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Research Article

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False-Positive Results in a Population-Based Colorectal Screening Program: Cumulative Risk from 2000 to 2017 with Biennial Screening

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Abstract

Background: The aim of this study was to estimate the cumulative risk of a false-positive (FP) result in a fecal occult blood test (FOBT) through 7 screening rounds and to identify its associated factors in a population-based colorectal cancer screening program.

Methods: Retrospective cohort study, which included participants ages 50 to 69 years of a colorectal cancer screening program in Catalonia, Spain. During this period, 2 FOBTs were used (guaiac and immunochemical). A discrete-time survival model was performed to identify risk factors of receiving a positive FOBT with no high-risk adenoma or colorectal cancer in the follow-up colonoscopy. We estimated the probability of having at least 1 FP over 7 screening rounds.

Results: During the period of 2000 to 2017, the cumulative FP risk was 16.3% ($IC_{95\%}$: 14.6%–18.3%), adjusted by age, sex, and type of test. The median number of screens was 2. Participants who began screening at age 50 years had a 7.3% [95% confidence interval (CI), 6.35–8.51] and a 12.4% (95% CI, 11.00–13.94) probability of an FP with 4 screening rounds of guaiac-based test and immunochemical test, respectively. Age, the fecal immunochemical test, first screening, and number of personal screens were factors associated with an FP result among screenees.

Conclusions: The cumulative risk of an FP in colorectal screening using FOBT seems acceptable as the colonoscopy, with its high accuracy, lengthens the time until additional colorectal screening is required, while complication rates remain low.

Impact: It is useful to determine the cumulative FP risk in cancer screening for both advising individuals and for health resources planning.

Introduction

Colorectal cancer screening based on fecal occult blood test (FOBT) followed by a colonoscopy has been demonstrated to decrease colorectal cancer incidence and mortality (1, 2). In fact, there is sufficient evidence that screening for colorectal cancer with currently established FOBT [guaiac testing (gFOBT) or fecal immunochemical test (FIT)] or lower endoscopy (sigmoidoscopy or colonoscopy) reduces the risk of death from colorectal cancer and that the benefits outweigh the harms associated with each type of screening (2).

A higher performance of FIT in terms of an improved sensitivity for colorectal cancer, better detection of advanced adenomas, and greater screenee participation has led to the widespread adoption of the immunochemical test (3). Although the additional detection of FIT (OC-Sensor) requires approximately double the number of colonoscopies, the number of colonoscopies per significant neoplasia detection is approximately the same as the high-sensitivity gFOBT (Hemoccult II; ref. 4). In fact, the "number needed to screen" to prevent 1 colorectal cancer death over 13 years is 239 with a gFOBT (Hemoccult II) and 129 with a FIT (OC-Sensor, cut-off 30 μg/g; ref. 5). Positive test results lead to more invasive and expensive diagnostic testing procedures and psychological distress (6). For this reason, it is important to highlight that although undergoing colorectal cancer screening has clear benefits for some patients, others might only suffer from the harms of obtaining a false-positive (FP) result.

Reducing the probability of getting an FP result is important for colorectal cancer screening as it would improve the balance of benefits and harms of this preventive modality. There are few

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published studies that have investigated the risk factors for an FP result in a single FOBT (7–11).

The FP risk is usually assessed for each round, thus underestimating the cumulative negative effect of participation in several rounds, whereas the benefit of screening is usually measured as mortality reduction after participation in several screening rounds (12). However, to the best of our knowledge, only Hubbard and colleagues(13) has investigated the cumulative risk of an FP FOBT result across multiple screening rounds (14). They found that after 10 years of annual gFOBT, 20.5% of participants received an FP result. In contrast, there are more studies that have investigated the risk of cumulative FP but in other screening tests (15–17). For a better assessment of screening adverse effects, it is not only important to know the risk of an FP test after attending 1 screen, but also the cumulative FP risk over the course of a lifetime of screening. In Spain, colorectal cancer screening comprises a free, public, biennial, population-based screening programme using FOBT, which are provided free of charge to men and women ages 50 to 69 years.

In this study, we aimed to estimate the cumulative risk of an FP result over 7 biennial FOBT (gFOBT and/or FIT) screening rounds and to identify its associated factors in a population-based colorectal cancer screening programme in Catalonia (Spain).

