2 samples-FOBT, 17% gFOBT, 70% i-quantitative-1 sample-FOBT and 6% i-qualitative-FOBT) and 2011 (7% i-quantitative-2 samples-FOBT, 83% i-quantitative-1 sample-FOBT and 9% i-qualitative-FOBT).
[b]*P* value associated with the variable year, adjusted for sex, region and type of screening.

evaluated following EU recommendations (Segnan *et al.*, 2010), and the results obtained are within the standards proposed. The implementation of the programmes in Spain is the result of public investment and citizen collaboration with the CRC Alliance, which meets with professional and civic associations who have played an important supporting role in promoting the outreach of the programmes (Morillas *et al.*, 2012). By 2011, these programmes had become a basic service for the entire population (España. Orden SSI/2065, 2014).

Progressive implementation has continued, despite resource restrictions.

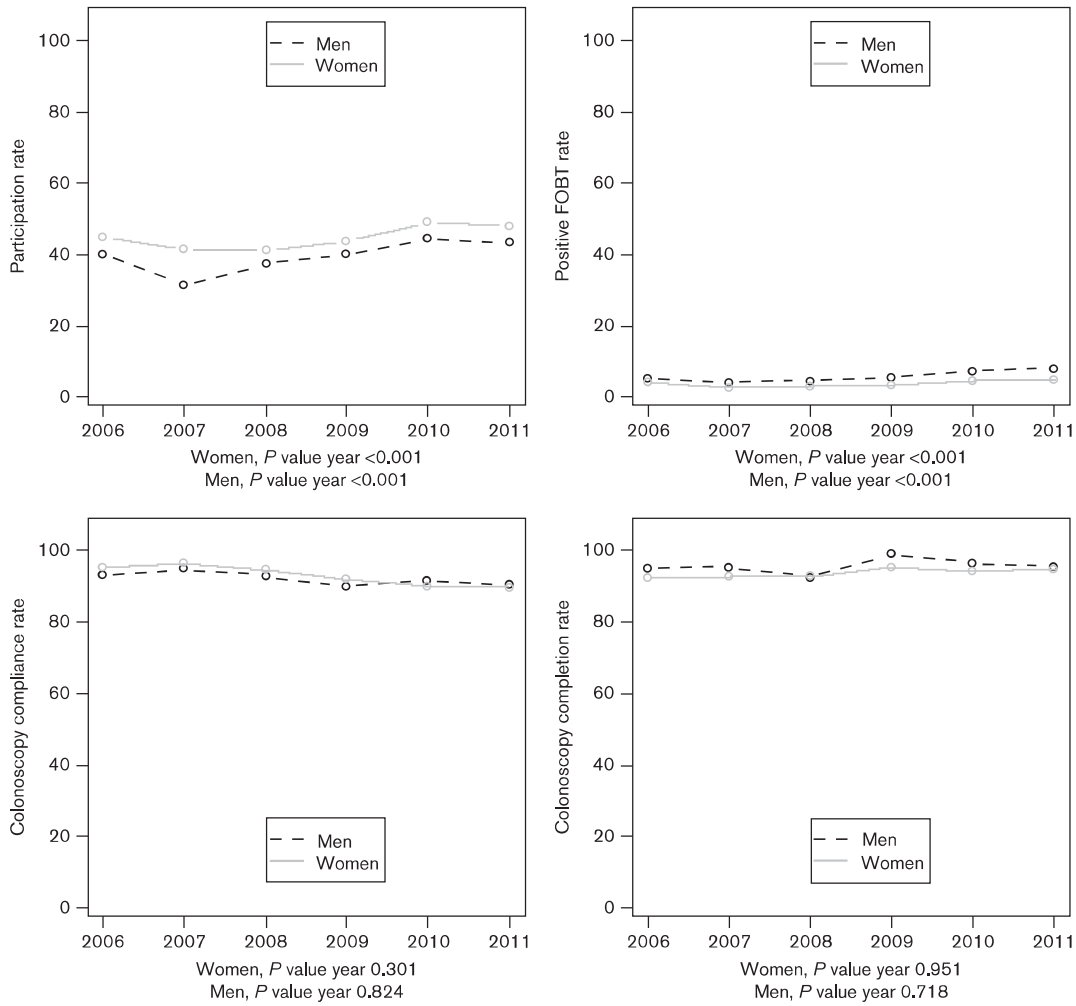
The participation rate is one of the most important indicators for measuring potential effectiveness. In recent years, it has remained at around 45%, despite an average of 43.83% throughout the study period. This participation rate suggests that efforts are needed to improve participation to further reduce mortality and increase survival. Comparison with other European programmes showed an intermediate position between programmes, emphasizing higher rates achieved by programmes in the UK and Finland (Steele *et al.*, 2010; Malila *et al.*, 2011; Parente *et al.*, 2011; Logan *et al.*, 2012; Digby *et al.*, 2013; Blom *et al.*, 2014; Lo *et al.*, 2015), and lower rates in other countries (Katicic *et al.*, 2012; Leuraud *et al.*, 2013; Suchanek *et al.*, 2014).

Some differences in results could be because of the invitation model (collection of the FOBT in pharmacies or health centres used by some programmes) and the use of the guaiac test at the beginning of the study period. The participation rate increased, showing an increase in confidence and acceptance of CRC screening.

The positive test rate increased over the period, coinciding with the switch to the FIT test.

In fact, participation and positive rates varied considerably during the period analysed. This variation could partly be explained by changes in the screening test used, from gFOBT to FIT, and the incorporation of new regional programmes. The positivity rate was higher in the last 3 years (except in 2006, when the data correspond exclusively to first-time invitations, although 71% were guaiac tests, when the pioneer programmes switched from the guaiac to the immunochemical test and the new programmes began directly with these tests). A recent meta-analysis reported a sensitivity for CRC of 79% (confidence interval 69–86%) and a specificity of 94% (confidence interval 92–95%), and the variation was related to the cut-off point (Halloran *et al.*, 2012; Lee *et al.*, 2014; Rabeneck *et al.*, 2014; Young *et al.*, 2015). In 2010 and 2011, 91 and 78% of tests, respectively, were performed in individuals who were invited for the first time, 90% with FIT. These tests have shown greater

Fig. 1



Colorectal cancer participation, positive faecal occult blood test (FOBT), colonoscopy compliance and colonoscopy completion in 2006–2011. Results of Poisson regression model.

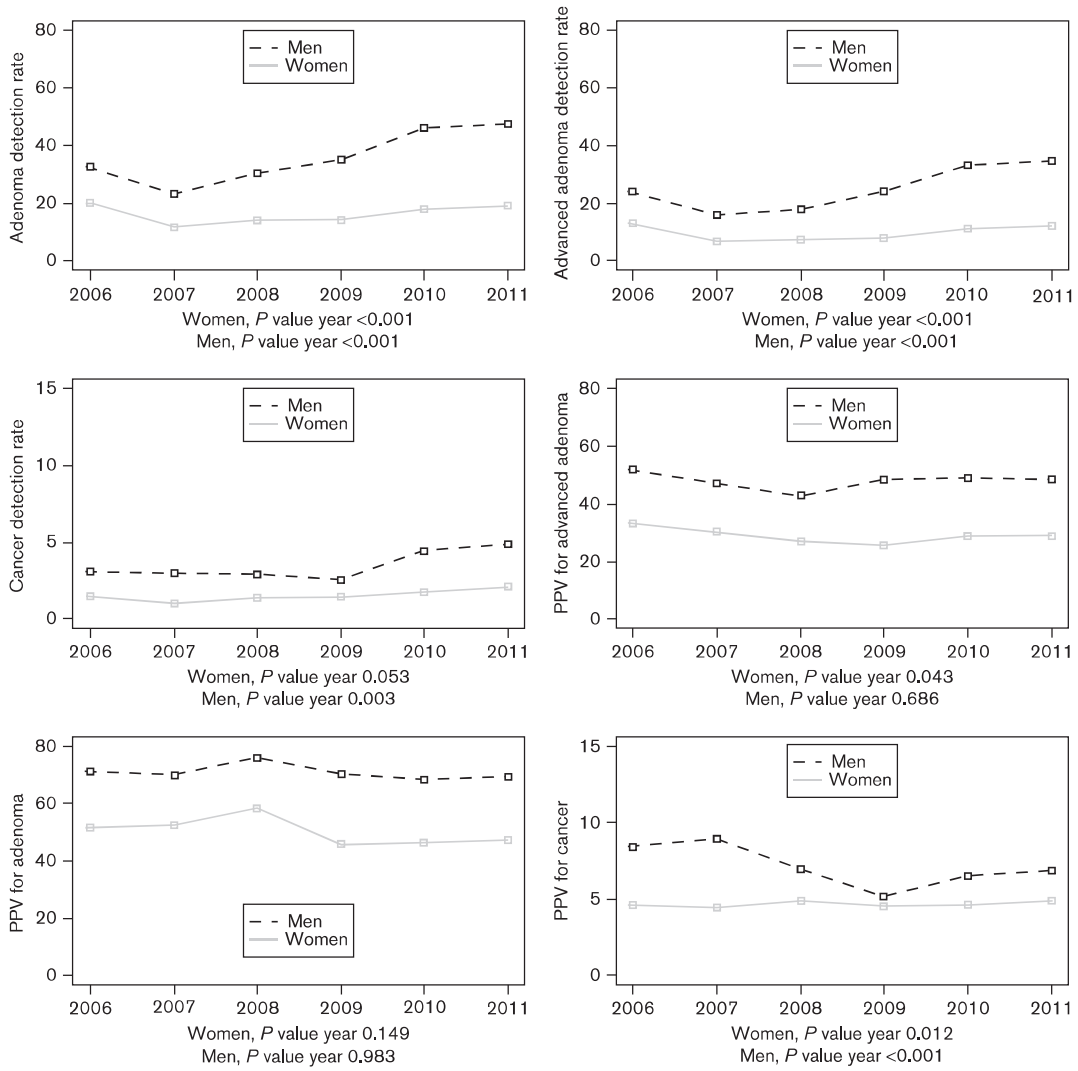
acceptance, with a higher positivity rate, and advanced adenoma and CRC detection rates, in line with guidelines and evidence.

Differences between sexes were found in all indicators. Participation rates were higher in women than in men, with the same pattern in other population-based programmes (Mansouri *et al.*, 2013; Lo, *et al.*, 2015); this has recently been evaluated in the case of FIT participation (Clarke *et al.*, 2015) and should be analysed also to improve programmes in Spain (Portillo *et al.*, 2013b; Salas *et al.*, 2014).

Advanced adenoma and CRC detection rates increased throughout the period, in keeping with the switch from the gFOBT to the FIT test and population coverage in the first invitation. Significant differences between men and women were found in the detection rate for advanced adenomas and cancer. In 2010 and 2011, when the proportion of FIT tests used was significant, the adenoma detection rate reached 27.09%, in line with European Guidelines (Segnan *et al.*, 2010).

The PPV followed the same pattern in our study and was similar to that in other programmes, and with wide ranges that should be taken into account for establishing age and sex strategies (Ferlistsch *et al.*, 2011). Colonoscopy compliance and completion were similar to those in other studies (Blom *et al.*, 2014; Morris *et al.*,

Fig. 2



Trend in the adenoma, advanced adenoma and cancer detection rates and PPV of colorectal cancer screening programmes, by sex, in Spain in 2006–2011. Results of the Poisson regression model. PPV, positive predictive value.

2014), and to EU Guideline standards (Moss *et al.*, 2012a, 2012b).

Although we found an appropriate performance level in the main indicators and the efforts of the SCSN to standardize screening criteria and methods, some limitations of the screening programme should be taken into account. First, the screening organization and the FOBT used differed from region to region and over the study period, with variations in the same region where the test was switched and organizational differences among regions. Another limitation is the analysis by rounds and deprivation level or side-effects of screening such as complications of colonoscopy and false-positive and false-negative results. These issues have been studied and standardized in the SCSN (Red de Programas de Cribado de Cáncer, 2012).

The main strength of this study is the number of participants in the screening programmes, which showed an encouraging increase over the study period. These results provide a picture of the performance and trends of screening programmes in Spain.

The results of this study show the overall performance of CRC screening in Spain in different regional programmes. Overall, our results are in line with those of other FOBT screening programmes. The participation rate increased over time and has now reached an acceptable level. Participation was lower in men, who nevertheless showed higher lesion detection rates, indicating an area for intervention.

