

Longitudinal Adherence to Immunochemical Fecal Occult Blood Testing vs Guaiac-based FOBT in an Organized Colorectal Cancer Screening Program



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Abstract

Longitudinal adherence is a critical component of the efficacy of stool-based screening programs because they should be repeated every 1–2 years. Few data have been published on the uptake in multiple rounds of fecal occult blood test-based (FOBT) colorectal cancer (CRC) screening. We calculated two measures of longitudinal adherence to biennial FOBT (guaiac fecal occult blood test:gFOBT or fecal immunochemical test: FIT) to better understand its impact on the programmatic effectiveness of a population-based CRC screening program (2000–2017). Ongoing population-based CRC program of men and women aged 50–69 years. Variables: Age at first CRC screening invitation, sex, number of screening invitations, number of screens, deprivation score, and uptake rate. Logistic regression models were used to assess the independent effect of sex, age at first invitation, deprivation, and the type of screening test offered on adherence. The uptake rate for

guaiac fecal occult blood test (gFOBT) was 23.9%, and for the fecal immunochemical test (FIT), it was 37.4%. The overall rate of consistently screened invitees after seven rounds of screening was 14.2%, being 20.6% for those individuals who used FIT and 14.3% for those who used gFOBT. Factors associated with continued participation (consistent vs. inconsistent screenees) showed that the longitudinal adherence was associated with age, screening test used, and number of invitations. Continued participation was lower in individuals who were screened using FIT than among those screened using gFOBT [OR, 0.68; 95% confidence interval (CI), 0.57–0.81]. The overall rate of consistently screened invitees for colorectal cancer screening was higher with FIT than gFOBT. Studying the rate of individuals being current for screening may help to anticipate potential benefits before the long-term outcome data are available.

Introduction

Colorectal cancer screening is a simple and effective public health intervention that prevents and minimizes the impact of colorectal cancer on the community. There is convincing evidence supporting the fecal occult blood

test (FOBT), sigmoidoscopy, and colonoscopy as screening tools (1–9).

Uptake is a key indicator of the potential effectiveness of any screening intervention because it reflects the degree to which a population is exposed to the intervention. Bulliard and colleagues (10) published a review of cancer screening uptake definitions and measures, focusing primarily on uptake in a single round of screening and noted that measures of uptake across multiple rounds of screening are complex. Several indicators measure adherence; the choice of the indicator depends on the objective. Determining who is eligible to be studied depends on the question of interest, and there are three possibilities: the entire population (studies focused on the proportion of the population in need of screening), people meeting the eligibility criteria for screening (relevant considerations for screening eligibility include those related to the risk level; invitation to screen; prior cancer, symptoms, or tests; and screening ascertainment), and people who have

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been previously screened (measure of the time to rescreening; refs. 10, 11).

Longitudinal adherence is a critical component of stool-based screening programs for screening efficacy because screens should be repeated every 1 to 2 years, and the attrition rate has important implications for the long-term effectiveness of the screening program (12, 13). The effectiveness of an FOBT screening program is highly dependent on uptake in multiple rounds (14). Ideally, eligible invitees accept the invitation to be screened in every screening round (12, 15). The best indicator to study the effectiveness is to calculate the percentage of consistently screened individuals among all invitees.

Few data have been published on the uptake in multiple rounds of FOBT-based colorectal cancer screenings in a large population-based open cohort. To compare the published data, the measure used to calculate longitudinal adherence, especially the screening eligibility criteria and the length of the study period, needs to be considered. The longitudinal adherence of individuals eligible for colorectal cancer screenings using the guaiac fecal occult blood test (gFOBT) ranges from 38.1% to 47.2% (4, 6, 16, 17). Invitees between 14.3% and 44.4% were consistently screened for colorectal cancer using the gFOBT (12, 15, 18–20). Screening programs using the fecal immunochemical test (FIT) reported 38.3% to 53.6% rates of consistently screened invitees (21–24). In all these studies, the number of rounds studied was at most three or four.