Materials and Methods

Screening procedure

Briefly, in 2000, a biennial screening programme was launched by Catalan Institute of Oncology in l'Hospitalet de Llobregat (Barcelona, Catalonia, Spain). From the first to the third round, gFOBT was used as the screening test (Hema-screen). In the fourth round, the FIT (OC Sensor) was introduced as an alternative test and remained as the only strategy in the fifth and following rounds. A detailed description of the FOBT performance of CRC screening programme in Hospitalet is provided elsewhere (18–20).

The target population, which was around 64,500 individuals in each screening round, included all men and women ages 50 to 69 years who lived in l'Hospitalet. The total crude participation rate increased from 17.2% in the first round to 38.7% in the last one. Subjects were excluded according to the following criteria: digestive symptoms, history of personal colorectal cancer, high-risk familial history of colorectal cancer, adenomas or inflammatory bowel disease, criteria for hereditary colorectal cancer syndromes, colonoscopy in the previous 5 years or a FOBT within the last 2 years, terminal disease, and severe disabling conditions. Subjects with a positive FOBT plus a colonoscopy were excluded from subsequent FOBT analyses until 2011, when the exclusion criteria of the screening programme were changed and those with a diagnosis of low risk adenoma were no longer excluded and were invited to participate in the following round.

As previously reported (20), participants with gFOBT collected 2 samples of feces from each of 3 consecutive stool specimens with no dietary restriction. Results of the gFOBT could be (i) negative: 0 of 6 positive spots; (ii) positive: 5 or 6 positive spots in a first gFOBT or 1 to 6 positive spots after a weak positive gFOBT; (iii) weak positive: blood detected in 1 to 4 spots. Individuals with a weak positive were asked to repeat the test with dietary restriction, and depending of the results they had to perform a third test or a colonoscopy; (iv) inconclusive: expired samples (negative result with more than 14 days between stool collection and its analysis), lack of information in the kit (personal identification number, date of stool collection), or any technical failure or improper performance of the test. In FIT, the cutoff used to define a positive FOBT result was a hemoglobin level of 20 μg Hb/g (100 ng/mL). All screenees with a positive test result were offered a colonoscopy. The colonoscopy compliance was around 93%.

Study population

In this study we included all participants with a conclusive positive result of FOBT from 2000 to 2017 from the first participation and up until a colorectal cancer diagnosis, death, or exclusion criteria above mentioned. Individuals with an inconclusive result (negative results with more than 14 days between feces collection and its analysis), lack of information in the kit (personal identification number, date of feces collection), or any technical failure or improper performance of the test were asked to repeat the FOBT. If declined, they were considered as nonparticipants in that particular round. Also, participants with positive FOBT who did not undergo colonoscopy were considered as nonparticipants in that particular round. During the study period, 7 rounds have been performed in the Catalan colorectal cancer biennial screening programme. Despite an intended 2-year interval between rounds, delays occurred in the first 2 rounds due to programming and management constraints.

An FP result indicates that a screening test has suggested that a person has a specific disease or condition when the person actually does not have it. In the case of colorectal cancer screening, the target lesions are advanced adenomas and cancer. Other findings should be considered FP results. For this reason, an FP result was defined as a positive FOBT result followed by a colonoscopy result without any high-risk lesions or colorectal cancer. The quality standard for an Endoscopy Unit is to perform $\geq$90% of colonoscopies referred from the screening programme within 60 days. Some of the endoscopic procedures were delayed because of organizational constraints but 95% of the colonoscopies were done within 4 months after a positive screening test. Polyp specimens were classified according to WHO criteria, considering a high-risk adenoma (HRA) or advanced adenoma any polyp $\geq$10 mm, >2 adenomas, tubulo-villous or villous histology, high-grade dysplasia, or carcinoma in situ; low-risk adenoma, 1 or 2 adenoma <10 mm, with tubular histology and low-grade dysplasia. Subjects with more than one lesion were classified according to the most advanced lesion. During the study period, the European Guidelines for Quality Assurance in CRC Screening and Diagnosis (21) were published in 2011, and they subdivided HRA into 2 groups: HRA and intermediate risk lesions. Although we have maintained the initial risk classification for this study, recommendations for surveillance colonoscopies were made according to the most updated guidelines (Supplementary Table S1).

The colorectal cancer screening programme information system allowed collection of characteristics of both the patient and screening regimen.

