European Journal of Cancer 107 (2019) 53–59

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Changes in FIT values below the threshold of positivity and short-term risk of advanced colorectal neoplasia: Results from a population-based cancer screening program

Andrea Buron [a,b,c,*], Marta Román [a,b,c], Josep M. Augé [d,e], Francesc Macià [a,b,c], Jaume Grau [f], Maria Sala [a,b,c], Javier Louro [a,b,c], Montserrat Martinez-Alonso [g], Cristina Alvarez-Urturi [h], Montserrat Andreu [h], Xavier Bessa [h], Diana Zaffalon [h], Antoni Castells [e,i,j], Maria Pellisé [e,i,j], Marta Aldea [f], Liseth Rivero [e,i,j], Cristina Hernández [a,b], Isabel Torá-Rocamora [f], Xavier Castells [a,b,c]

[a] *Epidemiology and Evaluation Department, Hospital del Mar, Barcelona, Spain*
[b] *IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain*
[c] *REDISSEC (Health Services Research on Chronic Patients Network), Madrid, Spain*
[d] *Biochemistry and Molecular Genetics Department, Hospital Clínic, Barcelona, Spain*
[e] *IDIBAPS (August Pi i Sunyer Biomedical Research Institute), Barcelona, Spain*
[f] *Unit of Evaluation, Support and Prevention, Hospital Clinic, Barcelona, Spain*
[g] *Biomedical Research Institut of Lleida (IRBLLEIDA), Lleida, Catalonia, Spain*
[h] *Gastroenterology Department, Hospital del Mar, Barcelona, Spain*
[i] *Gastroenterology Department, Hospital Clínic, Barcelona, Spain*
[j] *CIBERehd (CIBER for Digestive and Liver Diseases), Madrid, Spain*

Received 7 August 2018; received in revised form 28 October 2018; accepted 1 November 2018
Available online 10 December 2018

KEYWORDS
Cancer;
Cancer screening;
Colon neoplasms;
Fecal occult blood test

Abstract ***Introduction:*** Increased values in the fecal immunochemical test (FIT) are correlated with increasingly severe colorectal neoplasia, but little attention has been given to FIT values below the cut-off point (negative FIT, nFIT). We analysed the relationship between the concentrations of two consecutive nFIT and the risk of following screen-detected advanced neoplasia and interval cancer (IC) in a population-based colorectal cancer screening program.

* *Corresponding author*: Hospital del Mar, Servei d'Epidemiologia I Avaluació, Passeig Marítim 25-29, Barcelona 08003, Spain.
E-mail address: aburon@parcdesalutmar.cat (A. Buron).

https://doi.org/10.1016/j.ejca.2018.11.004

Methods: FIT results were categorised into non-detectable nFIT (0–3.8 μg haemoglobin/g feces), low nFIT (3.9–9.9) and high nFIT (10.0–19.9). Multivariable adjusted logistic regression was used to estimate the odds ratios (OR) of advanced neoplasia and IC with the nFIT results in the first two screens.
Results: More than 90% of the 42,524 persons had non-detectable nFIT in the first and second screen; 4.5% and 5.8% had a low nFIT, respectively, and 2.2% and 2.9% had a high nFIT. The probability of testing positive and being diagnosed of advanced neoplasia or IC rose with increasing values of nFIT. Compared with those with two non-detectable nFIT results, the highest OR were found among those who had two high nFIT results (OR 21.75; 95% confidence interval: 12.44, 38.04) and those with one low nFIT and one high nFIT (ORs around 20).
Conclusions: Participants with nFIT results above the detection limit of the test had an increased risk of advanced neoplasia and IC in subsequent participations. This information could be used in the design of personalised screening strategies.