European guidelines for quality assurance in colorectal cancer screening and diagnosis have defined a standard for uptake; however, the desirable target would be to achieve an uptake rate of 65% (25). These guidelines recommend minimal uptake, but there is no recommendation for longitudinal adherence.

In the context of an intervention or program, studying longitudinal adherence may help to anticipate the potential benefits before long-term outcome data are available. Measuring longitudinal adherence may also help identify opportunities to develop interventions and programs that reduce disparities.

In 2000, Catalonia was the first region to launch a population-based colorectal cancer screening program using FOBT in Hospitalet de Llobregat (Barcelona, Spain; ref. 26). The first two screening rounds were part of the pilot study. Over time, the screening program was strategically modified to attain quality indicators and to make it more accessible to the population (26, 27). Nowadays, several regions of Spain have active colorectal cancer screening programs (28, 29).

We calculated two measures of longitudinal adherence to biennial FOBT (gFOBT or FIT) to better understand its impact on the programmatic effectiveness of a population-based colorectal cancer screening program from 2000 to 2017.

Materials and Methods

Seven rounds of the Catalan colorectal cancer biennial screening program were performed from February 2000 to June 2017 (first round from 2000 to 2002; second round from 2003 to 2005; third round from 2006 to 2008; fourth round from 2008 to 2010; fifth round from 2010 to 2012; sixth round from 2012 to 2014; and seventh round from 2014 to 2017).

Study population

The target population included 131,862 men and women aged 50 to 69 years who were residents in the screening area, Hospitalet de Llobregat, a municipality to the immediate southwest of Barcelona. The analysis evaluating screening adherence was restricted to the subjects invited to participate at least twice between 2000 and 2017 ($n = 103,122$).

To analyze the effect of the type of screening test used on longitudinal adherence, we compared subjects who were invited at least twice for gFOBT-based screenings irrespective of further invitations for FIT-based screenings with subjects who were invited at least twice for FIT-based screenings and had never been invited for gFOBT-based screenings ($n = 93,107$).

Screening procedure

This study was performed within our ongoing, population-based colorectal cancer screening program. The study design has been described previously (26, 27, 30). Briefly, a biennial population-based screening program for CCR using the FOBT was launched in Hospitalet de Llobregat, an industrial city of 260,288 inhabitants. Participants with positive screening results were referred for a colonoscopy. Participants with no lesions found during the colonoscopy were invited for another screening after 10 years if eligible. The program was free to the public and included men and women aged 50 to 69 years.

Exclusion criteria

Subjects were excluded if they had any of the following: a personal history of colorectal cancer or adenomas, familial colorectal cancer, inflammatory bowel disease, a colonoscopy in the previous 5 years or FOBT in the previous 2 years, or a terminal disease, or a severe disabling condition. Subjects with an invalid mailing address and removals from the screening area registry were also excluded because they could not be invited to a screening.

Screening test

The gFOBT was the only test used in the first three screening rounds (Hema-screen; Immunostics, Inc.). In the fourth round, the FIT (OC Sensor μ , Palex) was partially introduced and offered to 12,727 individuals to assess its

feasibility and acceptability (eligible population assigned to two Basic Health Areas randomly selected). The gFOBT was offered to the remaining target population ($n = 50,199$; eligible population assigned to 10 Basic Health Areas).

On the basis of the favorable results obtained with the FIT, the Catalan Cancer Strategy decided that the FIT would be used throughout Catalonia. Thus, in the fifth, sixth, and seventh rounds of colorectal cancer screenings, the FIT was the only test used.

Variables

Data on age at first invitation, sex, number of screening invitations, and number of screens were retrieved from the program database. Because no individual information on socioeconomic status (SES) was available, a deprivation score, elaborated by the Catalan Agency for Quality and Health Technology Assessment and calculated for basic healthcare areas of the Catalan territory, was used (31). This score combined several pieces of contextual data, such as income deprivation, employment deprivation, health deprivation, and average education, into a single deprivation score for a basic healthcare area (score: 0–100). Higher scores on this index represent greater socioeconomic deprivation.

The uptake rate was calculated as the number of participants (persons with an FOBT performed properly) relative to all eligible invitees. Uptake rates were calculated for each screening round.

