Research Article

Cancer Epidemiology, Biomarkers & Prevention

Characteristics of Adenomas Detected by Fecal Immunochemical Test in Colorectal Cancer Screening

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Abstract

Background: Fecal immunochemical test (FIT) diagnostic accuracy for colorectal adenoma detection in colorectal cancer screening is limited.

Methods: We analyzed 474 asymptomatic subjects with adenomas detected on colonoscopy in two blinded diagnostic tests studies designed to assess FIT diagnostic accuracy. We determined the characteristics of adenomas (number, size, histology, morphology, and location) and the risk of metachronous lesions (according to European guidelines). Finally, we performed a logistic regression to identify those variables independently associated with a positive result.

Results: Advanced adenomas were found in 145 patients (75.6% distal and 24.3% only proximal to splenic flexure). Patients were classified as low (59.5%), intermediate (30.2%), and high risk (10.3%) according to European guidelines. At a 100-ng/mL threshold, FIT was positive in 61 patients (12.8%). Patients with advanced adenomas [odds ratio (OR), 8.8; 95% confidence interval (CI), 4.76–16.25], distal advanced adenomas (OR, 6.7; 95% CI, 1.9–8.8), high risk (OR, 20.1; 95% CI, 8.8–45.8), or intermediate risk lesions (OR, 6; 95% CI, 2.9–12.4) had more probabilities to have a positive test. The characteristics of adenomas independently associated were number of adenomas (OR, 1.22; 95% CI, 1.04–1.42), distal flat adenomas (OR, 0.44; 95% CI, 0.21–0.96), pedunculated adenomas (OR, 2.28; 95% CI, 1.48–3.5), and maximum size of distal adenomas (mm; OR, 1.24; 95% CI, 1.16–1.32).

Conclusions: European guidelines classification and adenoma location correlates with the likelihood of a positive FIT result.

Impact: This information allows us to understand the FIT impact in colorectal cancer prevention. Likewise, it should be taken into account in the development of new colorectal adenomas biomarkers. *Cancer Epidemiol Biomarkers Prev; 23(9); 1884–92. ©2014 AACR.*

Introduction

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related death (1). Evidence from several studies has shown that colorectal cancer screening is cost saving (2) in average-risk population. Recommended colorectal cancer screening strategies fall into 2 groups: stool tests (occult blood and exfoliated DNA tests) and structural examinations (flexible sigmoidoscopy, colonoscopy, and computed tomography colonography). Stool tests primarily detect cancer, and structural examinations detect both cancer and premalignant lesions (3). Stool tests searching for occult blood, guaiac test and fecal immunochemical test (FIT), are predominantly implemented in Europe and Australia, whereas colonoscopy is the dominant screening modality in the United States.

Recently, a randomized pragmatic noninferiority trial has shown that FIT is equal to colonoscopy in terms of detecting colorectal cancer at the first round of colorectal cancer screening because of its elevated diagnostic accuracy and higher participation rate (4). Furthermore, recently published data have shown that FIT sensitivity for detecting colorectal cancer is more than 74% in colorectal cancer screening and symptomatic patients evaluation (5–11). However, the main pitfall of FIT as a colorectal cancer screening method is that detection rate and

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diagnostic yield for advanced adenomas is inferior to colonoscopy (4–6). Lower participation in screening colonoscopy (4) and conducting FIT periodic consecutive rounds (12) could reduce the difference in adenoma detection rate.

Several studies have tried to evaluate which characteristics of adenomas are associated with a positive FIT result. Number and size of adenomas, location, and pedunculated morphology seem to be related to a positive result (13–17). However, these findings need to be confirmed (14). Recently, we performed 2 cross-sectional diagnostic test studies to evaluate the most appropriate number of determinations and cutoff of an automated semiquantiative FIT for advanced neoplasia and colorectal cancer detection in average (8) and familial risk (7) colorectal cancer screening. FIT diagnostic accuracy for colorectal cancer and advanced neoplasia was equivalent in both cohorts (18). In the analysis we present here, we aimed (i) to analyze whether the presence of advanced adenomas, the risk of developing metachronous lesions, as well as the location (distal/proximal to splenic flexure) are associated with a greater likelihood of having a positive FIT result at 2 fecal hemoglobin threshold (50 and 100 ng/mL); and (ii) to determine the individual characteristics of adenomas independently associated with a positive test.