This analysis of the implementation of CRC screening programmes in Spain may help to improve the results of cancer screening policies in Spain and other countries.

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Conflicts of interest

There are no conflicts of interest.

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Social inequalities in a population based colorectal cancer screening programme in the Basque Country

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Abstract

Background: While it is known that a variety of factors (biological, behavioural and interventional) play a major role in the health of individuals and populations, the importance of the role of social determinants is less clear. The effect of social inequality on population-based screening for colorectal cancer (CRC) could limit the value of such programmes. The present study aims to determine whether such inequalities exist.

Methods: Data was obtained from the population-based screening programme administered in the Autonomous Community of the Basque Country, Spain, with a target population aged 50 to 69, first invited to participate between 2009 and 2011. The magnitude of inequality was analysed using the odds ratio (taking the least disadvantaged socioeconomic quintile as the reference population), the population attributable risk and the relative index of inequality, based on the regression, which is the ratio of the rates in the most and least disadvantaged socioeconomic groups.

Results: The target population comprised 242,394 people, with the test kit successfully sent to 95.1 % (230,510). The overall response rate was 64.3 % (67.1 in women and 61.4 % men).
Among women, the highest participation was in the third quintile (71.5 %) and the lowest in the first – the least disadvantaged (65.7 %). The lowest and highest rates of people with identified lesions were in the second and fourth quintiles (14.7/1000 and 17.0/1000 respectively).
Among men, the response rate was lowest in the fifth – most disadvantaged – quintile (60.2 %). The highest rate of identified lesions was in the fifth quintile; 38 % higher than the first (55.7/1000 compared to 41.0/1000).

Conclusions: Sex and socioeconomic group influence the rate of participation in the CRC programme and the rate of lesions found in the participants.
Any public health programme is morally and ethically obliged to strive for equity and effectiveness. Improving participation of men and socially disadvantaged groups should be taken in account.

Keywords: Social inequalities, Colorectal cancer, Screening programme

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Background

The health of individuals and populations depends on a wide range of factors, including biological variables, health-related behaviour and health system performance. There is growing evidence, however, that social determinants of health play a highly important role [1, 2]. The uneven distribution of these determinants according to different social stratification criteria - social class, educational level, degree of deprivation of area of residence, etc. - generates health inequalities, with those belonging to more disadvantaged socioeconomic groups or living in areas of greater social deprivation consistently evidencing worse health indicators and unhealthier lifestyles and habits [3–5].

The WHO Commission on Social Determinants of Health (CSDH) said in its 2008 report [1] that the organization and characteristics of health systems also play an important role in health equity, either reducing inequalities generated by other social determinants or, conversely, amplifying them. The "inverse care law", according to which the availability of health care tends to vary inversely with the need of the target population [6, 7], is a well-identified mechanism for explaining the amplification phenomenon. Despite their universal approach, population-based disease prevention and health promotion programmes implemented by health authorities do not always guarantee equal access for and impact on the various social groups, which can lead to a worsening of social inequalities in health [8]. Some postulate reduced responsiveness to disease prevention and health promotion messages among people living in disadvantaged socioeconomic areas - due to competition from or prioritization of more essential needs - while others identify reduced availability and implementation of programmes in such contexts [9].

Specifically, health-system-driven population screening programmes (including population-based CRC screening) help decrease the impact of certain diseases or health problems on the population, through early detection. The aim is to reduce the incidence of progressive disease and related mortality, which are high in all developed countries. According to WHO estimates CRC affected over 471.240 people in 2012, with almost 228.275 dying from the disease in the European Union. In Spain, CRC is in first place for incidence (32,240 people) and takes second place for mortality (14,700 deaths), outnumbered only by deaths from lung cancer [10]. Basque Country data follows the same trend, with a significant increase in incidence in the last two decades [11].

The ability of screening to reduce CRC mortality depends heavily on the degree of participation in the population, but also on the chosen screening method. A faecal occult blood test (FOBT) performed every two years can reduce mortality by 19 %, whereas first-line colonoscopy offers a 68 % reduction [12]. The guaiac-based FOBT has now been replaced by the faecal immunochemical test (FIT), thus increasing test sensitivity, and colonoscopy has improved in terms of equipment, training and quality assurance [13]. In Spain, according to National Cancer Strategy, FOBT every two years is recommended for 50–69 years old population and colonoscopy as a confirmatory test in positive cases, being included as a basic service for all population in 2014 [14].

With regard to participation, the literature shows that even in well-established programmes with high population coverage, significant social inequalities exist, by socioeconomic status, gender, age and ethnicity [15–22]. Women (perhaps due to their greater awareness of the importance of self-care, as well as their role as the household's main caregiver) and older people (>60) show the highest screening rates [15–17], while men evidence greater participation in invasive tests [18]. Most studies agree that the main causes of non-participation among the most disadvantaged socioeconomic groups are: lack of information about the disease, prioritization of other problems with a greater impact on everyday life, and not understanding the written communications that arrive in the post [15, 16].

In 2013, 11 of Spain's 17 regions had population-based CRC screening programmes in place, which, when combined, covered 20 % of the Spanish population aged between 50 and 69 [23]. The Basque Country was the region with the greatest coverage (97.9 %) in 2013, combined with high participation (64.3 %) [24], being their target population around 583,000 people, which 51.4 % are women. This can be attributed to a Primary Care programme that began in 2009, based on the use of a two-yearly FIT, with those patients that returned a positive FIT referred to the public hospital for colonoscopy under sedation, in order to confirm the diagnosis. A strategy of home delivery of testing kits combined with provision of a broad time band for delivering the samples to health centres was implemented to facilitate participation, as well as detailed programme information and access to a freephone information service. However, the potential existence of social inequalities in the various phases of screening may limit the effectiveness of the programme and bring the "inverse care law" into play. The aim of this article is thus to describe the magnitude of social inequalities in population-based CRC screening in the Basque Country between 2009 and 2011, according to the level of socioeconomic deprivation of the area of residence, focusing mainly on response rates and lesions identified. This data was reported with regard to sex in a previous publication [25]. Nowadays, the programme is continuing rolling-out with the same criteria inviting progressively in successive rounds all the target population.

Methods

This is a cross-sectional study of people aged 50 to 69 years invited to participate for the first time in the Basque Country's CRC screening programme between 2009 and 2011. The study was approved by the Euskadi Ethics Committees and each participant provided written informed consent.

Study subjects

People aged 50 to 69, living in the Basque Country and registered with one of the 60 health centres in which the CRC screening programme was implemented between 2009 and 2011, equivalent to about 50 % of the region's population in the given age range. The population covered by the programme at that time was not complete because of the colonoscopy capacity in hospitals was limited then. Exclusion criteria were: being under surveillance for previously diagnosed CRC, having a high-risk family history of CRC, or having colonoscopy/sigmoidoscopy follow-up for adenoma during the previous 5 years, or total colectomy or terminal/irreversible disease or unknown address.

Study variables

Successfully-invited population

People aged 50–69 years meeting no exclusion criteria, who were sent a letter of invitation that was not returned due to the address being incorrect.

Participant

Of all those who were successfully invited, those who handed in the kit and for whom a correct result was returned (negative/positive).

Positive FIT test

20 ng/ml according to manufacturer's instructions. OC-Sensor (2009–2011) and Sentinel (2009–2010) were used.

People with premalignant lesion, defined as the discovery after colonoscopy of advanced (medium- and high-risk) adenomas, as defined in the 2010 European Guidelines [26] and *malignant lesion* invasive carcinoma (≥pT1) according to the pathology report in the patient record.

Source of data

Socioeconomic status

Each study participant was assigned the socioeconomic deprivation index (DI) of their small area of residence. This composite index was calculated by the Basque Government Health Department's Health Research Service, using the Medea Project [26] criteria, from simple indicators in the 2001 Census: unemployment, manual workers, casual workers, insufficient education and insufficient education among young people. The DI was divided into quintiles, with the first being the least disadvantaged and the fifth the most disadvantaged. Participant data was linked to the DI variable using the Individual Health Card code, or the corporative identification code, in those cases where the participant did not have an Individual Health Card number. The DI was successfully assigned to 95.1 % of participants, while address information quality did not permit to link the remaining 4.9 %.

All data was obtained from the Basque Country's population-based CRC screening programme database, which is linked to patient records. This allows all cases to be followed, from submission of the sample, through analysis, colonoscopy, pathology and follow-up.

Statistical analysis

Age-standardized rates were calculated using the direct method for the different variables, for total participants and by level of deprivation, using Basque Country residents between 50 and 69 years in 2011 as the reference population. To obtain participation rates, the number of people who participated was divided by the *successfully-invited population*. To obtain lesion rates, the number of people in whom lesions were detected was divided by the total *participant* population. To obtain malignant lesion rates, the number of people in whom malignant lesions were detected was divided by the total *participant* population. To obtain the positive predictive value (PPV), the number of people with lesions detected was divided by the number of people with positive FIT results. The comparative analysis between men and women was performed using indirectly standardized ratios and between age groups, using odds ratios estimated by logistic regression models. The magnitude of inequalities was analysed using: (a) odds ratios estimated by logistic regression models, taking as the reference population the least disadvantaged socioeconomic quintile, (b) the population-attributable risk (PAR) and (c) the relative index of inequality (RII). RII is based on the regression and consists of the rate ratio between the most and least disadvantaged groups respectively. These results were estimated using logistic regression models. All analyses were performed separately for men and women. P value less than 0.05 was considered statistically significant using 2-sided test. The analysis was performed with R v. 2.13.1.

Results

Between 2009 and 2011, the target population comprised 242,394 people (50.9 % women), with the test kit successfully sent to 230,510 (95.1 %). Of this group, a DI was successfully assigned to 219,120 people (95.1 %) (Fig. 1).

The overall response rate was 64.3 % (67.1 in women and 61.4 % men). In 6.7 % of participants, the FIT result was positive (4.8 of women and 9.0 % of men). Of these,

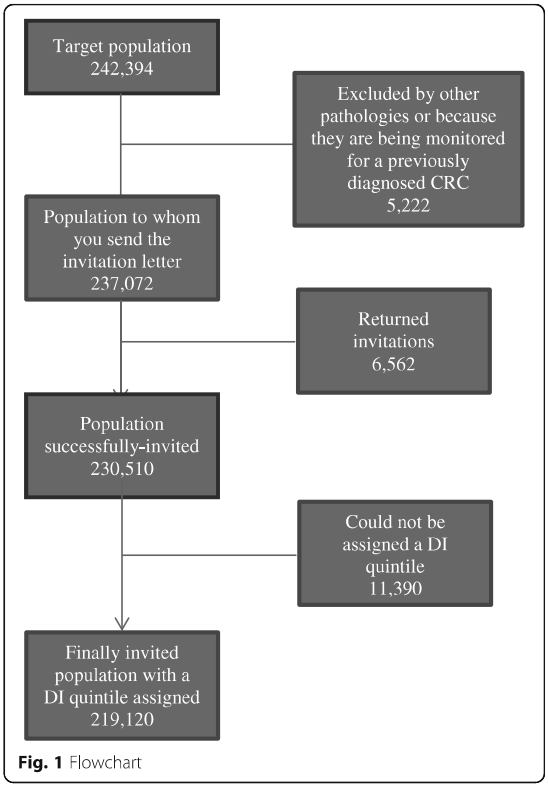

Fig. 1 Flowchart

92.6 % were given a colonoscopy (92.0 of women and 93.0 % of men), resulting in the detection of 4,523 lesions, of which 3,952 were premalignant and 571 were carcinomas, with 383 in stages I-II (Table 1).

Among participants, the standardized rate of people with lesions was 48.5/1000 in men, three times higher than the 15.7/1000 for women. The rate of people with malignant lesions was also 2.34 times higher in men than women (5.49/1000 vs. 2.42/1000). The PPV of the test was 52.2 % in men compared to 32.5 % in women (Table 2).

Both men and women aged 60–64 participated most in the programme, while those between 50–54 ages participated least. Lesion detection rates and people with malignant rates were higher in the older age groups. The rate of people with cancer in stages III and IV only increased with age in men ($p < 0.001$).

Among men, the PPV of the test increased with age, ranging from 43.60 % to 59.67 %. Among women, the lowest and the highest PPV were 31.62 % (50–54) and 33.01 (65–69), respectively.

The proportion of people who underwent a colonoscopy following a positive FIT result was not associated with age (Table 3).

