Adherence to screening in fit-based colorectal cancer screening programmes in the northwest of Europe

Esther Toes-Zoutendijk, Isabel Portillo, Sarah Hoeck, Isabel de Brabander, Philippe Perrin, Catherine Dubois, Monique E. van Leerdam, Iris Lansdorp-Vogelaar, Marc Bardou

Journal of Medical Screening

ABSTRACT

Background

This study compared adherence to four faecal immunochemical testing (FIT) based screening programmes for colorectal cancer (CRC) in Flanders, France, Basque country and the Netherlands to identify factors to further optimise FIT programmes.

Methods

Background information and data on performance indicators were collected and compared for the four CRC screening programmes.

Results

Invitation method, reminders, funding, FIT cut-off and follow-up after positive FIT differed between the four programmes. In France only an invitation letter is send by mail, while the sample kit needs to be collected at general practitioner (GP). In the other programmes, an invitation letter including the sample kit is send by mail. Participation rates varied substantially with method of invitation, with the highest participation rates in the Netherlands (73.0%) and Basque country (72.4%), followed by Flanders (54.5%) and France (28.6%). Basque country (92.8%) and France (88.4%), the two programmes with most active involvement of GPs in referral for colonoscopy, showed the highest participation rate with colonoscopy.

Conclusions

Large differences in screening participation were observed between programmes in line with the invitation method used. This finding suggests that changes to the design of the programme, such as including the sample kit with the invitation or active involvement of GPs, might increase participation.

INTRODUCTION

Many countries or regions have implemented colorectal cancer (CRC) screening by faecal occult blood testing (FOBT), in particular by means of faecal immunochemical testing (FIT).[1] FOBT as screening method is also recommended by the European Union.[2] The effectiveness of population-based screening programmes is not only driven by the sensitivity of the screening method, but also depends on the availability of resources, healthcare infrastructure and population preferences in each country. Population preferences will especially be reflected in participation rate.

To determine the most optimal screening method for the population, pilot studies were performed in the Basque country, Flanders and the Netherlands before the initiation of the regional or national screening programme. In the Basque Country a pilot study was carried out in 2009 and high participation rate with FIT screening of 64.3% was demonstrated.[3] In Flanders, a pilot study was performed to compare two invitation strategies: FIT directly send by mail or invitation to collect the FIT at the general practitioner (GP). Participation by mail was 52.3% versus 24.6% through the GP.[4] In the Dutch pilot studies different screening methods were compared. These studies showed that FIT screening resulted in the highest CRC detection per invitee compared to other screening methods like guaiac FOBT (gFOBT), colonoscopy and sigmoidoscopy screening.[5-7]

After choosing the best screening method, the organisational structure of the programme is crucial for optimal screening performance. Many different aspects how to organise the programme have been studied like pre-invitation letter, reminders, and FIT mailing.[4,8,9] However, almost all of these studies have been carried out in trials and not in real-life settings. In running programmes many more aspects are involved, for example organisation of healthcare systems and healthcare insurance. Besides, these organisational aspects have never been compared across programmes, but only in one specific group of individuals. It is unknown of all these different organisational aspects will work out the same for individuals residing in different countries. A national population-based CRC screening programme was initiated in 2002 in France using gFOBT, which was changed to FIT in April 2015. FIT screening was introduced in 2009 in the Basque country (Spain), in 2013 in Flanders (Belgium), and in 2014 in the Netherlands. As these programmes are geographically close and connected, all situated in Europe, and have recently been implemented similar outcomes with respect to CRC screening may have been expected. This study was able to evaluate similarities and differences between the organised population-based CRC screening programmes using FIT in France, Basque country (Spain), Flanders (Belgium), and the Netherlands and assesses how this may impact adherence to FIT-based programmes.

METHODS

Organisational structure of CRC screening programmes

Information was collected on year of initiation, target population, eligible population, screening interval, methods of invitation to FIT screening and to colonoscopy following a positive FIT, funding and executive organisation of the screening programmes. The target population was defined for each population-based CRC screening programme according to programme specific policies. The eligible population is the target population excluding those that are not eligible for screening based on exclusion criteria. Eligible population were all individuals that should have been invited in 2016. This number can deviate from the total target population, because of biennial screening or phased implementation of the national screening programme.