Materials and Methods

Study design

This is a *post hoc* analysis based on 2 blinded, multicenter, prospective cross-sectional studies of diagnostic tests performed in 3 Spanish tertiary hospitals between January 2010 and December 2011. These 2 studies aimed to determine the number and the best cutoff point of FIT determinations in average and familial-risk colorectal cancer screening (7, 8). A total of 1,317 individuals were recruited, and the most advanced lesion was a colorectal cancer in 9 patients, adenomas in 474 individuals, and nonneoplastic polyps in 179. The remaining 655 patients had a normal colonoscopy. Only patients with colorectal adenomas, as the most advanced lesion, were included in this analysis (Fig. 1).

Study interventions

Two stool samples from each subject were collected a week before the colonoscopy. FIT was assessed using the automated OCsensor (Eiken Chemical Co.), without specific diet or medication restrictions. The stool sample was collected by the subject and introduced immediately in the stool container, according to manufacturer's specifications. Only first FIT determination was taken into account for this analysis. FIT results were considered as a qualitative test with 2 cutoff concentrations: 50 and 100 ng hemoglobin (Hb)/mL. Spanish colorectal cancer population screening programs consider 100 ng Hb/mL as the cutoff point to invite for colonoscopy (19). Colonoscopy was performed blind to FIT result. Bowel cleansing, sedation, and colonoscopy procedure were performed according to the Spanish Guidelines on Quality of Colonoscopy in colorectal cancer screening (20). All colonoscopies were performed by experienced endoscopists (>200 colonoscopies per year; ref. 20). Anonymous data from each individual included and lesions detected were registered in an online database (www.coloncruzer.org).

Definition and classification of adenomas

The following characteristics of adenomas were collected: size (in mm), morphology according to Paris classification (ref. 21; pedunculated, sessile, and flat), villous architecture (>20%), high-grade dysplasia, and location (distal/proximal to splenic flexure). On the basis of the risk of developing a colorectal cancer, adenomas $\geq$10 mm in size, with villous architecture, high-grade dysplasia, or intramucosal carcinoma were classified as advanced adenomas (22). Subjects were classified according to the most advanced lesion, advanced adenomas or non-advanced adenomas, and the location, at least one lesion distal to splenic flexure or only lesions proximal to splenic flexure. According to the European guidelines for quality assurance in colorectal screening and diagnosis, individuals were classified as low ($\leq$2 non-advanced adenomas), intermediate (3–4 adenomas, 10–20 mm in size, <10 mm advanced adenomas), or high ($\geq$5 adenomas or $\geq$20 mm in size) risk for metachronous lesions (23).

Data analysis

Continuous variables were described using mean and standard deviation, and categorical variables by the absolute number and percentage value. Comparisons to identify differences in FIT positivity rate (at 50 and 100 ng Hg/mL threshold) between individuals according to baseline characteristics, the most advanced lesion, the adenoma's morphology and the location were performed using the χ^2 and the Cochran–Mantel–Haenszel test. We used the Student *t* test to detect differences in FIT positivity rate in relation to the characteristics of the adenomas. Finally, a logistic regression analysis with forward (likelihood ratio) entry was performed to detect those adenoma characteristics (per adenoma) independently related to a positive FIT result. Differences were reported as odds ratios (OR) with 95% confidence intervals (95% CI) and their significance. A *P*-value <0.05 was considered statistically significant. Statistical analyses were done using the SPSS statistical software, version 15.0 (SPSS Inc.).

Other aspects

The study was approved by the Galician Clinical Research Ethics Committee (codes 2009/123 and 2009/179) under resolutions dated 28 May 2009 and 10 September 2009. Patients' clinical charts were accessed for study purposes in accordance with the research protocols laid down by clinical documentation departments. Patients provided written informed consent. The study sponsors had no involvement in the