1. Introduction

Colorectal cancer (CRC) screening by means of fecal immunochemical tests (FITs) has been associated with a significant reduction in CRC mortality [1] and incidence [2]. FIT is currently the test of choice for many population-based screening programs because of both a higher uptake and a higher detection rate of advanced neoplasia [3] than the guaiac-based fecal occult blood test. However, even though increased fecal haemoglobin (Hb) content is significantly correlated with increasingly severe colorectal neoplasia [4,5] and quantitative FIT provides exact Hb concentrations, current screening programs use the test in a dichotomised manner: concentrations more than an agreed general cut-off point are considered positive and are offered a colonoscopy, whereas those below this threshold are labelled as negative and invited to repeat the test usually two years later.

CRC risk and FIT performance differs by age and sex, and it has been suggested that the cut-off point should be tailored based on these risk factors [6–9]. Furthermore, the risk of interval cancer (IC) (a CRC diagnosed after a negative FIT result (nFIT) and before the next scheduled screening) has been shown to be associated to the previous quantitative FIT result, and the sensitivity of screening programs varies as per the cut-off point [10–12]. Besides the risk of IC, little attention has been given to the association of the quantitative value of FIT results below the cut-off point (i.e., nFIT) with later screening outcomes. Because individuals are commonly screened biennially over the course of 20–25 years, should such an association exist, their history of previous nFIT values could be used to tailor subsequent screening strategies to their individual risk. However, so far, screening programs consider only the incident FIT value and one single "universal" threshold to classify those at higher risk and eligible to undergo a colonoscopy. In this study, we aim to analyse, within the context of an ongoing population-based program, the relationship between the fecal Hb concentrations of two consecutive negative screening tests and the risk of following screen detected advanced neoplasia and IC.

2. Materials and methods

2.1. Study setting, design and participants

The Barcelona colorectal cancer screening program (BCRCSP), started in December 2009, is entirely free of charge and following the European Guidelines [13] biennially invites men and women aged 50–69 years to a FIT test (OC-Sensor; Eiken Chemical Co. Ltd, Tokyo, Japan; cut-off point set at 20 μg hemoglobin [Hb]/g feces, equivalent to 100 ng Hb/ml buffer). Individuals with a nFIT receive a letter informing of this result and are invited to participate two years later. Individuals with a positive result are offered an appointment and undergo a colonoscopy. The organisation and operation of the BCRCSP and its first results have been published in more detail elsewhere [14].

In this longitudinal, retrospective cohort study, the population comprised those participants with two consecutive screening episodes with a nFIT result who afterwards either had a third screen (3S) or were diagnosed with an IC after their second screen (2S). The first screen (1S) took place between 2010 and 2011, the second between 2012 and 2013 and the third between 2014 and 2015.

2.2. Data sources and measures

Basic sociodemographic data (age, sex and postal address) and variables related to the screening process were drawn from the BCRCSP data system. The FIT values below the threshold between the first two screens and the difference between them were used as the

exposure variables. FIT results were categorised into three groups: non-detectable nFIT (FIT values ranging from 0 to 3.8), low nFIT (from 3.9 to 9.9) and high nFIT (from 10.0 to 19.9 μg Hb/g feces). The value of 3.8 μg Hb/g feces is said to be the limit of the detection of the OC-Sensor assay [15]. To summarise the change in the quantitative nFIT result between the first and the 2S, a variable including the nine possible combinations was created (see Tables 2 and 3).

The outcomes of the 3S, i.e., FIT positivity and relevant neoplasia colonoscopy results (CRC, and low-risk, intermediate and high risk adenoma as defined by the European Guidelines [13]), as well as IC between the 2S and 3S were regarded as the main outcomes. A combined end point including advanced neoplasia and IC was created. Advanced neoplasia was defined as adenoma with size ≥10 mm, villous histology or high-grade dysplasia [16] and includes invasive CRC.

The Public Health Agency of Barcelona provided the Medea deprivation index, a deprivation scale based on the results of the Medea Project [17]. Five groups were constructed on the basis of the index of the census tract quintiles of the city, where one corresponds to the least deprived and five to the most deprived quintile. Each person in the study population was assigned a deprivation index value and its corresponding deprivation quintile by linking that person's postal address with the BCRCSP database. Missing values due to non-match of addresses (2.5% out of the total study population) were included in all analyses.