All participants with an FP result were followed until December 2017 to identify whether a patient was diagnosed with a colorectal cancer, which could explain the FP result. Diagnoses of colorectal cancer were identified from the official regional hospital discharge administrative database (CMDB), which contains information on diagnoses and procedures for each hospital admission for all of the public hospitals in the region of Catalonia and has reasonable accuracy to identify cancer cases (22). Post-colonoscopy interval

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colorectal cancer was defined as a colorectal cancer diagnosed after diagnostic colonoscopy in which no intermediate or high risk lesion or colorectal cancer was detected, and before the date of the next recommended exam (21, 23). We calculated the rate of post-colonoscopy interval colorectal cancer after a negative colonoscopy.

Our colorectal cancer screening programme follows the Public Health laws and the Organic Law on Data Protection. The screening programme accomplishes the specific protocol based on the existing guidelines; the research protocol was approved by the Ethics Committee of the University Hospital of Bellvitge (PR138/12).

Data analysis

Descriptive statistical analysis for selected sociodemographic and screening characteristics of the participants in the colorectal cancer screening using FOBT were performed. Analyses were stratified by FOBT type (gFOBT only, gFOBT+FIT, FIT only) and chi-square tests and Fisher exact tests were conducted to explore associations between variables.

We analyzed the factors associated with an FP result (analysis I) and then estimated the cumulative risk of receiving at least one FP result over the course of the screening program at the person-level associated with these factors (analysis II).

We conducted analysis I using a discrete survival model for time to an FP FOBT result over the study period (an individual contributes as many times as he/she has been screened) in which estimates correspond to discrete hazards estimated via logistic regression adjusting for age (divided into 50–55, 55–60, 60–65, and 65–69), sex, screening test (gFOBT or FIT), and change of screening test (from gFOBT to FIT). We also included number of individual participations treated as a numeric variable (personal screening participation number) and modeled as categorical variable [divided into initial (first personal round) vs. successive (rest of personal screening rounds)]. Adjusted odds ratios (HR) and their 95% confidence intervals (CI) were estimated.

For analysis II, we estimated the person-level cumulative risk of FP results associated with biennial screening (probability that an individual will receive one or more FP result after seven screening rounds). We used a censoring bias model for estimating the cumulative risk of an FP screening test under-dependent censoring developed by Hubbard and colleagues (24). It allows for variation in FP risk as a function of covariates, personal screening participation number, and round at which a subject was censored.

In a first step, a logistic regression model was used to estimate covariate effects associated with the risk of a first FP test result using data from individual screening rounds and censoring time. The model predictions were then used in a second step to estimate the probability of an FP test for each screening round, conditional on a specific covariate profile. Finally, estimates from individual rounds were aggregated to the person-level to obtain the probability of receiving at least one FP test result over the seven screening rounds.

Models for the cumulative probability of FP result included sex and age at first screen and total number of screens before censoring. For each personal screening round the model included the test used (gFOBT or FIT) and whether or not the person changed from gFOBT to FIT.

Death, terminal disease, severe disabling conditions, inflammatory bowel disease, and high-risk adenoma or colorectal cancer diagnosis were treated as competing events and individuals were censored at the earliest of disenrollment from screening or the end of the study period. A bootstrap procedure was used to construct 95% confidence intervals for the cumulative risk of an FP.

Finally, we intended to predict cumulative FP risk for the 8 to 10th screening round for the model adjusted in the analysis II, which included sex, age at first screen, and the total number of screens before censoring and FOBT test, and change of test in each personal screening round. Quadratic multiple regression was the model that best fitted with a 99.9% of the variance explained. Statistical analysis was carried out using R statistical software (R Foundation for Statistical Computing).

Results

Over the 17-year study period, we analyzed 130,134 FOBTs from 48,499 individuals. Table 1 summarizes the demographic and screening characteristics of the participants according to the type of FOBT they received. The median number of screening participations per individual was 2. A total of 66.9% of the participants had at least 2 screenings but only 8,418 (17.4%) participated in 5 or more rounds.

The positivity rate was 1.3% with gFOBT and 4.8% with FIT. Overall, 2,191 of the 48,499 (4.5%) participants had at least 1 FP FOBT result. This 4.5% represents the number of FP among all the participants (2,191 of the 48,499). Among those, only 20 participants had 2 FP results and a single person received 3 FP results. Among participants receiving either gFOBT only or FIT only, 414 participants (3.4%) and 849 (4.4%) participants received an FP result, respectively. In contrast, among all the positive FOBTs (2,191 of the 4,101), 54.0% got a FP (gFOBT: $n = 718$, 58.1; FIT: $n = 3{,}383$; 53.1%). This 54.0% represents the number of FP among participants with a positive FOBT.