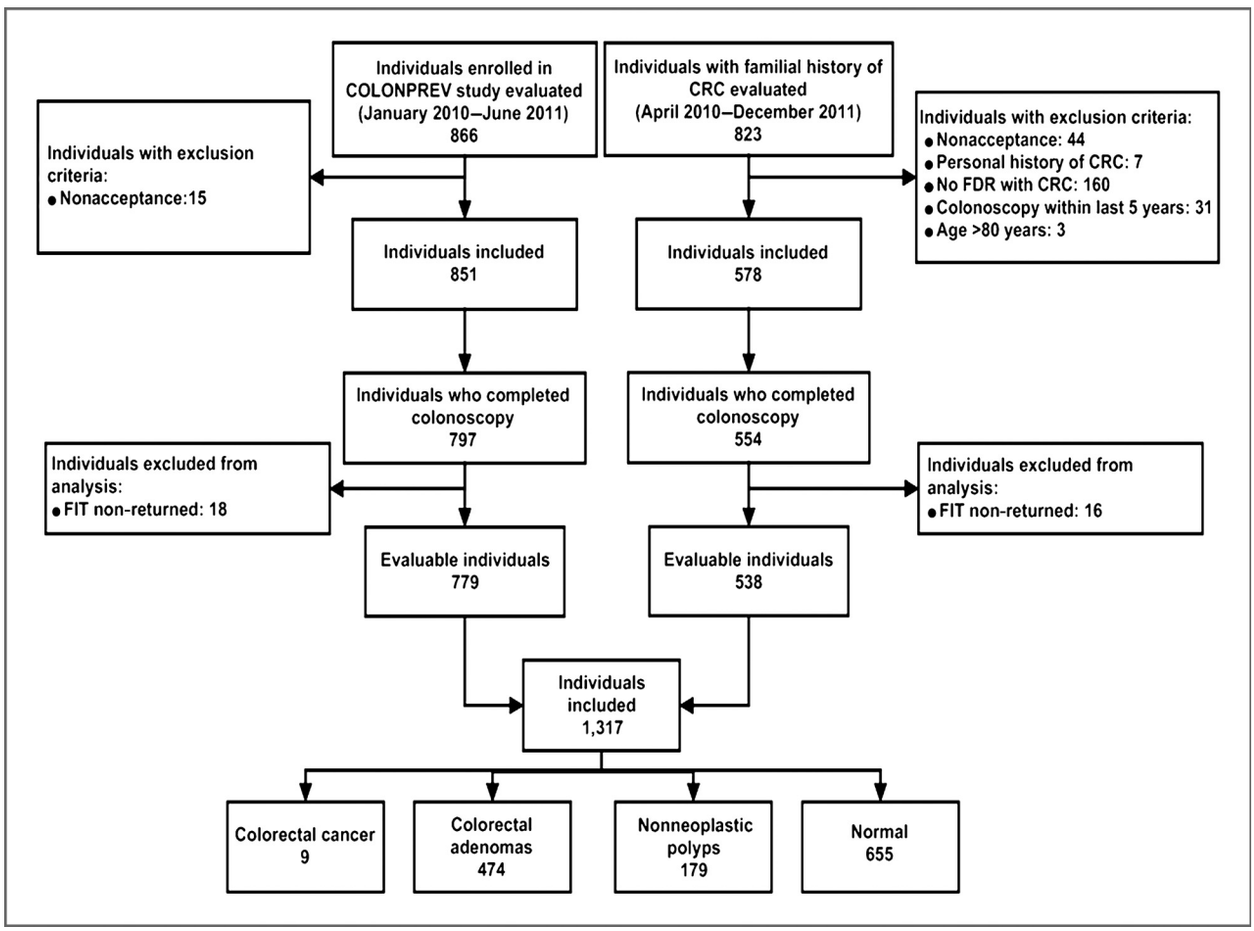

Figure 1. Enrollment of individuals included in the analysis.

collection, analysis, and interpretation of data; writing of the manuscript or in the decision to submit the manuscript for publication.

Results

Description of adenomas

A total of 925 adenomas were identified in the 474 patients included in the analysis (1.95 ± 1.8 adenomas/patient). In 377 patients (79%), ≤2 adenomas were detected, in 69 (14.5%), 3 or 4 adenomas were found and 28 (5.9%) patients had at least 5 adenomas. Their mean maximum size was 7.35 ± 5.92 mm (780, <10 mm; 116, 10–19 mm; 29, ≥20 mm). Mainly, the histology of the adenomas was tubular (840 tubular, 52 villous, 33 high-grade displasia, 10 villous and high-grade displasia), their morphology was sessile (485 sessile, 196 pedunculated, 227 flat), and most of them were located distal to splenic flexure (583 distal, 341 proximal). In 145 patients, 189 advanced adenomas were found (1.3 ± 1 advanced adenomas/patient), 119 (25.1%) patients had 1 advanced adenomas on colonoscopy, 20 (4.2%) had 2 advanced adenomas, and 6 (1.2%) had more than 2. Advanced adenomas were located preferentially in the distal colon (69%) and most of them were pedunculated (53% pedunculated, 29% sessile, 18% flat). Finally, the proportion of pedunculated adenomas (distal 26.2%, proximal 13.5%; $P < 0.001$) and pedunculated advanced adenomas (distal 62.6%; proximal 30%; $P < 0.001$) was significantly increased in the distal location.