2.3. Analysis

We compared the frequency distributions of the variables for the different outcomes. We used multivariable logistic regression to estimate the odds ratios (OR) and the 95% confidence interval (CI) of the association between the composite measure (advanced neoplasia or IC) and the nFIT results in previous screens. All models were adjusted for age, sex and socioeconomic deprivation index. P values lower than 0.01 were considered statistically significant using a two-sided test. Analyses were performed using SPSS, version 25.0.

2.4. Ethical considerations

The study followed the principles embodied in the Declaration of Helsinki and approval for this study was obtained from the Clinical Research Ethical Committee of the Parc de Salut Mar in March 2016. All databases were anonymised; addresses were erased after linkage to obtain the Medea deprivation index.

3. Results

3.1. Characteristics of the population based on their nFIT levels in the 1S and 2S.

In total, 42,524 persons had two consecutive screens with a nFIT result and afterwards either had a third screening episode or were diagnosed with an IC. Their sex, age and socioeconomic distribution as well as their categorised nFIT results in the 1S and 2S are described in Table 1. Overall, 93.4% and 91.3% had a non-detectable FIT result in 1S and 2S, respectively, 4.5% and 5.8% a low nFIT, respectively, and 2.2% and 2.9% a high nFIT, respectively. The proportion of both low and high nFIT was somewhat higher in men and increased with age in both the 1S and 2S.

Table 1
Sociodemographic characteristics of the study population and their distribution based on their negative (i.e., under the threshold) FIT values at the first and second screen (N = 42,524).

Variables	Total	FIT, 1st screen (N, %)						FIT, 2nd screen (N, %)					
		Non-detectable		Low negative FIT		High negative FIT		Non-detectable		Low negative FIT		High negative FIT	
Overall	42,524	39,701	93.4%	1903	4.5%	920	2.2%	38,831	91.3%	2470	5.8%	1223	2.9%
Gender													
Male	18,123	16,740	92.4%	904	5.0%	479	2.6%	16,387	90.4%	1133	6.3%	603	3.3%
Female	24,401	22,961	94.1%	999	4.1%	441	1.8%	22,444	92.0%	1337	5.5%	620	2.5%
Age in 1st screen (years)													
50–54	14,866	14,034	94.4%	561	3.8%	271	1.8%	13,801	92.8%	732	4.9%	333	2.2%
55–59	12,801	11,944	93.3%	590	4.6%	267	2.1%	11,694	91.4%	753	5.9%	354	2.8%
60–64	13,007	12,004	92.3%	667	5.1%	336	2.6%	11,681	89.8%	855	6.6%	471	3.6%
65–69	1850	1719	92.9%	85	4.6%	46	2.5%	1655	89.5%	130	7.0%	65	3.5%
Deprivation index													
1, least deprived	10,647	10,045	94.3%	403	3.8%	199	1.9%	9732	91.4%	615	5.8%	300	2.8%
2	9231	8635	93.5%	408	4.4%	188	2.0%	8514	92.2%	488	5.3%	229	2.5%
3	7825	7300	93.3%	354	4.5%	171	2.2%	7120	91.0%	480	6.1%	225	2.9%
4	8739	8109	92.8%	429	4.9%	201	2.3%	7963	91.1%	502	5.7%	274	3.1%
5, most deprived	5026	4624	92.0%	263	5.2%	139	2.8%	4536	90.3%	327	6.5%	163	3.2%
Missing	1056	988	93.6%	46	4.4%	22	2.1%	966	91.5%	58	5.5%	32	3.0%

FIT, fecal immunochemical test. Non-detectable comprises FIT values ranging between 0 and 3.8 μg/ml; low negative FIT, values between 3.9 and 9.9 μg/ml; high negative FIT, values between 10 and 19.9 μg/ml.