Performance indicators of CRC screening programmes

Data on performance indicators were extracted from each of the national or regional screening databases. Data from France were extracted from the database of French Public Health Agency (Santé Publique France) and Organized screening structure of the Big East region and the Pyrénées. Data from Flanders were extracted from the screening database, the Belgian Cancer Registry and reimbursement data from the Health insurance companies. All data from the Basque country were extracted from programme database (PCCR) which is linked with medical records, population and hospital cancer registries. All data from the Netherlands were extracted from the national database for screening programmes (ScreenIT). In France, data on the invitees starting in April 2015 to December 2016 were collected until June 2017, in the Basque country data on the invitees of 2016 were collected until December 2017, in Flanders and the Netherlands data on the invitees of 2016 were collected until 30 June 2017.

Data were collected on main performance indicators: participation rate, positivity rate of the FIT, participation rate to colonoscopy following positive FIT, detection rate of CRC or advanced neoplasia (AN) per participant, and diagnostic yield. Definitions of the indicators are in accordance with recommended definitions for performance indicators by the European Union CRC screening guidelines.[11]

1. *Participation rate* was calculated as the number of persons sending back the FIT sample divided by the number of persons receiving an invitation letter. For Flanders and France persons were only considered as participant if they returned the FIT sample within 12 months after the invitation. In the Basque Country persons were only considered participant if they returned an assessable FIT sample within six months after the invitation. In the Netherlands individuals were considered participant until the date of the invitation of subsequent screening round.

2. *Positivity rate* was calculated as the number of persons with a FIT result at or above the cut-off level divided by the number of persons with an assessable stool sample.
3. *Participation rate colonoscopy* was calculated as the number of persons undergoing a colonoscopy divided by the number of persons with a positive FIT result.
4. *Detection rate* was defined as the number of persons with AN detected during colonoscopy per participant. AN was considered as relevant abnormality within a CRC screening programme. AN was defined as CRC or any adenoma with histology showing >=25% villous component or high-grade dysplasia or adenoma with size >= 10 mm. In Flanders, only adenoma with any villous component and/or high grade dysplasia was counted as advanced adenoma, because no data were available on adenoma size or the amount of villous components. In the Basque country, in addition to histology, dysplasia and size, having ≥3 adenomas was also considered as advanced adenoma.
5. *Diagnostic yield of the programme* was defined as the number of persons with AN detected during colonoscopy divided by all individuals that received an invitation. In Flanders, data of colonoscopy yield is not linked to the date of invitees of the programme. The denominator can contain individuals invited in previous year.

Analysis

First, organisational structure of the four programmes were compared using thematic analysis to identify similarities or differences. Second, outcomes of the performance indicators for each of the four programmes were compared. To rule out that the observed difference is related to cultural differences between populations rather than organisational differences, the programme of Basque country in Spain was compared with the Basque country in France. These are two regions that are very close with respect to geographical location and cultural background. The different subgroups were compared using chi-squared test and p value <0.05 was considered statistically significant. Chi-square test was performed using R version 3.5.0.

RESULTS

Organisation of the programmes

The age range of the target population differed, with France and the Basque country having the lowest starting age of 50 years and the Basque country having the lowest stopping age of 69 years (Table 1). All four countries used a two years screening interval. Exclusion criteria prior to invitation differed between the four programmes, with very limited exclusion criteria in the Netherlands compared to the other three programmes: persons were only excluded based on a positive FIT in previous screening round (Table 1). France, Flanders and Basque country all excluded individuals with history of CRC, proctocolectomy, and recently