We found an inverse relation between the detection of flat adenomas and pedunculated adenomas. So, a pedunculated adenoma was found in 29 of 149 individuals (19.5%) with a flat adenoma. In contrast, a pedunculated adenoma was found in 115 of 325 individuals (35.4%, $P < 0.001$) without flat adenomas.

Patient characteristics

The baseline patients characteristics are summarized in Table 1. Considering European guidelines, 49 (10.3%) were classified as high risk, 143 (30.2%) as intermediate risk, and the remaining, 282 (59.5%), as low risk. However, 24.5% and 24.1% of the individuals had adenomas and advanced adenomas located only proximal to the splenic flexure, respectively.

Table 1. Baseline characteristics of patients with adenomas on colonoscopy

	Characteristics of the patients ($n = 474$)[a]
Age (y)	56.32 ± 7.92
Sex (male)	272 (57.4%)
FDR with colorectal cancer (yes)	202 (42.6%)
Hospital	
Ourense	259 (54.6%)
Vigo	190 (40.1%)
San Sebastian	25 (5.3%)
Previous colonoscopy (yes)	51 (10.8%)
Bowel cleansing (adequate)	399 (84.2%)
Complete colonoscopy (yes)	470 (99.2%)
Advanced adenoma (yes)[b]	145 (30.6%)
Location of the adenomas	
Distal to splenic flexure (yes)	357 (75.5%)
Only proximal to splenic flexure (yes)	116 (24.5%)
Location of the advanced adenomas (145)	
Distal to splenic flexure (yes)	110 (75.9%)
Only proximal to splenic flexure (yes)	35 (24.1%)
European classification[c]	
High risk	49 (10.3%)
Intermediate risk	143 (30.2%)
Low risk	282 (59.5%)

NOTE: Qualitative variables are expressed as absolute numbers and percentage. Quantitative variables are expressed as mean and standard deviation.

Abbreviation: FDR, first-degree relative.

[a]Individuals were classified according to the most advanced lesion.

[b]Adenoma >1 cm in size or with high-grade dysplasia or intramucosal carcinoma or with villous component (>20%).

[c]Low risk, ≤2 non-advanced adenomas; intermediate risk, 3 and 4 adenomas, 10 to 20 mm in size, <10 mm advanced adenomas; high risk, ≥5 adenomas or ≥20 mm in size.

Relation between patient characteristics and a positive FIT result

At a 100 ng/mL fecal hemoglobin threshold, 61 patients presented a positive result and at a 50 ng/mL threshold, 71 patients had a positive result. No statistical differences were found in terms of age (OR, 1.02; 95% CI, 0.98–1.06; $P = 0.2$), sex (OR, 0.67; 95% CI, 0.17–1.19; $P = 0.2$), colorectal cancer familial history (OR, 1.11; 95% CI, 0.64–1.9; $P = 0.7$), previous colonoscopy (OR, 0.72; 95% CI, 0.27–1.9; $P = 0.6$), bowel cleansing (OR, 1.1; 95% CI, 0.52–2.34; $P = 0.2$), and cecal intubation (OR, 0.43; 95% CI, 0.04–4.23; $P = 0.4$) at a 100 ng Hb/mL threshold. No statistical differences were found either at a 50 ng Hb/mL cutoff point. Individuals with advanced adenomas and high- or intermediate-risk lesions according to European guidelines had statistically more probabilities to get a positive FIT result at a 100 ng Hb/mL threshold (OR, 8.8; 95% CI, 4.7–16.2; OR, 20.1; 95% CI, 8.8–45.8; OR, 6; 95% CI, 2.9–12.4; $P < 0.001$). Individuals with only proximal adenomas (OR, 0.13; 95% CI, 0.04–0.4) or advanced adenomas (OR, 0.15; 95% CI, 0.1–0.5) had statistically less probabilities to have a positive FIT result at the same threshold. Furthermore, individuals with advanced adenomas both distal and proximal to splenic flexure had statistically more probabilities to have a positive FIT result (100 ng Hb/mL) than patients with only proximal advanced adenomas (37.5%, 8.6%; $P = 0.02$). These differences were maintained when a 50 ng Hb/mL cutoff point was evaluated (Table 2). Besides, the presence of at least 1 pedunculated adenoma was significantly associated with the risk of a positive FIT result at 50 ng/mL (OR, 7.2; 95% CI, 4.1–12.5) and 100 ng/mL (OR, 9.8; 95% CI, 5.2–18.4) cutoff points. In contrast, the presence of at least 1 flat adenoma was significantly associated with a reduction in the risk of a positive FIT result (100 ng/mL; OR, 0.4; 95% CI, 0.2–0.9).