Table 2
Distribution of FIT results at the third screen based on their FIT category at the first and second screen (N = 42,493[a]).

Variables	Total	FIT, 3rd screen (N, %)							
		Non-detectable		Low negative FIT		High negative FIT		FIT positive	
FIT, 1st screen									
Non-detectable	39,678	33,220	83.7%	3589	9.0%	1264	3.2%	1605	4.0%
Low negative FIT	1899	1222	64.3%	297	15.6%	160	8.4%	220	11.6%
High negative FIT	916	541	59.1%	136	14.8%	88	9.6%	151	16.5%
FIT, 2nd screen									
Non-detectable	38,812	32,676	84.2%	3432	8.8%	1193	3.1%	1511	3.9%
Low negative FIT	2465	1593	64.6%	407	16.5%	205	8.3%	260	10.5%
High negative FIT	1216	714	58.7%	183	15.0%	114	9.4%	205	16.9%
FIT, change from 1st to 2nd screen									
Non-detectable to non-detectable	36,589	31,167	85.2%	3115	8.5%	1030	2.8%	1277	3.5%
Non-detectable to low nFIT	2099	1433	68.3%	327	15.6%	149	7.1%	190	9.1%
Non-detectable to high nFIT	990	620	62.6%	147	14.8%	85	8.6%	138	13.9%
Low nFIT to non-detectable	1514	1046	69.1%	222	14.7%	107	7.1%	139	9.2%
Low nFIT to low nFIT	247	121	49.0%	54	21.9%	32	13.0%	40	16.2%
Low nFIT to high nFIT	138	55	39.9%	21	15.2%	21	15.2%	41	29.7%
High nFIT to non-detectable	709	463	65.3%	95	13.4%	56	7.9%	95	13.4%
High nFIT to low nFIT	119	39	32.8%	26	21.8%	24	20.2%	30	25.2%
High nFIT to high nFIT	88	39	44.3%	15	17.0%	8	9.1%	26	29.5%

FIT, fecal immunochemical test; nFIT, negative fecal immunochemical test. Non-detectable comprises FIT values ranging between 0 and 3.8 μg/ml; low negative FIT, values between 3.9 and 9.9 μg/ml; high negative FIT, values between 10 and 19.9 μg/ml. FIT positive comprises values 20 μg/ml and higher.

[a] Thirty-one persons were diagnosed with interval cancer after their second screen and hence did not undergo a third screen.

Table 3
Distribution of outcomes at the third screen and interval cancers based on the FIT category at the first and second screen (N = 42,524).

Variables	Total population at risk	Outcomes - 3rd screen (N, ‰)									
		Low risk adenoma		Intermediate risk adenoma		High risk adenoma		Cancer		Interval cancer (N, ‰)	
FIT, 1st screen											
Non-detectable	39701	356	9.0	277	7.0	138	3.5	31	0.8	23	0.6
Low negative FIT	1903	36	18.9	55	28.9	35	18.4	8	4.2	4	2.1
High negative FIT	920	34	37.0	44	47.8	24	26.1	9	9.8	4	4.3
FIT, 2nd screen											
Non-detectable	38831	341	8.8	242	6.2	139	3.6	26	0.7	19	0.5
Low negative FIT	2470	50	20.2	77	31.2	24	9.7	14	5.7	5	2.0
High negative FIT	1223	35	28.6	57	46.6	34	27.8	8	6.5	7	5.7
FIT, change from 1st to 2nd screen											
Non-detectable to non-detectable	36605	293	8.0	186	5.1	105	2.9	19	0.5	16	0.4
Non-detectable to low nFIT	2101	38	18.1	54	25.7	12	5.7	8	3.8	2	1.0
Non-detectable to high nFIT	995	25	25.1	37	37.2	21	21.1	4	4.0	5	5.0
Low nFIT to non-detectable	1515	23	15.2	32	21.1	19	12.5	3	2.0	1	0.7
Low nFIT to low nFIT	248	8	32.3	11	44.4	8	32.3	4	16.1	1	4.0
Low nFIT to high nFIT	140	5	35.7	12	85.7	8	57.1	1	7.1	2	14.3
High nFIT to Non-detectable	711	25	35.2	24	33.8	15	21.1	4	5.6	2	2.8
High nFIT to low nFIT	121	4	33.1	12	99.2	4	33.1	2	16.5	2	16.5
High nFIT to high nFIT	88	5	56.8	8	90.9	5	56.8	3	34.1	0	0.0