Table 1: Background information on screening programme

	France	Flanders (Belgium)	Netherlands	Basque country (Spain)
		1. General		
Year of introduction	Started in 2009 and switched nationally to the FIT in April 2015.	October 2013 Phased implementation by age groups. In 2015 the programme was fully implemented.	2014 Phased implementation by age group. In 2019 the programme will be fully implemented.	2009 Phased implementation by provinces. In 2014 the programme was fully implemented.
Piloting	Yes	Yes	Yes	No
Public Awareness Campaigns	Yes. Through dedicated websites: National Cancer Institute (INCa), Health Insurance, and some local initiatives.	Yes. Since 2015 short announcements on the Flemish television and since 2017 advertising in public transport. Both only during the month March (international CRC month).	Yes. Information on the website of the national institute of public health and the environment. Only at the start in 2014 there was extra media attention through television and radio. No advertising.	Yes. National yearly campaign by patient association and main results are presented in television, leaflets, radio, and social network.
Population-based programme	National	Regional	National	Regional
Age group	50-74 years	56-74 years Per July 1 2017 it was extended to 55-74 years and per July 2018 it was extended to 53-74 years	55-75 years	50-69 years
Screening interval	2 years	2 years	2 years	2 years
Cut-off level (Hb/g faeces)	30 µg	15 µg	47 µg	20 µg
Brand name of the test	OC-Sensor, Eiken, Japan	OC-Sensor, Eiken, Japan	FOB-Gold, Sentinel, Italy	OC-Sensor, Eiken, Japan
		2. Methods of invitation		
Pre-invitation letter	No	No	Yes, 3 weeks in advance	Yes, 4 weeks in advance
Invitation by mail including FIT	No, test to be collected at GP's office	Yes	Yes	Yes
Reminder letter	12 weeks and 24 weeks	8 weeks	6 weeks	4 weeks
Exclusion of individuals before invitation	Yes	Yes	No	Yes

Table 1: Background information on screening programme (continued)

	France	Flanders (Belgium)	Netherlands	Basque country (Spain)
Exclusion criteria mentioned in the invitation letter	No.	Past or current treatment of colorectal cancer, occult blood in stool, and unexplained and persistent change in the bowel movement patterns, colonoscopy in past ten years, stool test in past 2 years, higher risk at CRC, having one or more first relatives who have/had CRC.	Past or current treatment of colorectal cancer, occult blood in stool, and unexplained and persistent change in the bowel movement patterns.	Colonoscopy performed ≤ 5 years.
3. Methods of invitation to diagnostic colonoscopy				
Invitation to follow-up colonoscopy	By letter. Results are sent to the participant, the general practitioner and the structure in charge of organised CRC screening	By letter. Results are sent to the participant and the general practitioner.	By letter, including appointment for colonoscopy intake. Results are sent to the participant and if possible the general practitioner.	By letter. Results are sent to the participant. In that letter the participant is recommended to visit GP for colonoscopy referral.
Reminder following initial invitation colonoscopy	No	No, from 2019 persons receive a new invitation for colonoscopy intake 2 years after their positive FIT. When not following this second advice, 2 years later (4 years after the positive FIT) they will receive a new FIT.	Yes, persons receive a no show letter. In case of no response, persons received a new invitation for colonoscopy intake after 2 years after positive FIT (until 2017). From 2018 onwards persons will receive a new FIT after two years.	Yes, after 30 days the participant is reminded to make an appointment with the general practitioner for colonoscopy referral. If participants reject to have a colonoscopy follow-up they will receive a new FIT after 2 years.

Table 1: Background information on screening programme (continued)

	France	Flanders (Belgium)	Netherlands	Basque country (Spain)
		4. Organisation		
Funding of screen test	Free of charge, but not the GP's encounter to collect the kit that is covered at 70% by national public health insurance. The remaining 30% are being covered by complementary insurance if the participant has one.	Free of charge	Free of charge	Free of charge
Funding of colonoscopy	Standard healthcare insurance covers 70%. The remaining 30% is covered by complementary insurance if any.	Standard healthcare insurance and partially payment of personal funds (out of pocket costs).	Standard healthcare insurance. Note: Not in all situations colonoscopy costs are fully covered by the healthcare insurance. Up to 350 - 850 euro are paid of personal funds (out of pocket costs, only once a year a deductible excess of all healthcare costs).	Free of charge
Responsible organisation of the screening programme	INCa, National cancer institute, with dedicated screening structure in each of the departments. The latest are in charge of invitations.	Centre for Cancer Detection (CvKO). In Flanders CvKO consists of five regional screening programmes, but the invitation letter, reminder letter, and FIT results are organised by one central organisation. The five regional screenings programmes offer free telephone advice and are responsible for administration.	The national institute of public health and the environment is the responsible organisation of the programme. Five regional screening organisations are responsible for the execution of the programme. Those five regional screening organisations are brought together in one national cooperation.	The Basque Health Service is responsible for the execution of the programme, according with authorities planning, organising and monitoring the quality of the process and results. The final responsibility of the programme is the Regional Ministry of Health in the Basque Country.

performed colonoscopy before invitation. France and Flanders also excluded individuals with a recently performed FIT. Additionally, the Basque country excluded individuals with severe or terminal illness.