Relation between characteristics of adenomas and a positive FIT result

As Table 3 shows, maximum size (overall and distal), number of adenomas (overall and distal), advanced adenomas (overall and distal), adenomas with villous histology (overall and distal), adenomas with high-grade dysplasia (distal), and pedunculated adenomas (overall and distal) were statistically increased in individuals with a fecal hemoglobin ≥100 ng/mL. In contrast, total number of flat distal adenomas was statistically decreased in individuals with a positive FIT result. Using a logistic regression model, we found that adenoma characteristics such as number of adenomas (OR, 1.22; 95% CI, 1.04–1.42; $P = 0.01$), number of pedunculated adenomas (OR, 2.28; 95% CI, 1.48–3.5; $P < 0.001$), and maximum size of distal adenomas (mm; OR, 1.24; 95% CI, 1.16–1.32; $P < 0.001$), correlates with a positive result at 100 ng Hb/mL threshold. In contrast, total number of distal flat adenomas (OR, 0.44; 95% CI, 0.21–0.96; $P = 0.04$) correlates inversely with a positive FIT result.

However, the characteristics of adenomas statistically related to a positive result at a 50 ng Hb/mL cutoff were maximum size (overall and distal), number of adenomas (overall and distal), advanced adenomas (overall and distal), adenomas with villous histology (overall and distal), adenomas with high-grade dysplasia (proximal and distal), and pedunculated adenomas (overall and distal). In contrast, total number of flat distal adenomas was statistically associated with a negative result (Table 4). In summary, results from the logistic regression model showed that the variables independently related to a positive result were number of adenomas (OR, 1.24; 95% CI, 1.07–1.43; $P = 0.004$), number of distal flat adenomas (OR, 0.55; 95% CI, 0.31–0.98; $P = 0.04$), number of pedunculated adenomas (OR, 2.02; 95% CI, 1.32–3.1; $P = 0.001$), and maximum size of distal adenomas (mm; OR, 1.21; 95% CI, 1.13–1.28; $P < 0.001$).

Table 2. Fecal immunochemical test result according to neoplastic lesions detected in the subjects included

	Fecal Hb threshold 100 ng/mL				Fecal Hb threshold 50 ng/mL			
Colorectal lesion[a]	**<100 (413)**	**≥100 (61)**	**OR (95% CI)**	***P* value**	**<50 (403)**	**≥50 (71)**	**OR (95% CI)**	***P* value**
Advanced adenoma[b]								
Present (145)	100 (69%)	45 (31%)	8.8 (4.7–16.2)	<0.001	94 (64.8%)	51 (35.2%)	8.4 (4.8–14.8)	<0.001
Absent (329)	313 (95.1%)	16 (4.9%)	1		309 (93.9%)	20 (6.1%)	1	
Location of adenomas								
Distal to splenic flexure (357)	299 (83.8%)	58 (16.2%)	7.3 (2.2–23.9)	<0.001	291 (81.2%)	67 (18.8%)	6.4 (2.3–18.2)	<0.001
Only proximal to splenic flexure (116)	113 (97.4%)	3 (2.6%)	1		112 (96.6%)	4 (3.4%)	1	
Location of advanced adenomas								
Distal to splenic flexure (109)	67 (61.5%)	42 (38.5%)	6.7 (1.9–8.8)	0.001	64 (58.7%)	45 (41.3%)	3.4 (1.3–8.8)	0.014
Only proximal to splenic flexure (35)	32 (91.4%)	3 (8.6%)	1		29 (82.9%)	6 (17.1%)	1	
European classification[c]								
High risk (49)	27 (55.1%)	22 (44.9%)	20.1(8.8–45.8)	<0.001	26 (53.1%)	23 (46.9%)	16.9 (7.8–36.9)	<0.001
Intermediate risk (143)	115 (80.4%)	28 (19.6%)	6 (2.9–12.4)		109 (76.2%)	34 (23.8%)	5.9 (3.1–11.5)	
Low risk (282)	271 (96.1%)	11 (3.9%)	1		268 (95%)	14 (5%)	1	
Adenoma's morphology[d]								
Flat (any) (149)	138 (92.6%)	11 (7.4%)	0.4 (0.2–0.9)	0.01	132 (88.6%)	17 (11.4%)	0.6 (0.3–1.1)	0.1
Flat (no) (325)	275 (84.6%)	50 (15.4%)	1		271 (83.4%)	54 (16.6%)	1	
Sessile (any) (279)	248 (88.9%)	31 (11.1%)	0.7 (0.4–1.2)	0.1	241 (86.4%)	38 (13.6%)	0.7 (0.4–1.3)	0.3
Sessile (no) (195)	165 (84.6%)	30 (15.4%)	1		162 (83.1%)	33 (16.9%)	1	
Pedunculated (any) (144)	98 (68.1%)	46 (31.9%)	9.8 (5.2–18.4)	<0.001	95 (66%)	49 (34%)	7.2 (4.1–12.5)	<0.001
Pedunculated (no) (330)	315 (95.4%)	15 (4.6%)	1		308 (93.3%)	22 (6.7%)	1	