We have used two measures to calculate the longitudinal adherence. The first measure is the continued participation, which answers the research question: what is the prevalence of receiving regular screening? This measure gives information about long-term satisfaction with the screening program (10). Participants are studied and analyzed if they continue over time with screening. The denominator of this indicator is the number of individuals who have participated.

The second measure is the percentage of invited individuals with a consistent screening behavior, which answers the research question: who could potentially benefit most from cancer screening?

What proportion of invitees participates in all screening rounds? In this case, the denominator is the individuals invited to the cancer screening program and the numerator the individuals that have been tested as many times as invited. The measure gives information about the percentage of eligible population that can benefit from the program, the effectiveness of the screening program. Thus, this could be an intermediate indicator of mortality, which is a very expensive indicator and requires a lot of time to calculate it. Nevertheless, this measure depends on the individuals who enhance uptake in screening and those who continued being screened over time.

To classify individuals according to their screening behavior, we considered three categories: never screened individuals (no uptake in any round of the screening), inconsistent screenees (attending at least one round of screening but less than the total eligible number of screenings), and consistent screenees (attending all rounds of screenings when eligible). We have examined the proportion of individuals who participated in the screening after two or more invitations (late adopters) and those who discontinued screening (quitters) in the next round.

Statistical analyses

A descriptive analysis was performed to identify invitees with a consistent screening behavior over seven screening rounds and by the type of test. The Joinpoint Regression Program (Version 4.5.0.1, Statistical Methodology and Applications Branch, Surveillance Research Program, NCI, Bethesda, MD, USA) was used to analyze uptake trends for the whole population and to detect where a significant change in the trend occurred.

Multivariate logistic regression models were used to assess the independent effects of sex, age at first invitation (5-year category), deprivation (10-point category), and type of screening test offered, on screening adherence. All the models were further adjusted for the number of invitations and average uptake after the first screening invitation. These models provided ORs and 95% confidence intervals (CI) that allowed us to compare: (i) consistent versus inconsistent screenees, (ii) inconsistent screenees versus never screened individuals, and (iii) screenees (both consistent and inconsistent screenees) versus never screened individuals.

Ethics

Our colorectal cancer screening program, similar to all Spanish population-based screening programs, followed public health laws and the Organic Law on Data Protection. The study protocol was approved by the ethics committee of the University Hospital of Bellvitge (L'Hospitalet de Llobregat, Spain; PR261/17).

Results

Uptake

Over the seven screening rounds, the uptake rates increased significantly from 17.2% to 38.0%. Of the 131,862 individuals eligible for the seven screening rounds, 62.8% were "never participants," and 37.2% participated at least once (Table 1; Supplementary Fig. S1).

Consistently screened invitees

The number of times that invitees participated during the seven screening rounds displayed for the number of times that invitees were eligible is summarized

Table 1. Colorectal cancer screening uptake per rounds

Screening round number	Screening test	Number of BHA involved	Target population	Uptake ^a		Rescreening ^b %
				<i>n</i>	%	
1 (Pilot)	gFOBT	11	63,872	11,005	17.2	
2 (Pilot)	gFOBT	12	66,519	14,816	22.3	73.2
3	gFOBT	12	65,142	17,742	27.2	87.0
4	gFOBT	10	50,199	15,135	30.2	87.3
	FIT	2	12,727	4,625	36.3	
5	FIT	12	63,824	22,981	36.0	89.7
6	FIT	12	60,906	23,325	38.3	88.7
7	FIT	12	61,428	23,366	38.0	81.2
Overall	FIT or gFOBT	12	131,862	48,974	37.2	83.7

NOTE: Uptake trend. The percentage change per screening round from 2000 to 2012 was 20.10 and from 2012 to 2017 was 0.98 (derived from Jointpoint regression analysis).

Abbreviation: BHA, Basic Healthcare Area (There are 12 BHA in L'Hospitalet)

^aUptake: total number of people who have used and returned a screening test irrespective of result. This includes individuals with inadequate/incomplete results.