Methods of invitation differed between the four programmes. The eligible population in France received an invitation letter to collect the FIT sample kit at the GP. In Flanders individuals received an invitation including the FIT sample kit. In the Basque country and the Netherlands a pre-invitation letter was send prior to invitation followed by an invitation letter including the FIT sample kit. All four screening programmes used a reminder letter, but all at different time points ranging from 30 days (Basque country) until 6 months (France). France sent two reminder letters. All four programmes used another cut-off for a positive FIT for referral to colonoscopy: Flanders used the lowest cut-off of 15 µg Hb/g faeces, followed by the Basque country with 20 µg Hb/g faeces and France with 30 µg Hb/g faeces. The highest cut-off was used in the Netherlands with 47 µg Hb/g faeces (Table 1).

Performance indicators

A total of 18.9 million individuals were invited to participate in FIT screening among the four CRC screening programmes. Highest participation rate was observed in the Netherlands (73.0%), followed by the Spanish Basque country (72.4%), Flanders (54.5%) and France (28.6%, p <0.001). As a consequence of the different FIT cut-offs used, positivity rate differed between the four programmes, from 4.7% in France to 6.7% in Flanders (p <0.001). Highest participation rate for the colonoscopy following a positive FIT result was observed in the Basque country (92.8%), France (88.4%), Flanders (81.9%) and the Netherlands (82.8%) (p <0.001). Detection rate for AN per participant was highest in the Netherlands (2.3%) and lowest in Flanders (1.0%). Diagnostic yield for AN per invitee was highest in the Netherlands (1.6%) and lowest in Flanders (0.6%, p <0.001).

French versus Spanish Basque country

Despite cultural similarities, differences in screening performance indicators were observed between the French and the Spanish parts of the Basque country (Table 3). The participation rate in the Spanish part, with 72.4% was 2.5 times as high as the French part of the Basque country, with 24.6% (p <0.001; Table 3). Participation rate to colonoscopy was of the same magnitude in both regions: 92.8% in the Spanish part and 87.4% in the French part (p 0.37).

DISCUSSION

Large differences in screening participation were observed between programmes in line with invitation method used, such as a pre-invitation letter and including the FIT sample kit with the invitation. The high participation to colonoscopy in France might indicate that well

Table 2: Performance indicators for France, Flanders, the Netherlands and Basque country

	France	Flanders	Netherlands	Basque country	*p* value
Calendar year	2015-2016	2016	2016	2016	
Age (year)	50-74	56-74	59-76	50-69	
Target population	19,043,771	1,447,434†	Unknown	273,084	
Eligible population	16,701,387	830,665	1,543,223	239,601	
Invited	16,701,387 100%	571,034 68.7%†	1,457,976 94.5%	229,380 87.7%	
Number of participants	4,779,845	311,453	1,063,651	166,110	<0.001
Participation rate FIT	28.6%	54.5%‡	73.0%	72.4%	
Men	*27.8%*	*53.1%*	*71.1%*	*70.0%*	
Women	*30.8%*	*56.0%*	*74.8%*	*74.6%*	
Screen round	Any round	First and second	First and second	First to Fourth	
Cut-off level (Hb/g faeces)	30 µg	15 µg	47 µg	20 µg	
Positivity rate	4.7%	6.7%	5.4%	5.2%	<0.001
Participation rate colonoscopy	88.4%*	81.9%	82.8%	92.8%	<0.001
Detection rate					
AN	1.5%*	1.0%	2.3%	1.9%	<0.001
CRC	0.31%*	0.28%	0.35%	0.20%	<0.001
Diagnostic yield programme					
AN	0.4%*	0.6%	1.6%	1.4%	<0.001
CRC	0.09%*	0.15%	0.25%	0.15%	<0.001

† Eligible population in Flanders is the total amount of 56-74 years old for two year minus those excluded for invitation. Eligible population for 2016 only could not be provided.