NOTE: Qualitative variables are expressed as absolute numbers and percentage. Differences were analyzed with χ^2 test. Differences with $P < 0.05$ are considered statistically significant.

[a]Individuals were classified according to the most advanced lesion.

[b]Advanced adenoma: adenoma >1 cm in size or with high-grade dysplasia or intramucosal carcinoma or with villous component (>20%).

[c]Low risk, ≤2 non-advanced adenomas; intermediate risk, 3 and 4 adenomas, 10 to 20 mm in size, <10 mm advanced adenomas; high risk, ≥5 adenomas or ≥20 mm in size.

[d]Adenoma's morphology according to Paris classification.

Discussion

Our analysis has defined the subjects and adenomas characteristics associated with a positive FIT result at 2 cutoff points: 50 and 100 ng Hb/mL. We have shown that individuals with advanced adenomas and with higher risk of metachronous adenomas (according to European guidelines) have more probabilities to get a positive FIT. On the other hand, individuals with adenomas or advanced adenomas only in the proximal colon are less prone to a positive result. Finally, we have determined that adenomas' morphology (number of flat and pedunculated adenomas) as well as number of adenomas and maximum size of distal adenomas correlates with a positive result.

In a recently published randomized control trial, FIT colorectal cancer screening detected a similar number of patients with colorectal cancer than colonoscopy on the baseline screening examination. However, more adenomas were identified in those patients randomized to colonoscopy. Although participation rate was higher in the FIT group, the first round of FIT screening detected about half as many patients with advanced adenomas as colonoscopy (4). The superiority of colonoscopy for detecting advanced adenomas should be considered a potential advantage for this strategy in terms of reducing not only colorectal cancer mortality but also colorectal cancer incidence (3). However, it should be noted that FIT colorectal cancer screening is based on periodical consecutive rounds that may reduce an initial apparent disadvantage.

Several published studies have tried to delimitate what are the characteristics of the adenomas detected by FIT in colorectal cancer screening. Mainly, an association has been found with adenoma size, number, morphology, and location (13–17). Our results are consistent with previously published studies. Total number of adenomas, pedunculated adenomas, and maximum size of distal adenomas were independently related to a higher positive FIT

Table 3. Number and size of the adenomas according to fecal immunochemical test (100 ng/mL) result and location