FIT, fecal immunochemical test; nFIT, negative fecal immunochemical test. Non-detectable comprises FIT values ranging between 0 and 3.8 μg/ml; low negative FIT, values between 3.9 and 9.9 μg/ml; high negative FIT, values between 10 and 19.9 μg/ml.

3.2. Screening outcomes after two consecutive nFIT results

Table 2 shows the distribution of FIT results in the 3S based on their nFIT results in the 1S and 2S. The majority of the study population had non-detectable nFIT in both the 1S and 2S (36,589, 86.1%). Overall, the higher the FIT values in the 1S and 2S, the higher the values in the 3S. Those who had a non-detectable FIT in both the 1S and 2S had a positivity rate in the 3S of 3.5%; those whose FIT result increased from non-detectable in the 1S to low nFIT or to high nFIT in the 2S had a later positivity rate of 9.1% and 13.9%, respectively. The positivity rate reached 29.5% among those with two consecutive high nFIT.

The probability of being diagnosed an adenoma or cancer in the 3S or an IC after the 2S rose with increasing values of nFIT in the 1S and 2S (Table 3).

Out of those with non-detectable FIT result in both the 1S and 2S, the detection rate for low-risk, intermediate-risk and high-risk adenoma was 8.0%, 5.1% and 2.9%, respectively. These rates increased to 25.1%, 37.2% and 21.1%, respectively, when the FIT value increased from non-detectable in the 1S to high nFIT in the 2S, and to 56.8%, 90.9% and 56.8%, respectively, when both previous FIT values were high nFIT. Screen-detected cancer and IC rates also differed significantly based on previous FIT results. For instance, among those with a non-detectable nFIT result in the 1S and 2S, only 0.5% had a screen-detected cancer diagnosed in the 3S, whereas among those with two high nFIT, cancer detection rate was 34.1%.

3.3. Association between being diagnosed of an advanced neoplasia or an IC and previous nFIT results

The adjusted ORs for being diagnosed with either an advanced neoplasia in the 3S or an IC after the 2S for each combination of nFIT results in the 1S and 2S are presented in Table 4. Compared with those with non-detectable nFIT in the first two screens, those who had non-detectable nFIT in the 1S and low nFIT in the 2S had an OR of 4.02 (95% CI: 3.12, 5.19), and those who are from non-detectable in the 1S rose to high nFIT in the 2S had an OR of 7.45 (95% CI: 5.67, 9.78). The highest ORs were found among those who had two consecutive high nFIT results (OR: 21.75; 95%CI: 12.44, 38.04), those whose FIT results increased from low to high nFIT (OR: 20.38; 95% CI: 12.82, 32.40) and those with a high nFIT in the 1S and low nFIT in the 2S (OR: 19.64; 95% CI: 11.95, 32.26). Separate regression models were performed for men and women with very similar results and slightly higher OR for men than for women for those individuals with at least one high nFIT result in previous screens (data not shown).