‡ Coverage by examination, also including opportunistic screening by FIT or colonoscopy, resulted in 65.5% of the target population to be screened.

* In France the participation rate of colonoscopy and number of colorectal cancers and advanced neoplasia was based on data from April 2015 until December 2015.

Abbreviations: AN (Advanced Neoplasia); N.A. (Not available).

Advanced neoplasia was defined as CRC or any adenoma with histology showing >=25% villous component or high-grade dysplasia or adenoma with size >= 10 mm. In Basque country also ≥3 adenomas were considered AN. In Flanders, adenoma with a villous component and/or high grade dysplasia was counted as advanced adenoma. There were no data available on the size or the amount of villous components in an adenoma. Detection rate, invitees with CRC or AA per participant. Diagnostic yield, individuals with CRC or AN per invitees.

informed and motivated people that collect the FIT sample kit at the GP, are more likely to undergo a colonoscopy.

For the large difference in FIT participation we have several explanations. First, sending the FIT home is more effective than collecting it at the GP. Almost all studies were irrevocably showing a huge increase in participation when including the FIT sample kit with the invitation.[8,12-14] However, one Italian study showed only a modest increase in participation, but this study was performed in previously screened individuals (used to other screening

Table 3: Outcomes performance indicators Basque region

	Basque country in France	Basque country in Spain	*p* value
Year	2016	2016	
Age	50-74	50-69	
Invited	45,923	229,380	
Number of participants	11,293	166,110	
Participation rate FIT	24.6%	72.4%	<0.001
Cut-off level (Hb/g faeces)	30 µg	20 µg	
Positivity rate	4.6%	5.2%	0.07
Participation rate follow-up colonoscopy	87.4%	92.8%	0.37
Detection rate			
AN	1.4%	1.9%	<0.001
CRC	0.27%	0.20%	
Diagnostic yield			
AN	0.4%	1.4%	<0.001
CRC	0.07%	0.15%	

Abbreviations: AN (Advanced Neoplasia)

Advanced neoplasia was defined as CRC or any adenoma with histology showing >=25% villous component or high-grade dysplasia or adenoma with size >= 10 mm. In Basque country also ≥3 adenomas were considered AN. Detection rate, invitees with CRC or AN per participant. Diagnostic yield, individuals with CRC or AN per invitees.

strategy).[16] One French study showed low uptake rates with direct mailing of the FOBT.[16] This inconsistency may be due to the test modality, gFOBT instead of FIT, resulting in lower participation rates.[17] Second explanation for a higher FIT participation may be the advanced notification letter as illustrated by the higher participation rate in the Basque country and the Netherlands. However, this will only explain a small proportion of the total difference, as studies have shown that sending a pre-invitation letter results in a three percentage point increase.[9,10] Only one study from Australia showed a higher increase, nine percentage point.[18] Both direct mailing as well as the pre-invitation letter are in line with a recent systematic review.[19] However, one large difference is noteworthy. The review reported that GP involvement improved participation. We showed the opposite in this study; a country with no involvement of GPs like the Netherlands, participation rates were very high, while in a country with active involvement of the GPs like in France, participation rates were substantially lower. We hypotheses that GP endorsement can have a positive impact on participation, as long this requires no effort of the participant. This is in line with findings of the CRC screening programme in England, showing an increase in participation if the invitation letter was added with a GP endorsement banner. Our analysis of the two Basque regions in France and Spain showed that very similar cultures can have very different rates in screening participation, and that culture may not be the driving factor of performance

differences between programmes. However, we cannot rule out cultural differences completely. We know from literature that cultural difference in screening attitude is also observed in the participation rates of other cancer screening programmes, for example participation to breast cancer screening. In 2016, this was also lower in Flanders (51.9%) than in the Netherlands (77.6%) and the Basque country (80.1%), with France having the lowest participation rate (50.7%).[21-23] Remarkably, the participation rate for breast cancer screening in France is similar to Flanders, while there is a much larger difference in participation rate for CRC screening. Gender cannot explain this difference, as both men and women showing a similar pattern in participation. Thus, this again reflects the negative impact of using a different invitation method in France for CRC screening.