At their first FOBT, 302 (2.5%) and 523 (2.7%) had an FP with gFOBT and FIT, respectively. However, in the multivariable analysis, the change from gFOBT to FIT was not significantly associated with an FP result (OR = 1.12; 95% CI, 1.00–1.26; Table 2). The use of FIT, older age, initial screening, and number of personal

Table 1. Subject characteristics according to FOBT type received across all screening rounds (one observation per individual)

	gFOBT only *n* (%)	gFOBT + FIT *n* (%)	FIT only *n* (%)	*P* value
Participants	12,260 (25.3)	16,896 (34.8)	19,343 (39.9)	
Sex				
Male	5,853 (47.7)	7,377 (43.7)	8,704 (45.0)	<0.001[a]
Female	6,407 (52.3)	9,519 (56.3)	10,639 (55.0)	
Age				
50–54 years	2,386 (19.5)	10,002 (59.2)	10,775 (55.7)	<0.001[a]
55–59 years	2,202 (18.0)	4,661 (27.6)	3,404 (17.6)	
60–64 years	3,865 (31.5)	2,005 (11.9)	2,984 (15.4)	
65–69 years	3,807 (31.1)	228 (1.3)	2,180 (11.3)	
Total number of screening tests received				
1	6,132 (50.0)	0 (0.0)	9,905 (51.2)	<0.001[b]
2	3,711 (30.3)	1,499 (8.9)	5,746 (29.7)	
3	1,694 (13.8)	2,492 (14.7)	3,331 (17.2)	
4	723 (5.9)	4,487 (26.6)	361 (1.9)	
5	0 (0.0)	4,334 (25.7)	0 (0.0)	
6	0 (0.0)	2,908 (17.2)	0 (0.0)	
7	0 (0.0)	1,176 (7.0)	0 (0.0)	
False positive				
No	11,846 (96.6)	15,968 (94.5)	18,494 (95.6)	<0.001[b]
Yes	414 (3.4)	928 (5.5)	849 (4.4)	

[a]Chi-square test.
[b]Fisher exact test.

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Table 2. Factors associated with an FP result based on data from 7 biennial FOBT screening rounds

	Adjusted ORs[a]	95% CI	*P* value
Sex			
Female	1		0.48
Male	1.03	0.95–1.12	
Age			
50–54 years	1		<0.001
55–59 years	1.26	1.13–1.40	
60–64 years	1.60	1.42–1.81	
65–69 years	1.67	1.41–1.99	
Screening			
Successive	1		<0.001
Initial	1.49	1.30–1.72	
Personal screening participation (number)	1.07	1.02–1.11	0.002
Screening test			
gFOBT	1		<0.001
FIT	3.90	3.48–4.37	
Change from gFOBT to FIT			
No			0.06
Yes	1.12	1.00–1.26	

NOTE: A discrete-time proportional hazards model was performed. For that purpose, each individual contributed as many times as being screened.
[a]All variables are included in the multivariate analysis.

participations were associated with increased risk of an FP result (Table 2). The odds of an FP were 49% higher at the first screen compared with subsequent screens, and each round an individual participated in increased the odds of an FP result by 7%.

After seven rounds, participants who began screening at a median age of 55 years had an overall cumulative probability of having at least one FP of 16.3% (95% CI, 14.6–18.3; Fig. 1) in a screening colorectal cancer programme based on biennial FOBT.