By socioeconomic status, among women, the highest percentage participation was in the third quintile (71.5 %) and the lowest participation was in the - least disadvantaged - first quintile (65.7 %). This quintile also underwent the lowest colonoscopy rate following a positive FIT result (89.1 %). The lowest and highest rates of people with lesions identified were in the second and fourth quintiles respectively (14.7/1000 compared to 17.00/1000), although overall the effect of socioeconomic status was not statistically significant (p =0.600). Neither did the DI show any statistically significant association with the rate of people with malignant lesions ($p = 0.824$), rate of people with cancer in stages III and IV ($p = 0.853$), or the PPV ($p = 0.197$). No RII was calculated in women, since on reviewing the tables; no linear association was visible between the DI and the results (Table 4).

The PAR or percentage of preventable lesions if the total rates had been those of the DI quintile with the lowest lesion rate is 6.7 % in women, representing 81 fewer lesions if the rate of people with lesions for the whole population had been that of the second quintile.

Among men, the participation rate was significantly lower in the fifth – most disadvantaged – quintile (60.2 %) compared to other quintiles. The first quintile had the smallest proportion of people who underwent a colonoscopy after a positive result (90.5 %), followed by the fifth quintile (92.5 %), with the fourth quintile showing the largest (95.6 %). The rates of people with lesions identified were highest in the fifth quintile and were 38 % higher than those in the first quintile (55.7/1000 compared to 41.0/1000). The highest rate of malignant lesions was in the third quintile (6.9/1000), although this was not significantly higher than the reference quintile (OR 1.25, 95 % CI (0.92-1.69)). No significant association was found with the rate of people with cancer in stages III and IV ($p = 0.137$) or with the PPV ($p = 0.349$). The RII for the rate of men with lesions (premalignant and malignant) was 1.37 (95 % CI 1.21-1.55) (Table 4).

The PAR or percentage of preventable lesions in men was 16.0 %, which is equivalent to 529 fewer people with lesions if the overall rate had been that of the DI quintile with the lowest rate (first quintile).

Finally, if a rate similar to that obtained in the quintile with the highest rate of participation (71.5 % of women in the third quintile) had been achieved in all socioeconomic quintiles, 466 people with lesions would have been detected within this period (414 men), of which 56 would have been malignant (48 men).

Discussion

This study reveals socioeconomic inequalities in a number of quality indicators for the Basque Country's colorectal cancer screening programme between 2009 and 2011.

Table 1 Baseline table with data and distribution percentages

	Totals	%	Women	%	Men	%
Population	242,394		122,901		119,493	
age (years):						
50-54	81,605	33.7	41,065	33.4	40,540	33.9
55-59	59,633	24.6	30,130	24.5	29,503	24.7
60-64	61,266	25.3	31,176	25.4	30,090	25.2
65-69	39,890	16.5	20,530	16.7	19,360	16.2
Successfully-invited population, out of the total population	230,510	97.2	117,573	97.6	112,937	96.8
Participants, out of the successfully-invited population	148,265	64.3	78,916	67.1	69,349	61.4
FOBT results for participants						
Positive	9,961	6.7	3,751	4.8	6,210	9.0
Negative	138,165	93.2	75,091	95.2	63,074	91.0
Error	130	0.1	71	0.1	59	0.1
Lost	9	0.0	3	0.0	6	0.0
colonoscopy performed after positive FOBT						
No	735	7.4	300	8.0	435	7.0
Yes	9,226	92.6	3,451	92.0	5,775	93.0
Colonoscopy results						
Negative	4,639	50.3	2211	64.1	2,428	42.0
N/A or inconclusive	64	0.7	20	0.6	44	0.8
Premalignant or malignant lesion	4,523	49.0	1220	35.4	3,303	57.2
Type of premalignant or malignant lesion:						
Premalignant	3,952	87.4	1,034	84.8	2,918	88.3
Cancer	571	12.6	186	15.2	385	11.7
Cancer results:						
stage I/II	383	67.1	118	63.4	265	68.8
stage III/IV	181	31.7	65	34.9	116	30.1
stage unknown / N/A	6	1.1	2	1.1	4	1.0
stage lost	1	0.2	1	0.5	0	0.0

Men in the most disadvantaged socioeconomic class evidence the lowest participation rate, but also the highest rates of premalignant and malignant lesions, between 23 and 55 % higher than the least disadvantaged quintile. Among women, those in the groups with the lowest and highest socioeconomic status participate the least, and no differences are observed in the rate of people with lesions in the most disadvantaged groups. No differences in PPV are detected between socioeconomic groups, either in men or in women, and neither are there any differences between groups in the percentage of colonoscopies performed after a positive FIT result.

Overall participation rate (64.3 %) is close to the 65 % target set by the 2011 European Guidelines [26], although it is lower in men than in women, and lower in the youngest and oldest groups. A similar pattern is found in other CRC screening programmes [15, 19, 27–29].

Attempting to explain this differential behaviour by sex and age, some studies postulate that men might be less interested about their health, as well as being afraid of the diagnostic test, while women might assume the role of caregiver, leading more of them to worry about their health, for the sake of those around them [15, 16]. The influence of a dominant societal perception of masculinity has been described as an important factor in explaining inferior participation among men, since CRC screening entails the risk of having to undergo an invasive procedure - colonoscopy- that might conflict with normative "male" beliefs [30, 31]. In younger people, feeling healthy and less vulnerable to the disease could be a barrier to participation. Finally not being aware of the importance of screening or not having had their doctor recommend the screening process are some factors that might reduce participation in the older age groups

Table 2 Standardized rates and standardized rate ratio between sexes

	Women		Men			
Indicators	standardized rates[a]	(95 % CI)	standardized rates[a]	(95 % CI)	RR[b]	(95 % CI)
Participants from successfully-invited population	67.14	(66.67-67.62)	61.69	(61.23-62.16)	0.91	(0.91-0.92)
Lesions among participants	15.69	(14.82-16.61)	48.50	(46.84-50.20)	3.07	(2.96-3.17)
Cancer among participants	2.42	(2.08-2.80)	5.79	(5.22-6.41)	2.34	(2.12-2.58)
Stage III/IV cancer among participants	0.82	(0.63-1.05)	1.76	(1.45-2.12)	2.03	(1.69-2.43)
Colonoscopies performed after + FOBT	92.07	(88.99-95.23)	92.95	(90.52-95.44)	1.01	(0.99-1.04)
Lesions identified among colonoscopy patients	35.30	(33.33-37.36)	56.11	(54.17-58.10)	1.62	(1.56-1.67)
Lesions, out of those with + FOBT	32.50	(30.68-34.40)	52.19	(50.39-54.04)	1.63	(1.58-1.69)

[a]Rates per 1000 for lesions, cancer and cancer stage; percentage for participants, colonoscopy after + FOBT and colonoscopy patients with lesions
[b]Standardized rate ratio for men/women

[15, 16]. These hypothetical explanations should be treated with caution, however, since it is widely recognised that knowledge and health beliefs have a limited capacity to explain people's actual behaviour, and underlying motives are particularly difficult to ascertain [32].

The rate of people with premalignant and malignant lesions detected in colonoscopy is three times higher in men than in women. In the older group, it is 2.6 and 1.7 times higher than the younger group, for men and women respectively (5.02 and 2.4 times higher in the older group if we only take into account rates of people with malignant lesions). These figures corroborate the strong association of age and sex with the probability of detecting a premalignant or malignant lesion that has been reported in other studies [33–36].

The PPV for detection of premalignant and malignant lesions increases with age and is significantly higher in men than in women. These patterns are already known and are probably due in large part to differences in prevalence between certain subgroups [37–39].

The proportion of colonoscopy performed following a positive FIT result was not associated with age in either sex. Similar results were found by other authors (36-steel, 44-Dupont-Lucasa). The high compliance of the procedure in all the age groups (above 91.5 %) could have played a role in the lack of association.

In both sexes the socioeconomic groups with the lowest participation were, paradoxically, both the least and the most disadvantaged. The former could be due to greater access to private healthcare among the more privileged social classes. In fact public health services are available for all population, but the least deprived normally contract a private insurance as well, where colonoscopy is offered as an opportunistic screening. As already noted above, in reference to the research by Williams, explaining low participation among the most disadvantaged social classes is not a simple task. Lifestyles are composed mostly of actions performed automatically without forethought, with habits and the pursuit of social distinction being the key factors for explaining health and lifestyle, which accounts for the substantial gap between health knowledge and behaviour [32]. Caution is required, therefore, when assessing specific explanations postulated in other articles, such as greater fear of screening, the perception that it is harder to perform, doubts over whether screening is beneficial, lack of knowledge about the test, difficulty in understanding written information and lack of social support [15, 16, 19, 20].

While the published results of other screening programmes show that a lower proportion of those from more disadvantaged social strata attended for colonoscopy after a positive FIT result, it is not the case here [35, 40–42]. Participation among disadvantaged socioeconomic groups is a sign of good programme implementation. Dupont-Lucas et al., in a study that also showed no socioeconomic differences in the percentage of colonoscopies after a positive test, suggest that the voluntary nature of the programme (which is also the case in the present example) allows those members of disadvantaged social groups who would not have been willing to undergo colonoscopy to opt out [43]. On the contrary, the least deprived quintiles show the lowest percentage of colonoscopy for diagnostic confirmation, possibly because a greater proportion are able to access private clinics, whose data is not available to the current study.

The premalignant and malignant lesion detection rates show an inverse association with socioeconomic status in men but not in women. The influence of socioeconomic status on the incidence of CRC is not clear in the literature. Recent systematic reviews and large prospective studies show mixed results. While it appears that in the United States and Canada, lower socioeconomic status is associated with higher rates of CRC, especially in the proximal colon, the tendency in Europe seems to be in the opposite direction, i.e., lower incidence of CRC in lower socioeconomic strata [44–46]. Studies with a higher incidence of CRC among lower socioeconomic strata or those with less education, point to a higher prevalence of modifiable risk factors associated with CRC such as smoking, excessive alcohol consumption, obesity, low levels of

Table 3 PPV of the test, participation, lesion and colonoscopy rates following positive test result, by age group

Women						Men					
Age groups	successfully-invited population	no. of participants	% participation	OR	(95 % CI)	Age groups	successfully-invited population	no. of participants	% participation	OR	(95 % CI)
50-54	37379	24609	65.84	1.00		50-54	36221	21033	58.07	1.00	
55-59	27637	19375	70.11	1.22	(1.18-1.26)	55-59	26324	16692	63.41	1.25	(1.21-1.29)
60-64	28760	20434	71.05	1.27	(1.23-1.32)	60-64	26866	18144	67.54	1.50	(1.45-1.55)
64-69	18758	12635	67.36	1.07	(1.03-1.11)	64-69	17175	11457	66.71	1.45	(1.40-1.51)
				$p < 0.001$						$p < 0.001$	
Age groups	no. of participants	no. of lesions (premal. + malignant)	rate of lesions (premal. + malignant) among participants[a]	OR	(95 % CI)	Age groups	no. of participants	no. of lesions (premal. + malignant)	rate of lesions (premal. + malignant) among participants	OR	(95 % CI)
50-54	24609	302	12.27	1.00		50-54	21033	593	28.19	1.00	
55-59	19375	273	14.09	1.15	(0.97-1.35)	55-59	16692	777	46.55	1.7	(1.51-1.88)
60-64	20434	357	17.47	1.43	(1.22-1.66)	60-64	18144	1058	58.31	2.1	(1.93-2.37)
64-69	12635	257	20.34	1.66	(1.41-1.97)	64-69	11457	799	69.74	2.6	(2.31-2.87)
				$p < 0.001$						$p < 0.001$	
Age groups	no. of participants	no. of malignant lesions	rate of malignant lesions among participants[a]	OR	(95 % CI)	Age groups	no. of participants	no. of malignant lesions	rate of malignant lesions among participants	OR	(95 % CI)
50-54	24609	38	1.54	1.00		50-54	21033	47	2.23	1.00	
55-59	19375	37	1.91	1.24	(0.78-1.95)	55-59	16692	77	4.61	2.07	(1.45-3.00)
60-64	20434	59	2.89	1.87	(1.25-2.83)	60-64	18144	119	6.56	2.97	(2.13-4.20)
64-69	12635	47	3.72	2.40	(1.56-3.70)	64-69	11457	126	11.00	5.02	(3.62-7.10)
				$p < 0.001$						$p < 0.001$	
Age groups	no. of participants	no. of carcinomas stage III/IV	no. of carcinomas stage III/IV	OR	(95 % CI)	Age groups	no. of participants	no. of carcinomas stage III/IV	no. of carcinomas stage III/IV	OR	(95 % CI)
50-54	24609	16	0.65	1.00		50-54	21033	10	0.48	1.00	
55-59	19375	15	0.77	1.19	(0.58-2.41)	55-59	16692	19	1.14	2.40	(1.14-5.37)
60-64	20434	22	1.08	1.65	(0.87-3.19)	60-64	18144	37	2.04	4.33	(2.24-9.20)
64-69	12635	10	0.79	1.20	(0.52-2.61)	64-69	11457	44	3.84	8.23	(4.32-17.34)