4. Discussion

This study shows that among CRC screening participants with two consecutive FIT negative screens, those whose FIT results are above the limit of detection account for less than 15% but amass a greater risk of being diagnosed afterwards of advanced neoplasia or an IC. In particular, compared with those with non-detectable nFIT in both previous screens, the probability of being diagnosed with an IC or an advanced neoplasia in the following screening ranges between 4 folds for those with one result between the limit of detection and 9.9 μg Hb/g feces (low nFIT) and 22 folds for those with both FIT results between 10 and 19.9 μg Hb/g feces (high nFIT). The order of these results (1S and 2S) does not seem to affect the OR for advanced neoplasia and IC, e.g., ORs around four among those that have one non-detectable nFIT and one low nFIT, ORs around 7 among those that have one non-detectable nFIT and one high nFIT, and ORs around 20 among those with one low nFIT and one high nFIT.

Our results are in line with those of a recent Dutch study that correlates consecutive negative FIT results with the future risk of colorectal neoplasia [18]. In this cohort study with a cut-off point set at 10 μg Hb/g feces, Grobbee EJ *et al.* followed up around 8700 screening uptakers over 8 years, although less than half participated in three or more screens. The risk of advanced neoplasia for those with more than 8 μg Hb/g feces at the baseline was 8 folds higher than for those with a Hb concentration of zero, and for those with two consecutive results above 8 μg Hb/g feces, the risk was 14 folds the risk of those with two results of zero. Our study not only confirms these results with a much larger population but also adds external validity because our data come from an ongoing population-based screening program with a cut-off point of 20 μg Hb/g feces which has not been modified over the study period and is nowadays the cut-off point for many European programs [19]. Another study that analysed the relationship between quantitative fecal Hb in the first screen and the subsequent incidence of colorectal neoplasia was carried out in Taiwan and also obtained an increased risk for those with higher values of below the threshold fecal Hb [20].

Unlike in breast cancer screening where it is standard practice that radiologists consult previous mammograms to aid their decision, so far CRC screening programs take into account only the FIT level of the incident screen and do not include any further information from previous screens. The results of this study highlight the relevance of previous quantitative FIT

Table 4
Odds ratios (and 95% confidence intervals) of being diagnosed with either an advanced neoplasia at the third screen or an interval cancer after the second screen, for each combination of FIT results at the first and second screen (N = 42,524).

FIT, 1st screen	FIT, 2nd screen		
	Non-detectable	Low negative FIT	High negative FIT
Non-detectable	1.00	4.02 (3.12–5.19)	7.45 (5.67–9.78)
Low negative FIT	4.00 (2.99–5.35)	10.79 (6.97–16.72)	20.38 (12.82–32.40)
High negative FIT	6.99 (5.06–9.65)	19.64 (11.95–32.26)	21.75 (12.44–38.04)

FIT, fecal immunochemical test. Non-detectable comprises FIT values ranging between 0 and 3.8 μg/ml; Low negative FIT, values between 3.9 and 9.9 μg/ml; High negative FIT, values between 10 and 19.9 μg/ml.
Multiple logistic regression model adjusted for sex, age and socioeconomic level.

results and provide useful information to personalise screening strategies. The usage of three simple categories of FIT below the threshold, including the non-detectable one, facilitates the transferability of these results in the screening programs. Screenees whose previous nFIT results are associated with a 20-fold increased risk of advanced neoplasia or IC account for less than 1% of the total number of screenees with negative results, making it eventually feasible to offer them more intensive screening and preventative options. However, given the limited colonoscopy capacity and as most of these neoplasias are diagnosed within those testing positive in the following round, the focus should be on the potentially preventable ICs and on those no longer screened. Hence, a reasonable strategy could be to, among those with two consecutive high nFIT and those with one high and one low nFIT, reinforce the benefit of participating to those that fail to do so and to offer screening to those who are no longer invited (e.g., due to their age).

Among the strengths of this study are the large population sample, the setting, a running CRC population-based screening program in an urban context with no changes in their organisation over time, and the availability of socioeconomic status as an adjusting variable. This study also has several limitations. Only those with a FIT positive in the 3S were eligible for colonoscopy and hence could be diagnosed with a colorectal neoplasia making this study susceptible to verification bias. Given the observational nature of the study, we could not address this issue, but future studies including further screens and longer follow-ups will approach this aspect. The potential misclassification of the individual socioeconomic level related to the use of an ecological deprivation index and the time lag between calculation of the deprivation index (2001) and the start of the first round of the program (2009) have been described in more detail elsewhere [21] and are not likely to affect the validity of this variable.