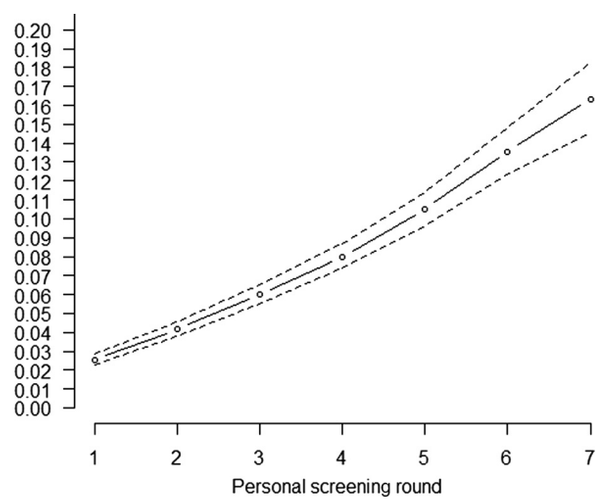

Figure 1

Cumulative risk of an FP result in a Catalan colorectal cancer screening program with biennial FOBT, 2000 to 2017. The horizontal axis indicates the number of personal screening rounds. The vertical axis scale indicates the proportion of subjects with at least one positive FOBT followed by a colonoscopy without CRC or high-risk lesions. Cumulative probabilities are based on risk estimates for each screening round. Dashed-dotted lines show the 95% CI. The model included the increased risk associated with a change from gFOBT to FIT.

The 20-year cumulative FP probability over biennial screening was estimated to be 27.5% (95% CI, 25.8%–29.5%) by a quadratic multiple regression model.

Risks were similar for women and men but differences in the probability of an FP between individuals were higher with FIT (Fig. 2). Men who began screening at age 50 had a 6.8% (95% CI, 5.6–8.2) and a 12.5% (95% CI, 10.9–14.2) probability of an FP with 4 screening rounds of gFOBT and FIT, respectively; whereas women who began screening at age 50 had an 8.0% (95% CI, 6.7–9.5) and a 12.2% (95% CI, 10.8–13.7) probability of an FP with 4 screening rounds of gFOBT and FIT, respectively.

Participants, irrespective of sex, who began screening at age 50 had a 7.4% (95% CI, 6.4–8.5) and a 12.4% (95% CI, 11.0–13.9) probability of an FP after four screening rounds of gFOBT and FIT, respectively.

Individuals with an FP had a median follow-up of 4.9 years from their last FP (5.3 and 6.2 years for negative and low-risk adenoma results, respectively). During surveillance, 5 patients were diagnosed with colorectal cancer (see Table 3) but only 4 (0.18%) of them were considered post-colonoscopy interval colorectal cancer (diagnosed before the date of the next recommended screening exam). Two patients had their diagnosis of colorectal cancer after a negative colonoscopy and 2 after a colonoscopy with low-risk adenomas. Although cecal intubation was confirmed in all colonoscopies, 2 colonoscopies had an inadequate bowel preparation and 1 had this data missing.

Discussion

In this study of FP FOBT results in a population-based colorectal cancer screening programme, we estimated a 16.3% cumulative FP risk after 7 screening rounds with biennial FOBT for participants who initiated screening with median age 55 years. Contrary to the higher probability of a positive FOBT for women compared with men when analyzing a single round that we have reported in previous studies (9, 10), the cumulative probability of an FP result was similar in males and females (Fig. 2). Older age, the fecal immunochemical test, and longer length of screening participation were factors associated with higher risks of an FP result.

Screening participation was summarized stratified by 2 variables: "initial" versus "successive" screening, which encapsulates the impact of first time participation on an FP result and the personal screening participation number which encompasses the effect of each additional screen. As other cancer screening programmes (25), the cumulative risk of an FP result was higher for first screenings, older age, and with increasing number of screening participations.

There are some studies that have analyzed the risk of cumulative FP results in other types of cancer screening programmes. European screening programmes based on biennial screening with mammography (26) have estimated that around 1 in every 5 women (a 15%–20% cumulative FP risk) have at least 1 FP screening result over the course of 10 biennial screening examinations. It is important to highlight that in contrast with breast screening, the participants in colorectal cancer screening with an FP result are infrequently invited to perform FOBT again as often they will be recommended a colonoscopy in 10 years. This explains why only 1 person received 3 FP results. In this particular case, the colonoscopy found a low-risk lesion twice (after an FP