Table 3 PPV of the test, participation, lesion and colonoscopy rates following positive test result, by age group *(Continued)*

				$p = 0.488$						$p < 0.001$	
Age groups	people with + FOBT	people who had colonoscopy	% colonoscopies	OR	(95 % CI)	Age groups	people with + FOBT	people who had colonoscopy	% colonoscopies	OR	(95 % CI)
50-54	955	881	92.25	1.00		50-54	1360	1259	92.57	1.00	
55-59	827	773	93.47	1.17	(0.82-1.69)	55-59	1458	1363	93.48	1.17	(0.87-1.57)
60-64	1083	991	91.51	0.90	(0.65-1.23)	60-64	1871	1739	92.94	1.06	(0.81-1.39)
64-69	785	720	91.72	0.91	(0.64-1.29)	64-69	1339	1266	94.55	1.40	(1.03-1.92)
				$p = 0.446$						$p = 0.150$	
Age groups	people who had colonoscopy	no. of lesions (premal. + malignant)	% lesions found in colonoscopy	OR	(95 % CI)	Age groups	people who had colonoscopy	no. of lesions (premal. + malignant)	% lesions found in colonoscopy	OR	(95 % CI)
50-54	881	302	34.28	1.00		50-54	1259	593	47.10	1.00	
55-59	773	273	35.32	1.05	(0.85-1.28)	55-59	1363	777	57.01	1.49	(1.27-1.73)
60-64	991	357	36.02	1.08	(0.89-1.30)	60-64	1739	1058	60.84	1.75	(1.51-2.02)
64-69	720	257	35.69	1.07	(0.87-1.31)	64-69	1266	799	63.11	1.92	(1.64-2.25)
				$p = 0.883$						$p < 0.001$	
Age groups	people with + FOBT	no. of lesions (premal. + malignant)	PPV	OR	(95 % CI)	Age groups	people with + FOBT	no. of lesions (premal. + malignant)	PPV	OR	(95 % CI)
50-54	955	302	31.62	1.00		50-54	1360	593	43.60	1.00	
55-59	827	273	33.01	1.06	(0.87-1.30)	55-59	1458	777	53.29	1.48	(1.27-1.71)
60-64	1083	357	32.96	1.06	(0.88-1.28)	60-64	1871	1058	56.55	1.69	(1.46-1.94)
64-69	785	257	32.74	1.06	(0.86-1.29)	64-69	1339	799	59.67	1.91	(1.64-2.23)
				$p = 0.919$						$p < 0.001$	

OR Odds ratios adjusted by DI quintile, *CI* Confidence interval; p: significance value of the likelihood ratio test for the association between age and outcome variable
[a]rates per 1000 inhabitants

Table 4 PPV of the test, standardized participation, lesion and colonoscopy following positive test result, by socioeconomic stratum of place of residence

Women						Men					
DI quintile	successfully-invited population	no. of participants	% participation	OR	(95 % CI)	DI quintile	successfully-invited population	no. of participants	% participation	OR	(95 % CI)
I (least disadvantaged)	26193	17228	65.73	1.00		I (least disadvantaged)	23947	14743	61.87	1.00	
II	24373	17026	69.89	1.21	(1.16-1.25)	II	23373	15079	64.91	1.14	(1.10-1.19)
III	22632	16160	71.46	1.30	(1.25-1.35)	III	21440	14086	66.07	1.20	(1.15-1.25)
IV	19927	13819	69.30	1.17	(1.13-1.22)	IV	19343	12349	64.07	1.10	(1.06-1.14)
V (most disadvantaged)	19409	12820	66.06	1.01	(0.97-1.05)	V (most disadvantaged)	18483	11069	60.25	0.93	(0.90-0.97)
				$p < 0.001$						$p < 0.001$	
DI quintile	no. of participants	no. of lesions (premal. + malignant)	rate of lesions (premal. + malignant) among participants[a]	OR	(95 % CI)	DI quintile	no. of participants	no. of lesions (premal. + malignant)	rate of lesions (premal. + malignant) among participants	OR	(95 % CI)
I (least disadvantaged)	17228	255	15.39	1.00		I (least disadvantaged)	14743	594	40.99	1.00	
II	17026	246	14.61	0.97	(0.81-1.16)	II	15079	705	48.73	1.18	(1.06-1.32)
III	16160	258	16.12	1.07	(0.90-1.27)	III	14086	703	50.76	1.25	(1.12-1.40)
IV	13819	233	16.99	1.11	(0.93-1.33)	IV	12349	617	49.83	1.23	(1.10-1.38)
V (most disadvantaged)	12820	197	15.40	1.01	(0.84-1.22)	V (most disadvantaged)	11069	608	55.68	1.38	(1.23-1.55)
				$p = 0.600$						$p = 0.002$	RII 1.37 (1.21-1-55)
DI quintile	no. of participants	no. of malignant lesions	rate of malignant lesions among participants[a]	OR	(95 % CI)	DI quintile	no. of participants	no. of malignant lesions	rate of malignant lesions among participants	OR	(95 % CI)
I (least disadvantaged)	17228	38	2,25	1,00		I (least disadvantaged)	14743	78	5,46	1,00	
II	17026	37	2,24	0,98	(0.62-1.54)	II	15079	85	6,14	1,08	(0.80-1.48)
III	16160	38	2,37	1,05	(0.67-1.65)	III	14086	93	6,89	1,25	(0.92-1.69)
IV	13819	31	2,35	0,97	(0.60-1.56)	IV	12349	45	3,60	0,66	(0.45-0.95)
V (most disadvantaged)	12820	37	2,90	1,25	(0.79-1.97)	V (most disadvantaged)	11069	68	6,37	1,14	(0.82-1.58)

Table 4 PPV of the test, standardized participation, lesion and colonoscopy following positive test result, by socioeconomic stratum of place of residence *(Continued)*

				$p = 0.824$						$p = 0.006$	
DI quintile	no. of participants	no. of carcinomas stage III/IV	no. of carcinomas stage III/IV	OR	(95 % CI)	DI quintile	no. of participants	no. of carcinomas stage III/IV	no. of carcinomas stage III/IV	OR	(95 % CI)
I (least disadvantaged)	17228	10	0.70	1.00		I (least disadvantaged)	14743	24	1.97	1.00	
II	17026	14	0.84	1.27	(0.59-2.76)	II	15079	27	2.03	1.00	(0.59-1.69)
III	16160	10	0.67	0.97	(0.42-2.22)	III	14086	20	1.52	0.75	(0.41-1.32)
IV	13819	12	0.89	1.23	(0.54-2.76)	IV	12349	12	0.94	0.49	(0.24-0.93)
V (most disadvantaged)	12820	13	0.99	1.44	(0.65-3.20)	V (most disadvantaged)	11069	22	2.13	1.02	(0.58-1.77)
				$p = 0.853$						$p = 0.137$	
DI quintile	people with + FOBT	people who had colonoscopy	% colonoscopies	OR	(95 % CI)	DI quintile	people with + FOBT	people who had colonoscopy	% colonoscopies	OR	(95 % CI)
I (least disadvantaged)	773	688	89.07	1.00		I (least disadvantaged)	1168	1056	90.51	1.00	
II	789	723	91.64	1.34	(0.96-1.89)	II	1295	1205	92.96	1.41	(1.06-1.89)
III	735	685	93.45	1.68	(1.17-2.44)	III	1292	1227	94.89	2.01	(1.47-2.77)
IV	688	647	93.99	1.94	(1.32-2.88)	IV	1154	1102	95.60	2.25	(1.61-3.18)
V (most disadvantaged)	665	622	93.65	1.78	(1.22-2.63)	V (most disadvantaged)	1119	1037	92.51	1.33	(0.99-1.80)
				$p = 0.003$						$p = <0.001$	
DI quintile	people who had colonoscopy	no. of lesions (premal. + malignant)	% lesions found in colonoscopy	OR	(95 % CI)	DI quintile	people who had colonoscopy	no. of lesions (premal. + malignant)	% lesions found in colonoscopy	OR	(95 % CI)
I (least disadvantaged)	688	255	37.01	1.00		I (least disadvantaged)	1056	594	55.46	1.00	
II	723	246	33.88	0.88	(0.70-1.09)	II	1205	705	57.23	1.10	(0.93-1.30)
III	685	258	37.72	1.03	(0.82-1.27)	III	1227	703	56.27	1.05	(0.88-1.24)
IV	647	233	36.14	0.95	(0.76-1.19)	IV	1102	617	54.97	0.99	(0.83-1.17)
V (most disadvantaged)	622	197	31.01	0.79	(0.63-0.99)	V (most disadvantaged)	1037	608	57.61	1.09	(0.91-1.30)
				$p = 0.143$						$p = 0.669$	
DI quintile	people with + FOBT	no. of lesions	PPV	OR	(95 % CI)	DI quintile	people with + FOBT	no. of lesions	PPV	OR	(95 % CI)

Table 4 PPV of the test, standardized participation, lesion and colonoscopy following positive test result, by socioeconomic stratum of place of residence *(Continued)*

		(premal. + malignant)						(premal. + malignant)			
I (least disadvantaged)	773	255	32.97	1.00		I (least disadvantaged)	1168	594	50.18	1.00	
II	789	246	31.05	0.92	(0.74-1.14)	II	1295	705	53.25	1.16	(0.99-1.36)
III	735	258	35.26	1.10	(0.89-1.36)	III	1292	703	53.49	1.16	(0.99-1.36)
IV	688	233	33.98	1.04	(0.83-1.29)	IV	1154	617	52.57	1.11	(0.94-1.31)
V (most disadvantaged)	665	197	29.00	0.85	(0.68-1.07)	V (most disadvantaged)	1119	608	53.29	1.14	(0.96-1.34)
				$p = 0.197$						$p = 0.349$	

OR Age-adjusted odds ratios, *CI* Confidence interval
DI quintile: Socioeconomic deprivation index quintile proposed by the MEDEA project; p: significance value of the likelihood ratio test for the association between DI and outcome variable; RII: relative index of inequality
[a]age-standardized rates per 1000 inhabitants (reference population Basque Country 2011)

physical activity or non-adherence to a Mediterranean diet, as well as greater psychological stress due to socioeconomic status, which may lead to increased susceptibility to disease in general. Moreover, opportunistic CRC screening, which is performed with greater frequency in higher social classes, leads to a higher percentage of cancers avoided in this group, due to lesions being detected in premalignant phases [45, 47, 48]. For the European studies that show a lower incidence of CRC in the lowest socioeconomic strata, it is argued that in addition to a lesser influence of the differential CRC screening effect in Europe, people also have better dietary habits or adhere more closely to a Mediterranean diet, especially in rural areas and southern countries [45–46].

In the Basque Country, according to the 2013 Basque Health Survey, the proportion of men who are smokers, obese or sedentary increases with decreasing social class or education level. Fruit and vegetable intake is also lower in the lower socioeconomic strata, while it seems that the only risk factor that occurs in greater proportion in the higher strata, is that of dangerously high levels of alcohol consumption [49]. The higher prevalence of risk factors in male members of the most disadvantaged groups in the Basque Country may partly account for the results obtained in this study. But not so in the case of women, where no inverse association between social class and lesion detection exists, findings similar to those published by Oliphant et al. with data from a CRC screening programme in the west of Scotland [50]. The authors of the Scottish study could not provide a clear explanation for this differential behaviour between the sexes, although they raised a number of possible reasons, including the possibility of some differences in risk factors between the sexes, such as excessive alcoholism in men or less physical activity in women. In the present study, the 2013 Basque Health Survey reveals that in the Basque Country while tobacco consumption among men increases as social class decreases, no pattern can be seen in women from the age of 45. Nevertheless, the highest prevalence of other risk factors occurs in the most disadvantaged social groups, meaning that the social inequalities in the screening results cannot be explained through these risk factors alone.