4.1. Conclusions

In summary, the results of this study add to the existing evidence that quantitative FIT results are strongly associated to the probability of advanced neoplasia by providing information for screenees with previous negative tests. The risk of advanced neoplasia and IC ranges between 4 and 22 folds when the nFIT results of the previous two screens are above the detection limit of the test. Those with a risk 10 times or higher account for less than 2% of the total population of screenees with two consecutive negative results. Furthermore, the results of this study could be used in the design of personalised screening strategies because it uses information readily available in all programs. Future studies will address the risk of developing neoplasia related to FIT under the threshold results, taking into account the effect of non-participation and longer follow-ups.

Conflict of interest statement

None declared.

Funding

This work was supported by a research grant from the European Regional Development Fund and the Carlos III Health Institute (grant number FIS PI16/00239).

Acknowledgements

The authors acknowledge the collaboration with Montserrat Garcia's research team in the Instituto Catalán de Oncología-IDIBELL. They would like to thank Vanessa Pereira for the contribution to the data collection, Julieta Politi for the help in the literature review and Montserrat Rue for the comments to the manuscript. The authors would also like to acknowledge all members of the PROCOLON group, the research group of Barcelona's Colorectal Cancer Screening Program, currently constituted by the following members: Rafael Abós-Herrándiz, Eva Abril, Marta Aldea, Cristina Álvarez, Marco Antonio Álvarez, Montserrat Andreu, Isis Araujo, Josep M. Augé, Anna Aymar, Guillermo Bagaria, Francesc Balaguer, Xavier Bessa, Montserrat Bonilla, Andrea Burón, Sabela Carballal, Antoni Castells, Xavier Castells, Mercè Comas, Rosa Costa, Míriam Cuatrecasas, Josep M. Dedeu, Maria Estrada, Imma Garrell, Jaume Grau, Rafael Guayta, Jordi Gordillo, Cristina Hernández, Mar Iglesias, María López-Cerón, Laura Llovet, Francesc Macià, Leticia Moreira, Lorena Moreno, M. Francisca Murciano, Gemma Navarro, Teresa Ocaña, Maria Pellisé, Mercè Pintanell, Àngels Pozo, Teresa Puig, Faust Riu, Liseth Rivero-Sánchez, Cristina Rodríguez, Maria Sala, Ariadna Sánchez, Agustín Seoane, Anna Serradesanferm, Judit Sivilla, Antoni Trilla and Isabel Torà.

References

[1] Zorzi M, Fedeli U, Schievano E, Bovo E, Guzzinati S, Baracco S, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut 2015;64:784–90. https://doi.org/10.1136/gutjnl-2014-307508.

[2] Ventura L, Mantellini P, Grazzini G, Castiglione G, Buzzoni C, Rubeca T, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver 2014;46:82–6. https://doi.org/10.1016/j.dld.2013.07.017.

[3] Hol L, van Leerdam ME, van Ballegooijen M, van Vuuren AJ, van Dekken H, Reijerink JCIY, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and

immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010;59:62–8. https://doi.org/10.1136/gut.2009.177089.

[4] Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007;146:244–55.

[5] Ciatto S, Martinelli F, Castiglione G, Mantellini P, Rubeca T, Grazzini G, et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer 2007;96:218–21. https://doi.org/10.1038/sj.bjc.6603534.

[6] Auge JM, Pellise M, Escudero JM, Hernandez C, Andreu M, Grau J, et al. Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. Gastroenterology 2014;147. https://doi.org/10.1053/j.gastro.2014.06.008. 628-636.e1.