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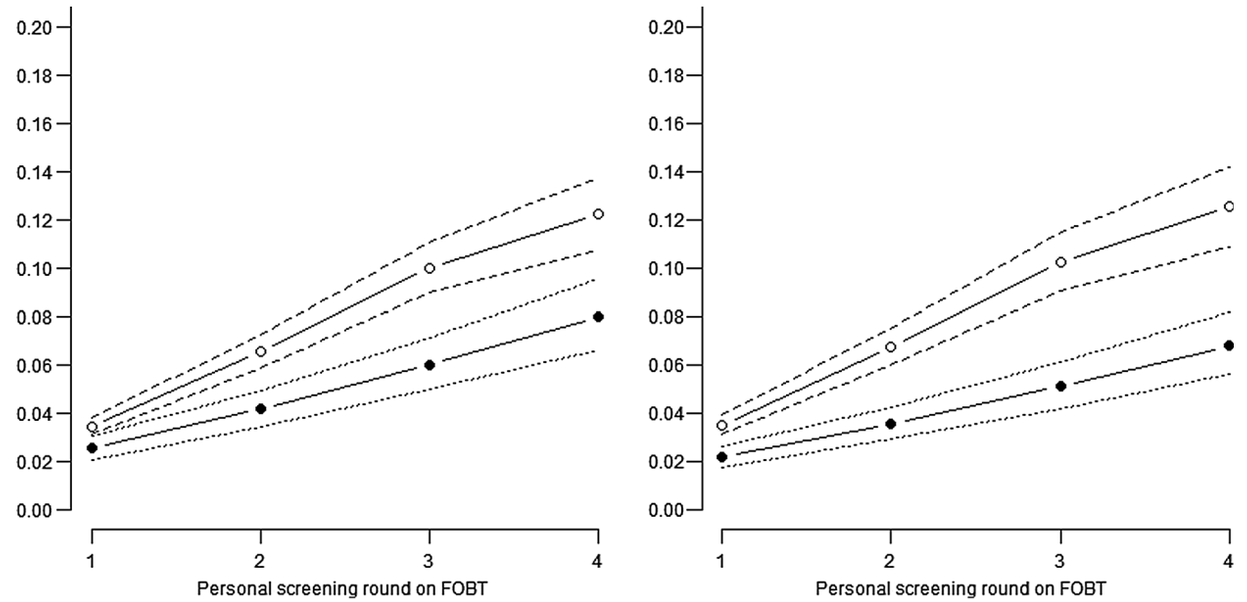

Figure 2.

Cumulative probability of an FP after 1 to 4 rounds of biennial FOBT screening stratified by starting type of test and sex. Starting age 50 years; left graph: female; right graph: male. The horizontal axis indicates the number of personal screening rounds, taking into account only individual participations with gFOBT or FIT. The vertical axis scale indicates the proportion of subjects with an FP result according to the type of FOBT used. Cumulative probabilities are based on risk estimates for each screening round. Dashed-dotted lines show the 95% CI. White dots refer to FIT, and black dots refer to gFOBT.

result) and, as the person was aged less than 68 years old, after each colonoscopy was invited again in the following FOBT round according to the European Guidelines (Supplementary Table S1; ref. 21). A randomized control trial estimated a person's cumulative probability of at least 1 FP in lung cancer screening after 2 annual examinations with low-dose computed tomography examinations and chest radiography at 33% and a 15%, respectively (16). Croswell and colleagues (17) estimated the general magnitude of FP that might be expected with a multimodal screening programme (prostate, lung, colorectal, and ovarian cancer) in a randomized trial. There, flexible sigmoidoscopy accounted for a cumulative false-positive risk of 41.8% (95% CI, 40.9%–42.7%) for men and 29.2% (95% CI, 28.3%–30.0%) for women after 2 examinations. The cumulative risk of an individual obtaining an FP result in a multimodal screening programme increased with number of screening tests.

As far as we know, only Hubbard and colleagues(13) have analyzed the cumulative risk of FOBT as previous studies have focused on test accuracy at a single screening round. Hubbard and colleagues (13) analyzed medical records for patients ages 50 to 79 years receiving FOBT screening with Hemoccult Sensa (gFOBT) between 1997 and 2009. They reported older subjects, males, and non-White patients were more likely to receive a positive gFOBT without a subsequent colorectal cancer diagnosis. Moreover, they estimated a probability of 20.5% for receiving at least one positive FOBT and no colorectal cancer after 10 years of annual gFOBT and 8.8% after 10 years of biennial gFOBT. Our cumulative risk with biennial gFOBT screening is similar, although our definition of FP also included no diagnosis of high-risk lesions in addition to colorectal cancer. In our study, we only found older participants were more likely to receive an FP result with gFOBT biennial screening. We did not find differences with sex and data regarding race was not available to analyze.