Limitations of this study include the fact that, during the study period (2009–2011), the centres participating in the CRC screening programme were not chosen at random, but by the ability of their corresponding referral hospitals to assume the task of performing colonoscopy for screening purposes. This does not preclude broad representation from all socioeconommic groups, since all three provinces are represented and more than 200,000 eligible individuals were included, representing about 50 % of the target population (not taking exclusion criteria into account), with sufficient numbers of people in all relevant variables. It seems, therefore, that the included target population would have similar differential characteristics to the rest of the hypothetical target population of the Basque Country. Further analysis should nevertheless be performed on the definitive data covering 100 % of the population (2014), to assess whether the behaviour is reproduced throughout the entire target population. Moreover, as mentioned above, the non-participant population would most likely have different clinical, social and cultural characteristics to the participating population, and their inclusion might modify the results of this study. Studies that included this non-participant population would be necessary to clarify this question. Finally, using aggregated census tract data to assign socioeconomic status to each individual may lead to incorrect classification of the socioeconomic level in some cases, altering the results to a greater or lesser extent. Numerous studies have, however, demonstrated the use of socioeconomic data of small areas as an approximation to the socioeconomic status of individuals in order to detect health inequalities [51–54]. The absence of individual socioeconomic data has thus been overcome by allocating to subjects the characteristics of the census tract of residence.

Conclusions

Gender and socioeconomic inequalities are relevant in CRC screening programmes. Both influence participation in the CRC programme and the number of lesions found.

Any public health programme is morally and ethically obliged to strive for equity and also improve programme effectiveness. Achieving a CRC screening programme that can improve participation of men and socially disadvantaged groups would make the programme more effective, and also more equitable. In this way, the Basque Country authorities have included indicators related to screening inequities in general strategies and annual evaluations. Some initiatives to increase men's participation have been carrying out involving civil associations, factory managers and Primary Care Centres focused in information improvements (video, web-site, training and open meetings), but others related to tackling root causes of hegemonic masculinity in our societies should also need to develop. Regarding most disadvantaged populations, specific qualitative studies will be necessary, so that their main barriers to participating in the programme are adequately understood.

Competing interests
The authors declare that they have no competing interests.

Authors' contribution
JLH: collaborator in the research Benefits and Harms of Colorectal Cancer Screening (multicenter research). Perspective of Primary Care involvement in participation facilities. AB: collaborator in the research Benefits and Harms of

Colorectal Cancer Screening (multicenter research). Perspective of Social Sciences in the participation barriers. MC: collaborator in the research Benefits and Harms of Colorectal Cancer Screening (multicenter research). Perspective of Public Health Service. Contribution to assign deprivation index. SE: collaborator in the research Benefits and Harms of Colorectal Cancer Screening (multicenter research). Perspective of Public Health Service. Contribution to analyze deprivation index in the programme related to other policies. NM: Researcher in the Public Health Service. Bibliography research and analysis for discussion. IP: Research leader in the research Benefits and Harms of Colorectal Cancer Screening (multicenter research). Perspective of indicators standardization and analysis. II: collaborator in the research Benefits and Harms of Colorectal Cancer Screening (multicenter research). Perspective of quality analysis in colorectal database. EM: Epidemiologist in the Public Health Service. Analysis of data base. EA: collaborator in the research Benefits and Harms of Colorectal Cancer Screening (multicenter research). Review methodology, main results and discussion to adapt them to publish. All authors read and approved the final manuscript.

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Not applicable.

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Colorectal cancer in a second round after a negative faecal immunochemical test

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Objective The faecal immunochemical test is one of the tests recommended by scientific societies for colorectal cancer (CRC) screening in average-risk populations. Our aim was to evaluate the characteristics of CRC detected in a second round of screening after negative results in a first round.

Methods We studied patients in whom CRC was detected in a screening programme. This programme included asymptomatic individuals between 50 and 69 years old and offered tests every 2 years. A total of 363 792 individuals were invited to participate in the first round of faecal immunochemical test screening and 100 135 individuals in the second round after a first negative result. The screening strategy consisted of faecal testing of a single sample using an automated semiquantitative kit, with a cut-off of 20 μg haemoglobin (Hb)/g faeces.

Results The rate of positive results was 6.9% (16 467/238 647) in the first round and 4.8% (3359/69 193) in the second round ($P < 0.0005$). Overall, 860 (0.36%) cases of CRC were detected in the first round and 100 (0.14%) in the second round ($P < 0.005$). The location of the cancer was proximal in 12.5 and 24% of cases detected in the first and second rounds, respectively ($P = 0.008$). Hb concentrations were higher in the first round (211 vs. 109 μg Hb/g faeces in the second round; $P = 0.002$). Multivariate analysis confirmed that, in the second round, CRC diagnosed was more often proximal (hazard ratio vs. first round, 2.4; 95% confidence interval, 1.3–4.4; $P = 0.003$) and the concentration of Hb/g faeces was lower (hazard ratio vs. first round, 2.1; 95% confidence interval, 1.3–3.5; $P = 0.003$).

Conclusion The CRC detection rate is lower in the second round of screening. Further, in the second round, CRC detected is more often in a proximal location and Hb concentrations are lower. Eur J Gastroenterol Hepatol 27:813–818

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth leading cause of cancer-related death [1]. Evidence from several studies has shown that CRC screening is effective and cost-effective in average-risk populations [2–6]. Specifically, randomized-controlled trials have shown that population-based screening for CRC with faecal occult blood tests reduces CRC mortality by 15–33% [7–10].

The faecal immunochemical test (FIT) is one of the tests recommended by scientific societies for CRC screening in average-risk populations [2]. In a recently published population-based randomized trial, FITs detected as many cases of CRC as colonoscopy in the first screening round, and the two techniques detected CRC at a similar stage [11]. Moreover, the FIT was associated with a higher participation rate than colonoscopy or the guaiac faecal occult blood test [12]. However, the sensitivity and specificity of FIT have been found to be 27–31% and 95–97%, respectively, for advanced neoplasia and 65.8–75% and 94.6–95% for CRC [13,14]. Because of this variability in the detection of advanced neoplasia, FIT screening is usually performed every 1–2 years after 50 years of age.

Denters *et al.* [15] describe the characteristics of four cases of CRC detected (0.19%) in a second round after a negative FIT result in the first round of screening. They observed that the distribution of the location of the cancer in the colon (proximal/distal) was similar to that in the first round. However, there is a lack of data on the detection rate of CRC with FITs, and the staging and characteristics of these tumours in a second round compared with the first round. The aim of this study was to evaluate the characteristics of CRC detected in a second round of screening after negative results in a first round.

Methods

Study population and data collection

Individuals with CRC detected in the CRC screening programme in the Basque country between April 2009 and

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Keywords: colorectal cancer screening, faecal immunochemical test, first round, negative faecal immunochemical test

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April 2013 were eligible for inclusion in the study [16]. This screening programme includes asymptomatic individuals between 50 and 69 years old and tests are performed every 2 years. Eligible individuals were invited to participate in the screening, and 2 weeks later, an FIT kit was sent to his/her home. The kit contained a plastic container for the stools, a probe and a collection tube together with a plastic bag in which to seal them, and written instructions on how to collect the sample for the test. Specifically, after one bowel movement, they were instructed to sweep the tip of the probe through the stool several times and then insert the probe into the collection tube. Participants then handed the sample in at their health centre the following day.

During the study period, 363 792 individuals were invited to participate in the first round of FIT screening (first round) and 100 135 individuals in the second round after a first negative result (second round). The eligible population was contacted progressively from April 2009. In April 2011, the second round was started in individuals who had obtained a negative FIT result.

Individuals were excluded from the study if they had any of the following: a personal history of CRC, adenoma or inflammatory bowel disease; a family history of hereditary or familial CRC (defined as ≥ 2 first-degree relatives with CRC or 1 diagnosed before the age of 60); or any severe comorbidities; as well as if they had undergone a previous colectomy; a previous CRC screening test in which faecal occult blood was detected in the last 2 years; or a sigmoidoscopy/colonoscopy in the last 5 years. Those who tested positive in the first round, were at least 70 years of age, had moved out of the region or had died were not invited to participate in the second round.

The screening strategy consisted of an FIT of a single sample using the automated semiquantitative OC-Sensor kit (Eiken Chemical Co., Tokyo, Japan) without any specific diet or medication limitations. Samples were processed as described previously [11]. Individuals with at least 100 ng haemoglobin (Hb) per ml of buffer solution (corresponding to 20 μg Hb/g faeces) were invited for a colonoscopy. In those undergoing colonoscopy, bowel cleansing and sedation was performed as described previously [17]. All colonoscopies were performed by experienced endoscopists (each performing > 200 colonoscopies per year) [18].

Tumours were staged according to the American Joint Committee on Cancer classification and stages III and IV were considered advanced [19]. The location was classified as proximal or distal, proximal indicating that the tumour lay between the cecum and the splenic flexure, and distal indicating that it lay between the splenic flexure and the anus. In addition to the FIT result, stage and location, we analysed histological findings, the degree of differentiation of the tumour and patient age and sex.

Statistical analysis

χ^2 and/or Fisher's tests were used to compare categorical variables, and *t*-tests were used to compare continuous variables between the groups (first round and second round). Faecal Hb concentrations are presented as medians and were compared using nonparametric Mann–Whitney *U* tests.

Logistic regression was used to analyse the independent effect of each variable on the probability of identifying CRC in the second round. All analyses were carried out using SPSS 17.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

A total of 363 792 individuals were invited to the first round and 100 135 individuals to the second round after a negative FIT result (Fig. 1). Of these, 238 647 individuals (65%) participated in the first round and 69 193 individuals (69%) participated in the second round ($P < 0.0005$). Of the patients who completed the FIT, 47% (112 164) in the first round and 45% (31 136) in the second round were men ($P < 0.0005$). The FIT positivity rate was 6.9% (16 467) in the first round and 4.8% (3359) in the second round ($P < 0.0005$). Of those with positive results, 62% in the first round and 58% in the second round were men ($P < 0.0005$).

We found CRC in 860 (0.36%) individuals in the first round and in 100 individuals (0.14%) in the second round ($P < 0.005$). The location of the CRC was proximal in 12.5% of cases in the first round and 24% in the second round ($P = 0.008$) (Table 1). There were no significant differences in terms of age, sex, stage, histological findings or degree of differentiation.

Quantification of faecal Hb showed that Hb concentrations were higher in those with higher stage CRC, with values of 167, 283, 260 and 212 μg Hb/g faeces for stages I, II, III and IV, respectively ($P < 0.005$). Significantly higher concentrations were found in the first round than the second round overall (211 vs. 109 μg Hb/g faeces, respectively), and in the case of stage I cancer for both distal and proximal locations (Table 2). However, in the case of stage IV CRC in a proximal location, Hb concentrations were actually higher in the second round, although the difference did not reach significance.

Variables that showed an independent effect on the likelihood of detecting CRC in the second round were proximal location [hazard ratio in the second vs. first round, 2.4; 95% confidence interval (CI), 1.3–4.4; $P = 0.003$] and bleeding (hazard ratio, 2.1; 95% CI, 1.3–3.5; $P = 0.003$). The probability of diagnosing CRC in individuals with Hb concentrations lower than 145 μg Hb/g faeces was twice as high in the second round as the first (hazard ratio, 2.1; 95% CI, 1.3–3.5; $P = 0.003$).

Endoscopic treatment was more common in cases detected in the first round than the second (30 vs. 18%; $P < 0.05$). There was no significant difference in stage between the first and the second round by location (proximal or distal) of the tumours.