Participation rate to follow-up colonoscopy was considerable high in all four screening programmes. However, the rate was below the recommend level of 85% in the Netherlands and Flanders. We hypothesize that higher participation to follow-up colonoscopy can be the result of the active involvement of GPs during the screening process. In France and the Basque country GPs play an active role in 1) defining the eligible population by excluding those with severe comorbidity from invitation, 2) selecting the population eligible for FIT screening at pick-up of the screening test or 3) following individual up after negative FIT. Consequently, those participating in FIT screening are all healthy enough to undergo follow-up colonoscopy. Other way around it also explains the lower participation to colonoscopy in the Netherlands, as there is no exclusion of individuals based on co-morbidities or medical history. Additionally, in France probably only the most motivated individuals collect the FIT sample kit at their GP practice and they may be more motivated to go for colonoscopy in case of a positive FIT. Only involving GPs for referral to colonoscopy, without involvement in selecting those eligible for FIT screening, will be less effective.[8] Reimbursement differences of the colonoscopy do not seem to explain participation differences. Although in the Basque country the colonoscopy is free of charge, the participation in France was only slightly lower, while French individuals may have significant expenses.

Positivity rate differed for all the four programmes. This is due to three important reasons: cut-off of the FIT, target age group and screening round (first or subsequent round).[24] The same explanations hold for the difference in detection rates and diagnostic yield of the programme. We could not restrict our analysis for the same age ranges, as the Netherlands is still in the implementation phase and not all age groups of the target population have been invited yet. Therefore, the outcomes of the positivity rate and detection rates should be addressed as exploratory, and further research is needed to explain the differences between these rates.

Our study has three strengths. It is the first that gives detailed information on organisational structure of four programmes provided by representatives of each country. These details are in general unknown, as key elements of CRC screening programmes are only described in its own country language: Flemish, French, Spanish/Basque, and Dutch. These details can

be used by other countries/regions considering CRC screening and are valuable for policy makers. Also, our study showed very recent outcomes of four large population-based programmes, all using the same test modality (FIT). Lastly, our study compared screening programmes of neighboring countries with cultural similarities and differences, and can thus address the impact of cultural and organisational aspects in the uptake of CRC screening.

The study has also some limitations. First, comparing quality indicators was challenging due to different definitions and differences in cut-off and number of screening rounds. Unfortunately, we could not restrict the comparison to first screen round data only as not all programmes had such detailed information. Second, data collection may be of a concern, for example France does not have a central data collection of quality indicators and diagnostic yield.

The findings of the study suggest that the organisational structure impacts the participation rate to FIT and follow-up colonoscopy, like sending out the FIT, pre-invitation letter, involvement of the GP in the whole screening process. These results can be used to optimise each of the four screening programmes or can be used as an example for other organised FIT-based CRC screening programmes. Possibilities for optimisation can be diverse for every programme as health care systems, funding of the colonoscopy and available resources differ. Interventions for optimisation will cost money and these results can therefore be used to explore the additional benefit and additional costs for each of the programmes. France already started optimising their screening programme, but maybe not in the good way. Indeed it has been decided to mail the FIT with the first reminder but only to those who had already been participating in previous round, whereas the study by Giorgi-Rossi and colleagues suggests that they may not be the best target.[15]

Although sending the FIT by mail and actively approaching FIT positives for the colonoscopy seems to be most effective, this can be considered as infringement of free will.[25] High participation should not be the goal of screening programmes, but the level of informed choice. However, there is no indication that high participation in the Netherlands for example, results in a lower level of informed choice.[26,27] Besides these ethical considerations, there is also a remaining difference in participation that cannot be explained by the organisational structure and is difficult to unravel. It seems to be a difference in attitude towards screening in general between the different regions or countries. It is unclear how this arises and can be solved.

In conclusion, this study shows that including the FIT with the invitation results in higher FIT participations rates. Actively involvement of the GP will result in higher participation rates to colonoscopy follow-up, but only if no effort of participants is required. Adjustments to the organisational structure of a screening programme may result in more screening benefit.