FP results are relevant to screening program evaluation because they lead to discomfort and risks from diagnostic and therapeutic procedures which, in the case of an FP test, represent pure harm as the individual does not have neoplasia and therefore cannot benefit from the testing process. Over time, if screening tests are repeated, the probability of receiving at least 1 FP test result necessarily increases. Three studies systematically reviewed the literature regarding complications and risk factors for colonoscopy (6, 27, 28) and the rate of complications estimated is around 4 perforations and 8 severe hemorrhages per 10,000 procedures performed after a positive FOBT (27). Our screening programme analyzed key quality indicators of 5 rounds and reported severe complications at around 10 per 1,000 (79% were post-polypectomy major bleeding; ref. 20). Furthermore, FP tests have the potential to generate anxiety, distress, and depression symptoms and changes in the overall perception of one's health status. Psychologic impact of being recalled for further assessment in colorectal cancer screening has been widely reported in other screening programmes such as breast or cervical cancer. However, the psychologic consequences among individuals found not to have an advanced neoplasia has been reported to be transient (6).

From the point of view of the endoscopist, these results show that only 1 of 79 with gFOBT and 1 of 21 with FIT will receive a colonoscopy, whereas if the population screening modality was colonoscopy, the resources needed would be much higher. Also, during the period 2000 to 2017, only 1 of 6 participants in the colorectal cancer biennial screening was recommended to undergo an unnecessary colonoscopy. There are different management strategies for individuals with a prior FP result in a FOBT and Haug

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Table 3. Post-colonoscopy colorectal cancers among individuals undergoing fecal occult blood testing

Case	Sex	Type of FOBT	Date PDSOF	Date colonoscopy	Endoscopic findings	Bowel preparation	Cecal intubation	Date diagnosis CRC	Age at CRC diagnosis (years)	Tumor location	Stage[a]	Interval diagnosis[b] (years)	Surveillance recommendation[c]	CRC interval
1[d]	Female	gFOBT	Oct 2006	Nov 2006	Negative (hemorrhoids)	Unknown	Yes	July 2010	57	Rectum	Unknown[e]	3.7	Colonoscopy at 10 years	Yes
2	Female	gFOBT	Jul 2007	Oct 2007	Negative (no findings)	Poor	Yes	Aug 2015	62	Sigma	II	7.9	Repeat colonoscopy[f]	Yes
3	Female	gFOBT	April 2000	May 2000	High-risk adenoma (one TA LGD 10 mm right colon)	Good	Yes	Oct 2012	74	Hepatic flexure	IV	12.5	Colonoscopy at 5 years	No
4	Male	FIT	March 2010	March 2010	Low-risk adenoma (one TA LGD 4 mm right colon, one TA LGD 6 mm transverse colon)	Excellent	Yes	May 2013	60	Splenic flexure	II	3.1	Colonoscopy at 5 years	Yes
5	Female	FIT	Feb 2012	March 2012	High-risk adenoma (one TA LGD 10 mm sigmoid)	Poor	Yes	July 2014	68	Hepatic flexure	IV	2.4	Repeat colonoscopy[f]	Yes

Abbreviations: CRC, colorectal cancer; LGD, low-grade dysplasia; TA, tubular adenoma.

[a]Eigth edition of the American Joint Committee on Cancer and the future of TNM.

[b]Interval diagnosis: time between date of last negative FOBT result and diagnosis of colorectal cancer.

[c]See Supplementary Table S1.

[d]This patient was diagnosed with a breast cancer and a second metastatic colorectal cancer in 2012. She was diagnosed with familial colorectal cancer after a negative genetic study (BRCA1, 2, and microsatellite instability).

[e]Patient treated in a private medical center. A probable stage III, as she was cured with surgery and neoadjuvant treatment. We do not have more information.

[f]Patients with poor/inadequate are usually recommended to repeat the colonoscopy instead of the usual recommendation.

and colleagues (29) compared them with a colorectal cancer microsimulation model. They compared the US Preventive Services Task Force strategy (individuals with an FP FOBT switch to screening colonoscopy with a 10-year interval; refs. 30, 31) and the European Guidelines for Quality Assurance in colorectal cancer Screening and Diagnosis (individuals with a prior FP FOBT re-enter the programme; ref. 21). The first one required the most resources without being more effective than the other strategies under the assumption of conditional independence of sequential FOBT testing. Our results can be useful to endoscopy units as they show the current need for this invasive procedure in 7 screening rounds. Additionally, it is important to note that with the European Guidelines we have found that very few patients will undergo a subsequent colonoscopy after a previous FP result.