First-round Hb concentrations among patients with CRC diagnosed in the second round were as follows: below 5 μg Hb/g faeces in 58 individuals (58%); between 5 and 9.9 μg Hb/g faeces in 18 individuals (18%); between 10 and 14.9 μg Hb/g faeces in 10 individuals (10%); and between 15 and 19.9 μg Hb/g faeces in 10 individuals (10%), whereas data was missing for four cases (4%) as errors were made during the collection of the sample and the test was not repeated. The mean Hb concentrations in the second round were 297, 248, 492, 865 and 651 μg Hb/g faeces for cut-off points of less than 5, 5–9.9, 10–14.9 and 15–19.9 μg Hb/g faeces and cases with missing first-round data (because of errors) in the first round, respectively. The Hb concentrations in the second round were

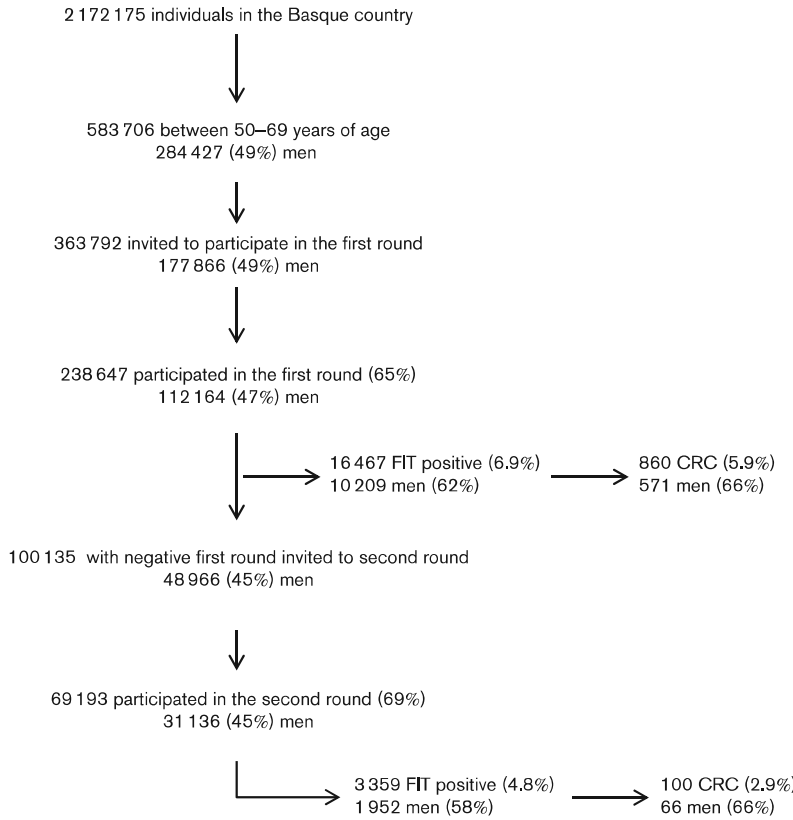

Fig. 1. Study recruitment and participant flow. CRC, colorectal cancer.

significantly lower in individuals with less than 10 μg Hb/g faeces than those with between 10 and 19.9 μg Hb/g faeces in the first round (285 vs. 674 μg Hb/g faeces; $P < 0.05$).

Discussion

In our study, fewer cases of CRC were diagnosed in second-round FIT screening than in baseline screening (CRC being found in 0.36% of participants in the first round vs. 0.14% in the second round). Van Roon *et al.* [20] found CRC in 0.36% (22/7229) and 0.3% (4/1280) of participants in the first and second rounds, respectively, and Denters *et al.* [15] found rates of 0.41% (12/2871) and 0.19% (4/2022), respectively, in these rounds, whereas Morikawa *et al.* [14] detected CRC in 0.36% (79/21 805) of participants in a first round.

Large polyps and colorectal tumours are more frequently ulcerated and bleed more than smaller polyps and small flat colorectal tumours. Hence, the diagnosis of the latter by FIT screening is more difficult. In our study, we observed that the Hb concentration detected in FITs increases with the CRC stage. Similar findings have been reported by other authors. For example, Morikawa *et al.* [14] obtained a mean sensitivity of 65.8% for invasive cancer, with sensitivities by Dukes' stage of 50.0% for stage A, 70.0% for stage B and 78.3% for stage C or D [14].

The location of the CRC was proximal in 12.5% of cases detected in our first-round FITs. Previous studies on consecutive series of patients with CRC found proximal CRC in 25% of cases [11,21,22]. These data suggest that around 12.5% of proximal CRCs are not detected in the first round of screening with a FIT. Similar figures have been reported for advanced neoplasia. Studies published by both Morikawa *et al.* [14] and Haug *et al.* [23] concluded that FIT screening has lower sensitivity for the detection of proximal than distal advanced neoplasia (16–20 vs. 31–33%, respectively). Similar results were found when FIT screening sensitivity was analysed for proximal versus distal CRC (56.5 vs. 69.6%, respectively) [14]. By contrast, other research has shown that this screening has a similar sensitivity for detecting proximal and distal neoplasia (38 and 37%, respectively) [13].

Several factors could explain more cases of proximal CRC being found in the second round than the first. First, cancer in the right colon is more likely to be sessile or flat than that in the left colon and rectum and may bleed less [24]. Second, some rapidly progressing cancers, such as those because of hereditary syndromes, may not have been present at the time of the first FIT [25]. Third, nonbleeding cancer remains in a nonbleeding state for a long time in the right colon and CRC may have an intermittent bleeding pattern. Fourth, Hb from proximal CRC may degrade before reaching the anus, which could affect the accuracy of FITs [26]. Fifth, because of differences in stool

Table 1. Characteristics of patients with CRC in the first round of FIT screening and second round after a first negative result

	First round ($n=860$)	Second round ($n=100$)	P
Sex (men) [n (%)]	571 (66)	66 (66)	0.5
Age (years)	61.5±5.3	61.4±4.9	0.7
Location [n (%)]			
Proximal	108/860 (12.5)	24/76 (24)	0.008
Stage [n (%)]			
I	428 (50)	45 (45)	0.5[a]
II	160 (19)	20 (20)	
III	201 (23)	26 (26)	
IV	71 (8)	9 (9)	
Haemoglobin concentration (μg Hb/g faeces) [median (IQR)][b]	211 (78–604)	109 (47–497)	0.002[c]
Histological findings			
Adenocarcinoma [n (%)]	842 (98)	97 (97)	0.6
Mucinous or signet-ring cell	14	2	
Carcinoid	4	1	
Differentiation [n (%)]			
Well-to-moderately	826 (96)	97 (97)	1.0
Poorly	34 (4)	3 (3)	
Haemoglobin concentration distribution (μg Hb/g faeces) [n (%)]			
<58	164 (19)	27 (27)	0.04
58–144	164 (19)	24 (24)	
145–311	180 (21)	13 (13)	
312–786	181 (21)	15 (15)	
>786	171 (20)	21 (21)	
<145[d]	328 (38)	56 (56)	0.001
>145	532 (62)	44 (44)	
Treatment [n (%)]			
Only endoscopy	258 (30)	18 (18)	0.08
Surgery±chemotherapy±radiotherapy	602 (70)	82 (82)	

CRC, colorectal cancer; FIT, faecal immunochemical test; Hb, haemoglobin.
[a]Linear trend.
[b]Interquartile range.
[c]Mann–Whitney U-test.
[d]Grouped according to the cut-off point for which there were the greatest differences between quartiles.

Table 2. Median haemoglobin concentration (μg Hb/g faeces) in the first and second rounds of FIT screening by stage and location

	Proximal			Distal		
	First round	Second round	P	First round	Second round	P
Stage I	214	46	0.01	176	88	0.02
Stage II	186	69	0.2	303	693	0.7
Stage III	194	168	0.9	277	63	0.2
Stage IV	110	570	0.1	271	165	0.6

FIT, faecal immunochemical test; Hb, haemoglobin.

consistency, blood may be more homogeneously distributed when originating from the right side and dominantly on the surface when originating from the left side, and this would also favour the detection of left-sided neoplasia [23]. In our study, the concentration of Hb in faeces was lower in patients with CRC diagnosed in the second round than the first (overall and in those with distal or proximal stage I cancer). Surprisingly, however, faecal Hb concentrations tended to be higher in the second round than the first round in the subset of patients diagnosed with stage IV proximal, although the difference did not reach significance.

There are many potential strategies to improve the diagnosis of proximal CRC. First, we could increase the frequency of screening to every year; however, a recent study, examining intervals of 1, 2 and 3 years, showed that the yield at the second screening round was not influenced by the interval length within this 1- to 3-year range [20]. Second, the number of tests per round could be increased, but data on the effect of this are conflicting. Analysing FIT results, one study showed that the sensitivity increased from 33 to 47% on testing three samples instead of one [27], and another showed that the positivity rate increased from 8 to 13% on adding a second sample [28], whereas the sensitivity for detecting colorectal neoplasia was reported to be 56% with the 1-day method, 83% with the 2-day method and 89% with the 3-day method [29]. By contrast, other studies examining the ability to detect CRC after two or three samples indicated no improvement in sensitivity or specificity. In addition, the requirement to take several faecal samples decreases participation in screening, whereas, conversely, the 1-day method may increase the acceptability of screening. Third, a lower cut-off could be used for Hb concentration. Cost-effectiveness analysis of different cut-offs concluded that the best cut-off point was 27.5 μg Hb/g faeces (115 ng/ml) [30]. A lower cut-off (10 μg Hb/g faeces) would increase the number of positive screenings and require more colonoscopies and more unnecessary colonoscopies. Fourth, different cut-offs could be used at different stages and under different circumstances, for example the cut-off could be set at 20 μg Hb/g faeces in the first round and 15 or even 10 μg Hb/g faeces in the second round, or the cut-off could be lower in the first round (15 or 10 μg Hb/g faeces) depending on colonoscopy capacity and costs. In our study, with a cut-off of 20 μg Hb/g faeces, the positivity rate was 6.9% in the first round and 4.8% in the second round. Applying a lower cut-off of 10 μg Hb/g faeces in the first round would have yielded a positive result for 20% of the individuals found to have CRC detected in the second round. Fifth, qualitative FITs could be used; however, when compared

with other FITs, the sensitivity and specificity are similar [31]. Finally, we should consider using new methods of stool analysis or combining the FIT with other tests, such as faecal DNA or combined faeces and blood tests, to improve the detection of proximal CRC [32,33].

This study has several strengths. All participants in this accuracy study were screening naive. They were consecutively invited to participate in the FIT screening. All FIT samples were collected, delivered, processed and analysed in accordance with the protocol, minimizing the risk of Hb degradation. To our knowledge, this is the first study to examine the characteristics of a large number of individuals with CRC who obtained negative results in a first-round FIT in a population screening programme. In other studies [15,20,34], the number of CRC cases analysed after a negative first-round FIT result was very small, ranging between three and seven cases.

Some limitations should also be recognized. First, it is unknown whether advanced CRCs were false negatives in the first round of FIT screening. Second, we have not determined the molecular characteristics of proximal tumours, and therefore, do not know whether they were present previously. Third, colonoscopy was not performed in participants with negative FIT results. Fourth, we cannot be sure whether all participants were completely asymptomatic.

In conclusion, our study indicates that the detection rate of CRC in a second round of FIT screening is lower than that in a first round. For CRC diagnosed in the second round after a negative FIT result in the first round, Hb concentrations in faeces were lower and the tumour was more likely to be proximal.

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Author contributions: L.B., A. Castells and M.P. developed the study concept and design and drafted the manuscript. J.C., I.G., A. Cosme, E.A., I.M., I.I. and I.P. obtained the clinical data, designed and analysed the database and interpreted the data. L.B. and C.S. carried out the statistical analysis of data and contributed toward the interpretation of data. All authors read and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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Appendix

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Population-based colorectal cancer screening: comparison of two fecal occult blood test

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Background: The aim of screening for colorectal cancer is to improve prognosis by the detection of cancer at its early stages. In order to inform the decision on the specific test to be used in the population-based program in the Basque Autonomous Region (Spain), we compared two immunochemical fecal occult blood quantitative tests (I-FOBT).

Methods: Residents of selected study areas, aged 50–69 years, were invited to participate in the screening. Two tests based on latex agglutination (OC-Sensor and FOB Gold) were randomly assigned to different study areas. A colonoscopy was offered to patients with a positive test result. The cut-off point used to classify a result as positive, according to manufacturer's recommendations, was 100 ng/ml for both tests.

Results: The invited population included 37,999 individuals. Participation rates were 61.8% ($n = 11,162$) for OC-Sensor and 59.1% ($n = 11,786$) for FOB Gold ($p = 0.008$). Positive rate for OC-Sensor was 6.6% ($n = 737$) and 8.5% ($n = 1,002$) for FOB Gold ($p < 0.0001$). Error rates were higher for FOB gold (2.3%) than for OC-Sensor (0.2%; $p < 0.0001$). Predictive positive value (PPV) for total malignant and premalignant lesions was 62.4% for OC-Sensor and 58.9% for FOB Gold ($p = 0.137$), respectively.

Conclusion: OC-Sensor test appears to be superior for I-FOBT-based colorectal cancer screening, given its acceptance, ease of use, associated small number of errors and its screening accuracy. FOB Gold on the other hand, has higher rate of positive values, with more colonoscopies performed, it shows higher detection incidence rates, but involves more false positives.