Adenoma's characteristics	Fecal hemoglobin concentration	Number of adenomas per patient		Number of adenomas distal to splenic flexure		Number of adenomas proximal to splenic flexure	
		Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
Maximum size (mm)	<100 ng/mL ($n = 413$)	6.22 ± 4.2	<0.001	4.23 ± 3.94	<0.001	2.75 ± 4.23	0.2
	≥100 ng/mL ($n = 61$)	14.11 ± 9		12.52 ± 8.15		4.23 ± 9.31	
Adenomas (no.)	<100 ng/mL ($n = 413$)	1.79 ± 1.49	0.002	1.11 ± 1.11	0.001	0.68 ± 1.23	0.3
	≥100 ng/mL ($n = 61$)	3.03 ± 2.93		2.07 ± 2.05		0.97 ± 2.16	
Advanced adenomas (no.)[a]	<100 ng/mL ($n = 413$)	0.3 ± 0.58	<0.001	0.19 ± 0.46	<0.001	0.1 ± 0.37	0.3
	≥100 ng/mL ($n = 61$)	1.1 ± 1.53		0.84 ± 0.97		0.26 ± 1.21	
Villous histology (no.)	<100 ng/mL ($n = 413$)	0.1 ± 0.34	0.01	0.07 ± 0.28	0.003	0.03 ± 0.17	0.2
	≥100 ng/mL ($n = 61$)	0.33 ± 0.65		0.2 ± 0.52		0.13 ± 0.62	
High-grade dysplasia (no.)	<100 ng/mL ($n = 413$)	0.08 ± 0.35	0.05	0.06 ± 0.28	0.033	0.02 ± 0.15	0.8
	≥100 ng/mL ($n = 61$)	0.18 ± 0.39		0.16 ± 0.37		0.02 ± 0.13	
Flat adenomas (no.)[b]	<100 ng/mL ($n = 413$)	0.5 ± 1.01	0.3	0.3 ± 0.69	0.005	0.2 ± 0.75	0.5
	≥100 ng/mL ($n = 61$)	0.36 ± 1.15		0.1 ± 0.47		0.26 ± 0.85	
Flat advanced adenomas (no.)	<100 ng/mL ($n = 413$)	0.07 ± 0.3	0.9	0.02 ± 0.18	0.6	0.04 ± 0.24	0.8
	≥100 ng/mL ($n = 61$)	0.07 ± 0.31		0.02 ± 0.13		0.05 ± 0.28	
Sessile adenomas (no.)[b]	<100 ng/mL ($n = 413$)	0.99 ± 1.21	0.3	0.57 ± 0.87	0.1	0.41 ± 0.81	0.6
	≥100 ng/mL ($n = 61$)	1.26 ± 2.11		0.9 ± 1.87		0.36 ± 0.8	
Sessile advanced adenomas (no.)	<100 ng/mL ($n = 413$)	0.11 ± 0.39	0.4	0.07 ± 0.31	0.4	0.04 ± 0.21	0.7
	≥100 ng/mL ($n = 61$)	0.16 ± 0.49		0.11 ± 0.41		0.05 ± 0.28	
Pedunculated adenomas (no.)[b]	<100 ng/mL ($n = 413$)	0.27 ± 0.52	<0.001	0.21 ± 0.48	<0.001	0.06 ± 0.25	0.2
	≥100 ng/mL ($n = 61$)	1.38 ± 2.01		1.03 ± 1.03		0.34 ± 1.82	
Pedunculated advanced adenomas (no.)	<100 ng/mL ($n = 413$)	0.11 ± 0.34	<0.001	0.09 ± 0.32	<0.001	0.02 ± 0.14	0.3
	≥100 ng/mL ($n = 61$)	0.85 ± 1.46		0.69 ± 0.85		0.16 ± 1.16	

NOTE: Quantitative variables are expressed as mean and standard deviation (SD). Differences between quantitative variables were analyzed with Student *t* test. Differences with $P < 0.05$ are considered statistically significant.

[a]Advanced adenoma: adenoma >1 cm in size or with high-grade dysplasia or with villous component (>20%).

[b]Adenoma morphology was classified according to Paris classification.

likelihood. In contrast, the number of flat adenomas was associated with a lower positive FIT probability. In fact, we confirm previous data that suggested a relation between pedunculated adenoma morphology and a positive result (14). The inverse relation between number of flat distal adenomas and a positive FIT result deserves special attention. This association may be because of the intrinsic characteristics of flat adenomas: mainly non-advanced, located proximally, and less prone to bleed when compared with pedunculated adenomas. Besides, we have found an inverse relation between flat and pedunculated adenomas, especially in the distal colon that could explain this relation. However, we cannot clearly explain the inverse relation we have detected between distal flat adenomas and a positive FIT result.

Sensitivity of FIT according to location deserves special attention. Sigmoidoscopy, as a colorectal cancer screening test, is performed to detect distal advanced neoplasia and, if present, complete colonoscopic exploration. Recent studies have found that sigmoidoscopy reduces colorectal cancer mortality and incidence only because of a reduction in distal colorectal cancer without affecting right-sided colorectal cancer incidence or mortality (24, 25). It is well known that up to 45% of the individuals with advanced proximal neoplasia do not present distal advanced lesions (26). In fact, in our analysis up to 24% of the patients had advanced adenomas confined only in the right colon. A combined screening strategy based on sigmoidoscopy and FIT has been proposed in order to increase the diagnostic yield for proximal colonic neoplasia (27). Recently, a systematic literature review has tried to determine the sensitivity of FIT for proximal neoplasia on the basis of previously published articles. Most of the studies showed a higher sensitivity of fecal occult blood test for advanced neoplasia in the left colon versus right colon. However, the available literature is scarce and not entirely consistent (14). Our analysis has demonstrated that a patient with distal advanced adenomas has 6.67 more probabilities to get a positive FIT result than a patient with only advanced proximal adenomas. This difference was also maintained if patients with only proximal advanced adenomas were compared with patients with proximal and distal advanced adenomas.