^bRescreening (refers to two consecutive rounds): total number of people invited for screening in Round *n* and Round *n*-1 who participated in both rounds.

in Table 2. The overall screening rate after seven rounds of screening was 14.2% (18,681/131,862). According to the number of invitations, it ranged from 16.03% to 12.51% (Table 2). The overall screening rate according to the type of test is shown in Table 3 (14.3 for gFOBT and 20.6 in FIT).

Inconsistent screenees

Inconsistent screenees can be classified in two main groups: those who changed screening behavior over time (late adopters and quitters) and those with an erratic behavior regarding screening. Table 4 shows the proportion of individuals who participated in the screening after two or more invitations (late adopters) and those who stopped being screened (quitters; Table 4).

Late adopters

Individuals who enhanced uptake after being invited one time in the previous round and not having participated was 11.2% for the gFOBT and 12.6% for the FIT (Supplementary Tables S2 and S4).

Quitters

The proportion of quitters for both tests was approximately 25% after their first screen. The percentage of participants who withdrew after two and three rounds of

screenings was greater for the FIT than for the gFOBT and for three rounds (FIT: 13.8% and 8.7%; gFOBT: 7.1% and 5.4%, respectively; Supplementary Tables S2 and S4).

Continued participation

Table 5 provides the results of the multivariate logistic regression analysis examining the predictors of longitudinal adherence in colorectal cancer screenings. Model 1 analyzed the factors associated with continued participation (consistent vs. inconsistent screenees), longitudinal adherence was associated with age, screening test used (gFOBT or FIT), and number of invitations. Continued participation was lower among individuals who used the FIT than among those who used the gFOBT (OR, 0.68; 95% CI, 0.57–0.81).

No differences in sex or deprivation index were observed. The age at first invitation (5-year change) was associated with adherence to colorectal cancer screenings. Elderly individuals were more likely to be adherent than their younger counterparts.

The model that compared inconsistent screenees versus never screened individuals (model 2) revealed that screening uptake was associated with sex, deprivation index, and test type. The ORs showed that women participated more than men, especially those with a lower deprivation index and those who were invited to participate in screenings

Table 2. Number of times invitees participated in the colorectal cancer screening program displayed for the number of times they were eligible

Number of participations		Number of invitation							Total
		1	2	3	4	5	6	7	
Number of participations	0	24,820	18,546	12,257	9,683	7,678	6,004	3,900	82,888
	1	3,920	3,472	2,334	1,797	1,781	1,441	938	15,683
	2		4,205	2,009	1,562	1,340	1,308	774	11,198
	3			2,680	1,748	1,358	1,222	692	7,700
	4				2,356	1,483	1,136	715	5,690
	5					2,200	1,446	769	4,415
	6						2,067	968	3,035
Total		28,740	26,223	19,280	17,146	15,840	14,624	10,009	131,862
Consistently screened invitees^a			16.0%	13.9%	13.7%	13.8%	14.1%	12.5%	14.2%^b

^aConsistently screened invitees: being tested as many times as getting invited.

^bWhen excluding the Pilot Screening Rounds (round 1 and round 2), the overall percentage of consistently screened invitees is 20.9% (Supplementary Table S1)

Table 3. Individuals invited to a colorectal cancer screening program by the test used and number of invitations

Screening test ^a	Number of invitations	Individuals invited to screening program					
		Never screened		Inconsistent screenees		Consistent screenees	
		<i>N</i>	%	<i>n</i>	%	<i>n</i>	%
gFOBT ^b	2	19,740	72.1	3,556	13.0	4,082	14.9
	3	15,690	63.5	5,495	22.2	3,541	14.3
	4	13,106	58.3	6,327	28.2	3,031	13.5
	All	48,536	65.1	1,5378	20.6	10,654	14.3
FIT ^b	2	5,892	63.6	1,309	14.1	2,059	22.2
	3	4,514	54.7	2,208	26.8	1,532	18.6
	4	470	45.9	325	31.7	230	22.4
	All	1,0876	58.7	3,842	20.7	3,821	20.6

^aIndividuals who were offered gFOBT were included in the analysis, irrespective of further invitation for FIT-based screening ($n = 74,568$).