Keywords: immunochemical fecal occult blood test, population screening, health outcomes research, health impact assessment, colorectal cancer

INTRODUCTION

Colorectal cancer (CRC) is the third leading cancer and the fourth leading cause of cancer deaths worldwide, with 1.2 million estimated new cases and 609,000 estimated deaths in 2008 (Karsa et al., 2010). In the European Union (EU), as well as in Spain, CRC is the third leading newly diagnosed cancer, after lung cancer and prostate cancer in males and the second after breast cancer in females and the second leading cause of overall cancer deaths (Karim-Kos et al., 2008). Due to its high frequency, mortality and morbidity rates, and the high socio-economic burden associated with this disease, CRC has become an important and challenging public health problem (Karsa et al., 2010).

In the Basque Country (one of 17 Autonomous Regions of Spain), once age-adjusted at European standard population, CRC incidence (86.37/100,000 among men and 39.75/100,000 among women in 2009), and mortality rates (20.6/100,000 in 2009), have shown moderate increases, mainly in men from 1986 to 2008 (Izarzugaza et al., 2010).

Nowadays, a substantial amount of information is available on CRC etiology and prognosis. Its slow growth from benign lesions is currently well known and this makes many of these lesions detectable and removable at an early stage (Scottish Intercollegiate Guidelines Network [SIGN], 2011).

Primary prevention is based mainly on the adoption of healthy lifestyle measures including changes in dietary habits (Kahi et al., 2008). However, the benefits of both healthy lifestyle measures become visible in the long-term. It is therefore necessary to design and implement programs that allow early detection and management of pre-cancerous and cancer lesions (secondary prevention; von Karsa et al., 2008).

The new European Code against Cancer (2003/878/EC; European Code Against Cancer, 2012) includes among its recommendations that "men and women from 50 years of age and older should participate in CRC screening." Both the EU and the Comprehensive Cancer Plan of the Spanish Ministry of Health, Social Services and Equity (2006; Ministerio de Sanidad y Política Social, 2010) include the implementation of screening programs among their recommendations for CRC prevention. Nationwide CRC screening programs are currently being implemented in several European countries as well as Spain. Effective screening methods have been shown to decrease CRC incidence rates by 20% and mortality rates by 33% (Mandel et al., 1993; Shaukat et al., 2013).

Up to now, the guaiac fecal occult blood test (g-FOBT) was considered the standard screening test used in CRC detection programs. However, recently marketed immunochemical tests (I-FOBT) have become widely accepted due to several advantages over g-FOBT (Rozen et al., 2009; Oono et al., 2010), and its use is recommended for population-based programs (Segnan et al., 2011). Advantages include a higher sensitivity, specificity for human hemoglobin (Allison et al., 2007), fewer stool samples required and no diet or medications restrictions are needed. Additionally, the quantitative nature of I-FOBT results allows for an optimal cut-off point to be set for a nationwide screening program (Castiglione et al., 2002; Wong et al., 2003; Fraser et al., 2006; Guittet et al., 2007; Levi et al., 2007), based on pre-specified criteria.

Adherence rate is of paramount importance to ensure CRC screening programs effectiveness. In this sense, immunochemical tests show higher adherence (Cole et al., 2003; Van Rossum et al., 2008; Hol et al., 2010) and detection rates (Smith et al., 2006; Guittet et al., 2007; Van Rossum et al., 2008) than g-FOBT.

The I-FOBT testing samples can be analyzed automatically, which involves important advantages in terms of quality assurance and costs (Levi et al., 2007).

The Basque Ministry of Health approved in 2008 the implementation of a population-based screening program through the detection of fecal occult blood (FOB) using I-FOBT as the screening method every 2 years and colonoscopy as a confirmation test. An important issue to be dealt with was decision on the particular I-FOBT to be used as two commercial diagnostic kits were available in the Spanish market at the time screening activities were about to start.

A comprehensive literature search did not yield consistent information regarding comparison of analytical and operational characteristics among marketed immunochemical tests. Just one journal article addressing the compared diagnostic efficacy of two different I-FOBTs was found, with no definitive results (Rubeca et al., 2006).

Therefore, we aimed to compare the two available I-FOBT tests: OC-Sensor (Eiken Chemical Co., Tokyo, Japan) and FOB Gold (Sentinel Diagnostics SpA, Milan, Italy) in terms of diagnostic performance, ease of use, acceptance, and operational features within the context of the pilot phase of a CRC population-based screening program. The outcomes of that study would then inform the decision-making process to choose the screening test for the ulterior full implementation.

METHODS

This study involved the first round of a CRC population-based screening program in the Basque Country – restricted to some previously determined health districts – from January 2009 to March 2010, and invited residents aged 50–69, from the Basque Health Service database ($n = 37{,}999$). People with colorectal cancer resection (CCR) history and who had undergone a previous colonoscopy within the past 5 years were excluded.

Participation was voluntary and was offered to all subjects residents who lived in the areas designated for the study and had a general practitioner (GP) assigned.

The Screening Management Centre sent a letter explaining the aims and methods of the screening program to all eligible subjects. After 7–10 days, a second letter was sent with a request for them to participate in the program, including a kit package specifically suited to collect a single sample of feces, and stickers with the uptake's data to be attached to the tube. Participants could leave the kit sample at the Primary Care Centers during working hours (from 8:00 am to 8:00 pm). Samples were processed by trained laboratory staff following the instructions provided by the manufacturers. At health-district level, neither health professionals nor administrative staffs were aware that a comparison of screening kit tests was being conducted. Each assay test was randomly assigned by an independent researcher to each of five health districts where the program was being implemented. According to both manufacturer's instructions, tests were considered positive when the sample contained at least 100 ng/ml of hemoglobin by buffer. A colonoscopy was offered to all positive participants by their GP. When errors were identified by any laboratory before or after analyzing the sample, a new kit was sent to the participant and the new sample analyzed. True positives were defined by colonoscopy examination and pathology analysis. CRC screening performance measures were assessed following the National Guidelines published in 2009 (Castells et al., 2009). Every case was codified by expert staff in the Screening Management Centre. Advanced adenoma was considered: >10 mm, or 3–10 adenomas or villous morphology, or high degree of dysplasia. Cancer colorectal was considered pT1.

This study was conducted under real practice conditions, which is why we did not perform colonoscopies for patients with a negative FOBT test. To control the false negatives interval cancers are followed, as recommended by the European Guidelines (von Karsa et al., 2008).

The study was submitted and approved by the Ethics Committees of screened areas.

STATISTICAL ANALYSIS

Colorectal cancer screening performance measures were assessed following the European Guidelines (Segnan et al., 2011). Chi-square tests were used to compare proportions between relevant subgroups. Log-binomial regression models (Barros and Hirakata, 2003) were fitted to yield age and sex-adjusted comparisons among assessed kits, in terms of corresponding participation rates, positive predictive values, error rates, and cancer and advanced adenomas incidence rates. In order to assess magnitude and statistical significance of the effects of predictors of interest, average marginal effects (AME; mean change in predicted probabilities of the

response variable across all sampled individuals when the categorical predictor changes by one level with respect to the reference level, keeping all other predictors at observed values) were calculated (Bartus, 2005). In some instances, to provide additional information on the magnitude of effects, relative estimates are given in the form of relative risks (RR) as estimates of prevalence ratios. Standard errors that took the cluster (health district assignment of kits) structure of the data into account were estimated using the delta method. Estimated models included statistically significant interactions. As gender–age group interactions were most often encountered, AME are shown by gender and age stratum combinations to ease interpretation of effects. Significance level was set to 5%.

Statistical analyses were performed using Stata 12 for Windows (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

RESULTS

PROGRAM COVERAGE

The target population included 39,566 individuals. Finally, a total of 37,999 individuals aged 50–69 and who met the participation criteria, were invited to participate. **Table 1** shows the characteristics of this population and performed procedures. Statistically significant differences in age distribution were found between invited individuals assigned to the study kits [mean age for population receiving FOB Gold 58.6 years (SD: 5.6) and 59.1 (5.8) for population receiving OC-Sensor; $p = 0.000$]. The same pattern of overall and strata-based age differences was found between individuals of both participants groups [mean age for FOB Gold 58.9 (5.5) and 59.5 (5.7) for OC-Sensor]. No statistically significant differences were found in gender distribution between invited people (50.2% of people receiving FOB Gold test were women vs. 50.8% in population receiving OC-sensor; $p = 0.233$).

Overall participation rate was 60.4% (OC-Sensor assay 61.8% vs. 59.1% for the FOB Gold, $p = 0.008$). It was consistently and significantly higher for females with an overall marginal effect estimate of 6.8% increase in participation rate relative to men (**Tables 2** and **3**). Participation rate with OC-Sensor test was higher for both sexes (65.1 vs. 62.6% in women and 58.3 vs. 55.6% in men) and kept consistently higher (range of differences: 1.5–3.5%) across all age groups. However, this difference was not statistically significant when the cluster-randomized design was accounted for in the analysis (RR = 1.05; 95% CI = 0.93–1.18) Participation rates increased significantly with age in both groups, showing a gradient which reached its highest value in those aged 60–64. An interaction between gender and age was found in the two oldest strata, reflecting a larger increase in rates among men with stabilization in the oldest strata and a smaller increase among women aged 60–64 with a moderate reduction in the oldest age group. Estimates of marginal effects on participation are, hence, presented separately by gender (**Table 3**).

Table 1 | Invited population, age, and sex distribution of participants and tests performed as a result of the screening program.

	OC-Sensor		FOB Gold		Overall	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (year) of invited individuals	59.1	5.8	58.6	5.6	58.8	5.7
	n	**%**	***n***	**%**	***n***	**%**
Invited population	18,064	100	19,935	100	37,999	100
Participants	11,162	61.8	11,786	59.1	22,948	60.4
Age distribution (year)						
50–54	2729	24.5	3163	26.8	5892	25.7
55–59	2711	24.3	3156	26.8	5867	25.6
60–64	3096	27.7	3169	26.9	6265	27.3
65–69	2626	23.5	2298	19.5	4924	21.4
Gender						
Male	5187	46.5	5529	46.9	10716	46.7
Female	5975	53.5	6257	53.1	12232	53.3
I-FOBT results						
Positive	737	6.6	1,002	8.5	1,739	7.6
Negative	10,416	93.3	10,723	91.0	21,139	92.1
Result not available	9	0.1	61	0.5	70	0.3
Patients with colonoscopy performed	686	93.1[1]	914	91.2[1]	1,600	92.0[1]
Colonoscopic result available	686	93.1[1]	912	91.0[1]	1,598[2]	91.9[1]

[1] *Percentages of participants with the I-FOBT test positive;*
[2] *1,576 colonoscopies with conclusive results.*

Table 2 | Results of participation rates and true positive rates by gender, age, and type of kit administered (true positive rates based on 1,576 colonoscopies performed with conclusive results).

	Female			Male		
	OC-Sensor	**FOB Gold**	**Total**	**OC-Sensor**	**FOB Gold**	**Total**
Participation rates (%)						
Total	65.1	62.6	63.8	58.3	55.6	56.9
Age (year)						
50–54	59.5	57.8	58.5	51.0	49.7	50.3
55–59	67.0	63.6	65.2	57.6	55.6	56.5
60–64	69.3	67.2	68.2	63.4	59.9	61.5
65–69	64.9	62.5	63.8	62.8	59.3	61.1
True positive rates (%)						
Total	35.2	31.0	32.8	54.3	49.1	51.3
Age (year)						
50–54	36.8	32.9	34.2	41.7	36.5	38.3
55–59	33.3	29.6	31.3	52.3	44.5	48.0
60–64	35.4	31.3	32.9	56.9	53.1	54.8
65–69	35.8	30.2	32.9	59.2	57.5	58.3

Table 3 | Influence of the type of kit administered, gender and age on uptake and true positive rates.