From a public health point of view, we believe that the FOBT, though imperfect, is a good screening test given that the probability of receiving more than one FP is very low in contrast with breast screening where after an FP result women will be invited again after 2 years. Moreover, we want to highlight that, as one of the most important harms related to FP results is the anxiety provoked in participants before malignancy is ruled out, subjects participating in a screening programme should be informed of this risk, especially those presenting related factors such as hemorrhoids. Indeed, predicting the risk of FP FOBTs may be an important way to educate participants about screening and to deal with the emotional consequences of abnormal results. If subjects understand their risks of FP FOBTs, they might be less anxious when an abnormality is found.

Despite the fact that colonoscopies were performed to the highest standard by expert endoscopists, in a few patients a colorectal neoplasia could have been missed and consequently patients would have been misclassified as a final FP result. For this reason, we have analyzed whether a patient had been diagnosed with post-colonoscopy colorectal cancer. We had a median follow-up of 4.9 years. In our cohort, only 4 patients out of 1,571 had a post-colonoscopy colorectal cancer after a negative colonoscopy. The cumulative incidence of a post-colonoscopy colorectal cancer with a 5-year follow-up was 0.08% (incidence rate of 0.19 cases per 1,000 person-years). There is a wide variation in the methodological evaluation of interval colorectal cancers across studies (23). Post-colonoscopy colorectal cancer rates have been reported between 1 in 130 to 1 in 1,000 colonoscopies (32). However, the most comparable study is by Rivero-Sánchez and colleagues(33) who found a rate of post-colonoscopy cancers of 0.8 per 1,000 person-years of follow-up after a negative colonoscopy. Differences in incidence rates may be partially attributed to a statistical variability due to small numbers and different lengths of follow-up.

To our knowledge, this is the first study that has analyzed the cumulative FP of a population-based screening programme using FIT and examined the effect of a change in screening test (from gFOBT to FIT). Although gFOBT is currently used in few countries (34), we wanted to analyze a real-life scenario of a screening programme which undergoes a change of test. FIT is superior to gFOBT in sensitivity for detecting colorectal cancer and advanced neoplasia, with slightly reduced specificity (35).

Our study has several limitations that should be considered. The analysis was performed with the initial European risk classification which considered an HRA or advanced adenoma any polyp $\geq$10 mm, >2 adenomas, tubulo-villous or villous histology, high-grade dysplasia, or carcinoma *in situ*. Current guidelines

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follow European Guidelines for Quality Assurance in colorectal cancer Screening and Diagnosis (21) recommendation where intermediate-risk lesions are defined as 3 to 4 tubular adenomas measuring <10 mm with low-grade dysplasia or as ≥1 adenoma measuring 10 to 19 mm, whereas HRA were defined as ≥5 adenomas or ≥1 adenoma measuring ≥20 mm (Supplementary Table S1). We could not provide information on bowel preparation using the Boston bowel preparation scale (36) for the patients who had a post-colonoscopy colorectal cancer as in the study period this scale was not used. Preparation was described as poor, regular, good, or excellent. We did not have data regarding the diagnosis of upper gastrointestinal lesions after an FP result. Whether an FP FOBT may lead to further diagnostic work-up such as an esophagogastroduodenoscopy, this was not within the scope of our analysis. According to recent literature (37, 38), the current body of evidence is not sufficient to recommend for or against routine esophagogastroduodenoscopy in order to detect upper gastrointestinal neoplasia for patients with a positive FOBT but a negative follow-up colonoscopy in a population-based colorectal cancer screening programme. In a previous investigation, our group reported on FP results from colorectal cancer screening in Catalonia with FIT. We conducted follow-up for all FP patients ($n = 254$) and only 4% had an upper endoscopy performed, and in 2.6% of patients an upper-gastrointestinal endoscopy found a potential bleeding lesion (9).

In conclusion, the cumulative risk of an FP in colorectal cancer screening using FOBT seems acceptable, as benefits outweigh the harms of colorectal cancer screening. However, we believe it is important to communicate the probability of an FP FOBT to the target group. In addition, the diagnostic procedure (colonoscopy), with its high accuracy, lengthens the time between screening tests, reducing the number of FPs an individual will need to receive.

Disclosure of Potential Conflicts of Interest

V. Moreno reports receiving commercial research grants from Bioiberica S.A.U. and Universal DX, has ownership interest (including patents) in Aniling, and is a consultant/advisory board member for Ferrer S.A. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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