^bIndividuals who were offered FIT as the only screening test of choice ($n = 18,539$).

using the FIT. Similar findings were found with the model that compared those never screened with screenees (both consistent and inconsistent screenees; model 3); and women with a lower deprivation index and those who used FIT were more likely to have been screened at least once (Table 5).

Discussion

This population-based study calculated two longitudinal adherence indicators to colorectal cancer screening with FOBT. The results showed a longitudinal decrease in adherence over seven screening rounds. In addition, it was observed that the overall rate of consistently screened invitees for colorectal cancer screening was higher with FIT than gFOBT despite lower continued participation. Factors associated with initial uptake were quite different from those relating to adherence in the subsequent rounds of screenings. Continued participation was associated with age, screening test used (gFOBT or FIT), and number of invitations.

Monitoring longitudinal screening adherence is important (22, 24, 32), especially for FOBT, because individuals

are more likely to adhere to screening options that require fewer screenings over time (33). There is little information on the uptake patterns in any screening program that is predicated on repeated invitations at regular intervals (15, 18, 19, 21–24; Supplementary Table S3). To the best of our knowledge, no study has compared the longitudinal adherence (neither continued participation among screenees nor proportion of consistently screened invitees) of both the tests (gFOBT and FIT).

Given the scarcity of information on the impact of repeated FIT or gFOBT screenings, such data are of major importance for countries considering or planning the implementation of population-based FIT or gFOBT screening programs. The replacement of the gFOBT with quantitative FIT screenings should increase uptake. When comparing the FIT and the gFOBT in terms of continued participation, in our screening program, is lower in the FIT, but instead, the number of people who join the screening program was greater in FIT than in the gFOBT and, therefore, the percentage of consistently screened invitees was still greater with the FIT. The latter measure gives information about how many individuals could potentially benefit most from cancer

Table 4. Participation and withdrawal according to the number of previous participations

Number of previous invitations	Number of previous participations	Participation to the current round				All
		No		Yes		
		<i>N</i>	%	<i>N</i>	%	
		Never screened		Late adopters		
1	0	18,546	92.4	1,525	7.6	20,071
2	0	12,257	93.2	901	6.8	13,158
3	0	9,683	92.7	761	7.3	10,444
4	0	7,678	90.8	782	9.2	8,460
5	0	6,004	90.8	609	9.2	6,613
6	0	3,900	91.5	362	8.5	4,262
		Quitters		Consistent screenees		
1	1	1,947	31.6	4,205	68.4 ^a	6,152
2	2	503	15.8	2,680	84.2	3,183
3	3	279	10.6	2,356	89.4	2,635
4	4	185	7.8	2,200	92.2	2,385
5	5	174	7.8	2,067	92.2	2,241
6	6	78	5.9	1,253	94.1	1,331

NOTE: Late adopters, individuals who enhance participation after ≥ 2 invitations; Quitters, individuals who discontinued screening for the next round; Consistent screenees, individuals who participate every time they get a screening invitation.

^aWhen excluding Pilot Screening Rounds (round 1 and round 2), the percentage of consistent screenees after two invitations is 80.0%.

Table 5. Factors associated with continued participation and uptake in a population-based screening program for colorectal cancer

Independent variables	Continued participation		Uptake			
	Model 1: Consistent vs. inconsistent screenees		Model 2: Inconsistent screenees vs. never screened		Model 3: Screenees ^a vs. never screened	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex (ref men)	1.00		1.00		1.00	
Women	1.01	[0.97-1.06]	1.20	[1.16-1.24]	1.21	[1.17-1.24]
Age at first invitation (5-year change)	1.04	[1.01-1.07]	0.98	[0.96-1.00]	1.00	[0.99-1.02]
Deprivation index (10-point change)	0.98	[0.96-1.01]	0.88	[0.87-0.90]	0.87	[0.86-0.88]
Invitations number (2)	1.00		1.00		1.00	
Three invitations	0.58	[0.54-0.61]	1.96	[1.87-2.05]	1.51	[1.46-1.57]
Four invitations	0.48	[0.45-0.52]	2.52	[2.38-2.67]	1.84	[1.76-1.93]
Type of test (ref gFOBT)	1.00		1.00		1.00	
FIT	0.68	[0.57-0.81]	1.68	[1.47-1.91]	1.38	[1.25-1.53]
Average participation at first invitation (1-percent change)	1.04	[1.03-1.05]	0.99	[0.98-1.00]	1.01	[1.00-1.01]