[7] Garcia M, Milà N, Binefa G, Benito L, Gonzalo N, Moreno V. Fecal hemoglobin concentration as a measure of risk to tailor colorectal cancer screening: are we there yet? Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP 2015;24:321–7. https://doi.org/10.1097/CEJ.0000000000000090.

[8] Arana-Arri E, Idigoras I, Uranga B, Pérez R, Irurzun A, Gutiérrez-Ibarluzea I, et al. Population-based colorectal cancer screening programmes using a faecal immunochemical test: should faecal haemoglobin cut-offs differ by age and sex? BMC Cancer 2017;17:577. https://doi.org/10.1186/s12885-017-3555-3.

[9] Wieten E, Schreuders EH, Nieuwenburg SAV, Hansen BE, Lansdorp-Vogelaar I, Kuipers EJ, et al. Effects of increasing screening age and fecal hemoglobin cutoff concentrations in a colorectal cancer screening program. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2016;14:1771–7. https://doi.org/10.1016/j.cgh.2016.08.016.

[10] Digby J, Fraser CG, Carey FA, Lang J, Stanners G, Steele RJ. Interval cancers using a quantitative faecal immunochemical test (FIT) for haemoglobin when colonoscopy capacity is limited. J Med Screen 2016;23:130–4. https://doi.org/10.1177/0969141315609634.

[11] Portillo I, Arana-Arri E, Idigoras I, Bilbao I, Martínez-Indart L, Bujanda L, et al. Colorectal and interval cancers of the colorectal cancer screening program in the Basque country (Spain). World J Gastroenterol 2017;23:2731–42. https://doi.org/10.3748/wjg.v23.i15.2731.

[12] Burón A, Macià F, Andreu M, Pellisé M, Castells X, Grau J. Population-based colorectal cancer screening: interval cancers and relationship with the quantitative faecal immunological test. Med Clin (Barc) 2018. https://doi.org/10.1016/j.medcli.2018.06.022.

[13] European Commission, International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis. 1st ed. Luxembourg: Office for Official Publications of the European Communities; 2010.

[14] Burón A, Grau J, Andreu M, Augé JM, Guayta-Escolies R, Barau M, et al. Colorectal cancer early screening program of Barcelona, Spain: indicators of the first round of a program with participation of community pharmacies. Med Clínica 2015;145:141–6. https://doi.org/10.1016/j.medcli.2014.05.027.

[15] Carroll M, Piggott C, Pearson S, Seaman H, Halloran S. Evaluation of quantitative faecal immunochemical tests for haemoglobin. NHS Bowel Cancer Screening Southern Programme Hub; 2013.

[16] Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844–57. https://doi.org/10.1053/j.gastro.2012.06.001.

[17] Domínguez-Berjón MF, Borrell C, Cano-Serral G, Esnaola S, Nolasco A, Pasarín MI, et al. Constructing a deprivation index based on census data in large Spanish cities(the MEDEA project). Gac Sanit 2008;22:179–87.

[18] Grobbee EJ, Schreuders EH, Hansen BE, Bruno MJ, Lansdorp-Vogelaar I, Spaander MCW, et al. Association between concentrations of hemoglobin determined by fecal immunochemical tests and long-term development of advanced colorectal neoplasia. Gastroenterology 2017;153. https://doi.org/10.1053/j.gastro.2017.07.034. 1251-1259.e2.

[19] Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N. Cancer screening in the European Union (2017). Report on the implementation of the Council Recommendation on cancer screening (second report). International Agency for Research on Cancer (IARC); 2017.

[20] Chen L-S, Yen AM-F, Chiu SY-H, Liao C-S, Chen H-H. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. Lancet Oncol 2011;12:551–8. https://doi.org/10.1016/S1470-2045(11)70101-2.

[21] Buron A, Auge JM, Sala M, Román M, Castells A, Macià F, et al. Association between socioeconomic deprivation and colorectal cancer screening outcomes: low uptake rates among the most and least deprived people. PLoS One 2017;12:e0179864. https://doi.org/10.1371/journal.pone.0179864.