REFERENCES

1. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637-49.
2. Luxembourg: Council of the European Union. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri-OJ:L:2003:327:0034:0038:EN:PDF. [Cited September 21 2017].
3. Portillo I, Idigoras I, Ojembarrena E, Arana-Arri E, Zubero MB, Pijoan JI, et al. Principales resultados del programa de cribado de cancer colorrectal en el Pais Vasco. Gac Sanit. 2013;27(4):358-61.
4. Van Roosbroeck S, Hoeck S, Van Hal G. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. Cancer Epidemiol. 2012;36(5):e317-24.
5. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut. 2010;59(1):62-8.
6. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. Lancet Oncol. 2012;13(1):55-64.
7. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135(1):82-90.
8. Rat C, Latour C, Rousseau R, et al. Interventions to increase uptake of faecal tests for colorectal cancer screening: a systematic review. Eur J Cancer Prev. 2018; 27(3):227-236.
9. Senore C, Ederle A, DePretis G, et al. Invitation strategies for colorectal cancer screening programmes: The impact of an advance notification letter. Prev Med. 2015;73:106-11.
10. van Roon AH, Hol L, Wilschut JA, et al. Advance notification letters increase adherence in colorectal cancer screening: a population-based randomized trial. Prev Med. 2011;52(6):448-51.
11. Moss S, Ancelle-Park R, Brenner H, International Agency for Research on Cander. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Evaluation and interpretation of screening outcomes. Endoscopy. 2012;44 Suppl 3:SE49-64.
12. Piette C, Durand G, Bretagne JF, et al. Additional mailing phase for FIT after a medical offer phase: The best way to improve compliance with colorectal cancer screening in France. Dig Liver Dis. 2017;49(3):308-11.
13. Ponti A, Anttila A, Ronco G, et al. Cancer Screening in the European Union. Report on the implementation of Council Recommendation on Cancer Screening. Brussels: European Commission; 2017. Available from : https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf. [Cited October 24 2018].
14. Vanaclocha-Espi M, Ibanez J, Molina-Barcelo A, et al. Factors influencing participation in colorectal cancer screening programs in Spain. Prev Med. 2017;105:190-6.
15. Giorgi Rossi P, Grazzini G, Anti M, et al. Direct mailing of faecal occult blood tests for colorectal cancer screening: a randomized population study from Central Italy. J Med Screen 2011;18: 121-7.
16. Denis B, Gendre I, Perrin P. Participation in four rounds of a French colorectal cancer screening programme with guaiac faecal occult blood test: a population-based open

cohort study. J Med Screen. 2015;22(2):76-82.

17. Moss S, Mathews C, Day TJ, et al. Increased uptake and improved outcomes of bowel cancer screening with a faecal immunochemical test: results from a pilot study within the national screening programme in England. GUT. 2017;66(9):1631-1644.
18. Cole SR, Smith A, Wilson C, et al. An advance notification letter increases participation in colorectal cancer screening. J Med Screen 2007;14: 73-5.
19. Duffy SW, Myles JP, Maroni R, et al. Rapid review of evaluation of interventions to improve participation in cancer screening services. J Med Screen 2017;24: 127-45.
20. Wardle J, von Wagner C, Kralj-Hans I, et al. Effects of evidence-based strategies to reduce the socioeconomic gradient of uptake in the English NHS Bowel Cancer Screening Programme (ASCEND): four cluster-randomised controlled trials. Lancet 2016;387: 751-9.
21. The Spanish screening cancer network. Available in: www.cribado de cancer.es [Accessed January 13, 2018].
22. Monitoring report of the Flemish Colorectal Cancer Screening Programme 2017. Available from: https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/atoms/files/Jaarrapport2017_DEF_0.pdf [Cited January 13 2018}.
23. Monitoring report of the French screening programme 2016-2017. Available from: https://bit.ly/2HIc0BP. [Cited April 13 2018).
24. Arana-Arri E, Idigoras I, Uranga B, 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(1):577.
25. Hofmann B. Ethical issues with colorectal cancer screening-a systematic review. J Eval Clin Pract. 2017;23(3):631-41.
26. de Haan MC, de Wijkerslooth TR, Stoop E, et al. Informed decision-making in colorectal cancer screening using colonoscopy or CT-colonography. Patient Educ Couns. 2013;91(3):318-25.
27. van Dam L, Korfage IJ, Kuipers EJ, et al. What influences the decision to participate in colorectal cancer screening with faecal occult blood testing and sigmoidoscopy? Eur J Cancer. 2013;49(10):2321-30.