^aScreenees includes both consistent and inconsistent screenees.

screening (some individuals who have been screened sporadically may also get some benefit from being screened; ref. 14).

The longitudinal decrease in adherence may be partially explained by screening fatigue. Invitees lose the motivation to participate because of a false perception of decreased colorectal cancer risk after several negative test outcomes (34). Screening fatigue considerably reduces screening effectiveness and is a potential threat for FOBT screening programs because repeated testing is important to achieve reasonable sensitivity for detecting advanced neoplasia. Furthermore, colorectal cancer risk increases with age, stressing the importance of uptake among older individuals (35).

Late adopters (individuals who participate in colorectal cancer screenings after several invitations) contributed to overall uptake. Here, previous nonattenders were reinvited every 2 years, irrespective of whether they had previously responded, because this practice improves uptake (36). Increased awareness of colorectal cancer screening and sufficient information on colorectal cancer and FIT screenings may enhance the uptake in successive rounds because the target population is screening-naïve when first approached (36). It is important to keep inviting the previous nonparticipants because, in our study, up to 8.4% of the population participated after three invitations, regardless of the type of test (gFOBT or FIT). In cancer screening programs where uptake is less than 45%, any intervention is important to increase uptake, especially when the intervention mainly involves sending an invitation letter and a reminder.

In addition, it is important to consider the percentage of quitters, especially when uptake is <45%. Almost 25% of the participants do not participate again in the next round. Primary care professionals should be closely involved in interventions designed to improve longitudinal adherence. The general practitioner role is pivotal not only to increase uptake in FOBT screenings but also to ensure adherence with repeat testing for people with negative FOBT results (18). General practitioners could increase their

involvement in colorectal cancer screening if they had more involvement with patient information at different stages of the screening process. Their privileged mode of communication remains face-to-face consultation with the patient (37).

The strengths of our study include access to a large cohort of an average-risk population composed of participants of the age ranges that are typically invited for colorectal cancer screening programs worldwide. Our study also had several limitations. First, SES could only be assigned by postal code, as a proxy for individual level SES. Second, 17 years have passed since the screening program was implemented, and many organizational changes have occurred. These changes may have contributed to uptake modification and longitudinal adherence; however, these changes have not been monitored and, therefore, cannot be identified as confounding factors. Third, the first two rounds of screenings were pilot rounds with uptake values of 17.2% and 22.3%, respectively, which conditioned full adherence. When we excluded these two rounds, the full adherence over five rounds of screenings improved by six percentage points (from 14.2% to 20.6%).

To improve the comparability of longitudinal adherence indicators in cancer screening interventions, the definitions and associated terminology need to be explicit, standard terms should be favored, and the use of the same term for different meanings needs to be avoided (10).

In summary, there are differences in the longitudinal adherence of FIT and gFOBT screening; the FIT increased the overall uptake but decreased the continued participation. In programs with an overall uptake of less than 45%, it is considered appropriate to focus on the interventions that improve initial uptake. When the uptake is 45% or higher, then it is important to design specific interventions focused on maintaining adherence. Identifying the proportion of consistently screened individuals is important to anticipate the population benefits of screening before having the mortality data available.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Benito, C. Vidal, J. Espinosa, M. Garcia
Development of methodology: L. Benito, G. Binefa, C. Vidal
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Benito
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Benito, N. Travier, M. Garcia
Writing, review, and/or revision of the manuscript: L. Benito, N. Travier, G. Binefa, C. Vidal, J. Espinosa, N. Milà, M. Garcia
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Benito
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