Participation rates (%)						
Factor	**AME**	**CI**	***p*-Value**			
Female	6,8	(5.9/7.6)	0.000			
	Males			**Females**		
Factor	**AME**	**CI**	***p*-Value**	**AME**	**CI**	***p*-Value**
Kit	2.6	(−5.1/10.2)	0.513	2.4	(−4.8/9.6)	0.512
Age (55–59)	6.2	(3.8/8.7)	0.000	6.7	(5.9/13.3)	0.000
Age (60–64)	11.2	(8.5/13.9)	0.000	9.6	(5.9/13.3)	0.000
Age (65–69)	10.7	(6.2/15.1)	0.000	5.1	(1.9/8.3)	0.002
True positive rates						
Factor	**AME**	**CI**	***p*-Value**			
Female	−18.3	(−22.1/−14.6)	0.000			
	Males			**Females**		
Factor	**AME**	**CI**	***p*-Value**	**AME**	**CI**	***p*-Value**
Kit	4.1	(−0.4/8.6)	0.074	4.4	(−4.9/13.8)	0.354
Age (55–59)	9.4	(3.5/15.4)	0.002	−3.5	(−11.7/4.7)	0.402
Age (60–64)	16.1	(11.7/20.6)	0.000	−1.7	(−3.6/0.3)	0.096
Age (65–69)	19.6	(11.4/27.7)	0.000	−2.0	(−12.8/8.9)	0.721

Results are presented separately for men and women as there was evidence of interaction between gender and age. AME, average marginal effects; CI, 95% confidence intervals. Reference groups are males and 50–54 years age group.

OUTCOMES WITH FECAL OCCULT BLOOD TESTING

Positive rate for OC-sensor was 6.6 and 8.5% for FOB Gold (RR = 0.77; 95% CI = 0.69–0.87; $p = 0.000$). FOB Gold had consistently higher positive rates than OC-Sensor across all age and sex strata, except for women in the 54–59 year age-group, where rates were very similar (OC-Sensor 4.6 vs. 4.5% for FOB Gold).

True positive rates were higher for OC-Sensor across all age-sex strata (**Table 2**). Due to age–gender interaction, results are again shown separately for men and women. Among men this

difference among kits was statistically significant on the relative scale (RR = 1.07; 95% CI = 1.00–1.14) and marginally significant on absolute scale (**Table 3**). Among women differences were not statistically significant on either scale (RR = 1.04; 95% CI = 0.84–1.29). Increasing age was significantly associated with substantially higher positive rates only among men (**Table 3**).

Significant differences were found between the compared kits in relation to the total number of errors [error rate for OC-Sensor 0.24% and for FOB Gold 2.35%, AME: −2.1 (−0.2/−4.0)]. Being female was marginally associated to a lower error rate [RR = 0.85 (0.72–1.01), $p = 0.06$]. Increasing age was also associated to a higher error rate. Again there was interaction between age and sex, with the highest risk in men of 60–64 years of age [RR = 1.62 (1.36–1.92)] and in women of the 65–69 years stratum [RR = 2.14 (1.71–2.67)]. Most of the errors found in the case of FOB Gold were produced as a result of an incorrect sample manipulation by the participants.

OUTCOMES WITH COLONOSCOPY

The results of the colonoscopies are shown in **Table 4**. No significant differences were observed between OC-Sensor and FOB Gold groups. Although 80% of cancers detected in the OC-Sensor group were early cancers (stages I–II) vs. 56.8% in the FOB Gold group, due to the small number of malignancies detected, this difference was not statistically significant.

Table 5 shows the detection rates of advanced adenomas and cancerous lesions among screening participants. FOB Gold assay users showed higher rates overall and in most age-sex strata. Statistically significant interactions were found between type of kit and gender with age strata and, in order to ease interpretation of results, marginal predicted rates are used. Differences in marginal predictions were highly statistically significant according to type of kit assay ($p = 0.000$) with almost 10 more lesions detected with FOB Gold per 1,000 participants as compared to OC-Sensor. Being female was also strongly associated with a lower detection of pre-malignant and malignant lesions ($p = 0.000$) whereas increasing age was significantly associated with consistently higher detection rates ($p = 0.000$; **Table 5**).

DISCUSSION

When a population-based screening program is to be implemented, one key issue to deal with is selection of the screening test to use. In the Basque Country initial decision considered that the population-based CRC screening program was to be based on I-FOBT. Accordingly, in the context of a progressive implementation of the CRC population-based program, a quasi-experimental study has been carried out aimed to compare the diagnostic accuracy and operational characteristics of the two available marketed I-FOBT tests, FOB Gold and OC-Sensor. Manufacturers' recommended cut-off levels have been used (Vilkin et al., 2005; Rubeca et al., 2006; Levi et al., 2007). In our study, several remarkable differences have been found between the diagnostic kits compared. It may be possibly attributable to differences in the quantity of buffer and other features (NHS Purchasing and Supply Agency, 2009; Moss et al., 2010).

Overall participation rate (60.4%) in this pilot program is well above the minimum acceptable recommended (Segnan et al., 2011) and similar or higher than reported rates in other pilot or established screening programs (UK Colorectal Cancer Screening Pilot Group, 2004; Department of Health, 2006; Málaga López et al., 2010). This may be partly attributed to the use of an invitation approach based on mail contact with the target population that included sending the fecal sampling kit (Van Roosbroeck et al., 2012). Participation rates were almost 7% higher in women and increased with aging in both sexes reaching a peak in the 60–64 age group. This result is in agreement with most but not

Table 4 | Results of the colonoscopies and stage distribution of diagnosed cancers.

	OC-Sensor			FOB Gold			
	n	%	95% CI	*n*	%	95% CI	*p*-Value
Normal	201	29.3	25.8–32.8	302	33.1	30.1–36.3	n.s
Polyp	39	5.7	4.0–7.7	52	5.7	4.3–7.4	n.s
Not advanced adenoma	106	15.4	12.8–18.3	156	17.1	14.7–19.7	n.s
Advanced adenoma	282	41.1	37.4–44.9	338	37.1	33.9–40.3	n.s
Cancer*	35	5.1	3.6–7.0	44	4.8	3.6–6.5	n.s
Stage I	18	51.4	35.1–67.5	17	38.6	24.4–54.5	n.s
Stage II	10	28.6	15.5–45.0	8	18.2	8.2–32.7	n.s
Stage III	6	17.1	7.2–32.3	13	29.5	16.8–45.2	n.s
Stage IV	1	2.9	0.7–14.9	5	11.4	3.8–24.6	n.s
Unknown	0	0	0–10.0	1	2.3	0.06–12.0	n.s
Non-neoplasic pathology	8	1.2	0.5–2.2	9	1.0	0.4–1.9	n.s
Inconclusive	15	2.2	1.2–3.6	11	1.2	0.6–2.1	n.s
Total	686	100	–	912	100	–	

*n.s., non-significant. *Percentages for stages of cancer are based on the total number of cancers instead of total number of colonoscopies.*

Table 5 | (a) advanced adenoma and (b) cancer detection incidence rates according to gender, age group, and kit assay; (c) estimated marginal predictions of advanced adenomas and cancer detection rates according to gender, age group, and kit assay (based on health-district adjusted log binomial regression model including interactions between kit and gender with age group).

	Female			Male		
	OC-Sensor	**FOB Gold**	**Total**	**OC-Sensor**	**FOB Gold**	**Total**
(a) Advanced adenoma detection rates (‰)						
Total	12.6	14.3	13.4	39.8	45.1	42.5
Age (year)						
50–54	8.3	12.9	10.8	18.6	35.9	21.5
55–59	13.1	11.9	12.5	44.6	35.9	39.9
60–64	11.9	14.8	13.0	45.3	55.6	50.5
65–69	17.2	18.8	17.9	51.0	70.7	60.4
(b) Cancer detection rates (‰)						
Total	2.0	2.4	2.2	4.4	5.2	4.8
Age (year)						
50–54	1.4	2.9	2.2	0.8	2.7	1.8
55–59	1.4	0.6	0.9	0.8	5.4	3.3
60–64	1.8	3.0	2.4	7.1	2.7	4.8
65–69	3.6	3.4	3.5	8.9	11.6	10.2
(c) Marginal predicted detection rates (‰)						
Gender	**Predicted**	**95% CI**				
Male	68.4	64.8–72.0				
Female	40.8	37.9–43.7				
Age (year)						
50–54	28.4	26.5–30.3				
55–59	43.2	37.7–48.7				
60–64	50.4	46.6–54.3				
65–69	64.0	57.8–70.1				
Kit						
FOB Gold	50.6	49.0–52.3				
OC-Sensor	40.8	37.9–43.8				

all FOBT-based screening programs conducted in Europe and Australia (Von Euler-Chelpin et al., 2010; Australian Institute of Health and Welfare, 2012). There was a significant decline in participation among women of the oldest group, but not among men. Other papers have reported a drop in participation rates in oldest age groups as well (Von Euler-Chelpin et al., 2010). This finding cannot be compared with results from the single published randomized comparison of diagnostic performance of both tests (Rubeca et al., 2006) as participation required using both diagnostic kits simultaneously. However, one of the main strengths of our study is that it was conducted in standard of care conditions.

The use of OC-Sensor assay resulted in a consistently increased but not statistically significant absolute participation rates of around 2–3% which might have actual practical relevance though. Gender and age-related participation patterns were similar for both assays. As we did not survey participants or qualitatively analyzed on individual characteristics or potentially relevant operational issues such as ease of use of received kits or other factors, we cannot make any conclusive statement about the reasons for this observed differences. Rates of positive tests were higher than referred in most screening programs that employed any of these tests with 100 ng/ml as cut-off level on average-risk individuals (Castiglione et al., 2002; Rubeca et al., 2006). Rates were significantly higher among FOB Gold users which resulted in this group undertaking an increased amount of colonoscopies (26% increases) compared to OC-Sensor users. These results are in conflict with the work by Rubeca et al. (2006) which found slightly higher positive diagnostic rates among OC-Sensor users. Several screening strategies have established different cut-off points for positive results using OC-Sensor assay (Van Rossum et al., 2009; Wilschut et al., 2011; Faivre et al., 2012), 50–75 ng/ml, but in our population, based on observed positivity rates, lowering the cut-off may not be appropriate without careful consideration of the amount of extra resources (colonoscopy and pathology

procedures) involved and the iatrogenic consequences of false positives.

With regard to true positive rates (positive predictive values), several results are remarkable. First of all, true positive rates were much higher among men across all age strata. Secondly the use of OC-Sensor assay was associated with higher rates. The higher percentage of participation found among women when compared to men across all age levels is according with other studies (UK Colorectal Cancer Screening Pilot Group, 2004; Department of Health, 2006; Málaga López et al., 2010; Moss et al., 2010). Participation with OC-Sensor was higher than with FOB Gold, for both sexes and across all age groups, but this differences were not statistically significant when the health-district unit of assignment was considered in the analysis.

With respect to the relationship between age and participation, most studies indicated an inverted "U" shaped function with lowest rates of participation in 50–55 years old and those 70–80 (Australian Institute of Health and Welfare, 2012; Faivre et al., 2012). Our results, although do not include individuals 70 years of age and older, seem to be in agreement with this functional relationship.

A differential gender pattern of true positive responses was found. Whereas among women neither age nor the kit utilized influenced the probability that a positive result was in fact due to a premalignant or malignant lesion detectable by colonoscopy, among men increasing age and the use of OC-Sensor kit were associated to a higher prevalence of true positives.

We have also observed that gender and age are related to differences in the detection rates of advanced adenomas and cancer; with higher rates in men and higher rates by age group. We have observed that in our population detections rates of adenomas are higher than in other studies (Bartus, 2005; Vilkin et al., 2005; Smith et al., 2006). When we analyze the results by type of kit with FOB Gold we can conclude that: on the one hand, it has higher rate of positive values, with more colonoscopies performed, and on the other hand, it shows higher detection rate but involves more false positives.

We believe the strengths of this study include quasi-experimental design, comparison of two I-FOBT tests following manufacturer's recommendations.

Possible Limitations of the study: (i) cluster randomized design with small number of clusters leading to baseline imbalance (but we have used analytical techniques that take clustering effect into consideration) (ii) lack of measurement on potentially important covariates either at individual level (socioeconomic level, education, etc.) or at cluster level (deprivation index, ethnic distribution, etc.). As a result there might be important predictors confounding the estimates of effect of the type of kit used. The characteristics of the baseline population in the Basque Country (homogeneity) and the randomization of the assignment of the kits could counterbalance the effects of this lack of measurement.

CONCLUSION

OC-Sensor test appears to be superior for I-FOBT-based CRC screening, given its acceptance, ease of use, associated small number of errors and its screening accuracy. The goal of screening programs is the early detection and removal of neoplasms and, above all, the secondary prevention of colorectal cancer in the general population. Although the interval cancer period is required to establish a proper comparison, the advantages found in this analysis are consistent and lead to the selection of OC sensor as the kit to be used in the CRC population-based program in our region.

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