Table 4. Number and size of the adenomas according to the fecal immunochemical test (50 ng/mL) result and location

Adenoma's characteristics	Fecal hemoglobin concentration	Number of adenomas per patient		Number of adenomas distal to splenic flexure		Number of adenomas proximal to splenic flexure	
		Mean ± SD	*P* value	Mean ± SD	*P* value	Mean ± SD	*P* value
Maximum size (mm)	<50 ng/mL ($n = 403$)	6.2 ± 4.21	<0.001	0.58 ± 3.48	<0.001	5.84 ± 4.47	0.06
	≥50 ng/mL ($n = 71$)	13.2 ± 8.71		12.25 ± 0.77		10.03 ± 11.48	
Adenomas (no.)	<50 ng/mL ($n = 403$)	1.76 ± 1.46	<0.001	1.1 ± 1.1	<0.001	0.66 ± 1.2	0.1
	≥50 ng/mL ($n = 71$)	3.03 ± 2.82		2 ± 1.95		1.03 ± 2.2	
Advanced adenomas (no.)[a]	<50 ng/mL ($n = 403$)	0.28 ± 0.57	<0.001	0.18 ± 0.45	<0.001	0.1 ± 0.35	0.1
	≥50 ng/mL ($n = 71$)	1.06 ± 1.45		0.77 ± 0.94		0.28 ± 1.15	
Villous histology (no.)	<50 ng/mL ($n = 403$)	0.1 ± 0.34	0.01	0.07 ± 0.29	0.003	0.03 ± 0.18	0.2
	≥50 ng/mL ($n = 71$)	0.3 ± 0.62		0.2 ± 0.5		0.11 ± 0.57	
High-grade dysplasia (no.)	<50 ng/mL ($n = 403$)	0.07 ± 0.33	0.02	0.05 ± 0.27	0.02	0.02 ± 0.15	0.6
	≥50 ng/mL ($n = 71$)	0.2 ± .0.43		0.17 ± 0.41		0.03 ± 0.16	
Flat adenomas (no.)[b]	<50 ng/mL ($n = 403$)	0.49 ± 1.02	0.5	0.29 ± 0.7	0.04	0.2 ± 0.75	0.6
	≥50 ng/mL ($n = 71$)	0.41 ± 1.1		0.15 ± 0.5		0.25 ± 0.82	
Flat advanced adenomas (no.)	<50 ng/mL ($n = 403$)	0.07 ± 0.28	0.7	0.02 ± 0.18	0.5	0.04 ± 0.22	0.4
	≥50 ng/mL ($n = 71$)	0.08 ± 0.37		0.01 ± 0.12		0.07 ± 0.35	
Sessile adenomas (no)[b]	<50 ng/mL ($n = 403$)	0.97 ± 1.2	0.1	0.57 ± 0.87	0.1	0.39 ± 0.75	0.5
	≥50 ng/mL ($n = 71$)	1.34 ± 2.08		0.86 ± 1.75		0.48 ± 1.05	
Sessile advanced adenomas (no.)	<50 ng/mL ($n = 403$)	0.1 ± 0.37	0.1	0.07 ± 0.3	0.2	0.03 ± 0.2	0.3
	≥50 ng/mL ($n = 71$)	0.2 ± 0.52		0.13 ± 0.44		0.07 ± 0.3	
Pedunculated adenomas (no.)[b]	<50 ng/mL ($n = 403$)	0.27 ± 0.5	<0.001	0.2 ± 0.46	<0.001	0.06 ± 0.25	0.2
	≥50 ng/mL ($n = 71$)	1.25 ± 2		0.96 ± 1.03		0.3 ± 1.68	
Pedunculated advanced adenomas (no.)	<50 ng/mL ($n = 403$)	0.11 ± 0.34	<0.001	0.09 ± 0.31	<0.001	0.02 ± 0.14	0.3
	≥50 ng/mL ($n = 71$)	0.76 ± 1.38		0.62 ± 0.82		0.14 ± 1.07	

NOTE: Quantitative variables are expressed as mean and standard deviation. Differences between quantitative variables were analyzed with Student *t* test. Differences with $P < 0.05$ are considered statistically significant.

[a]Advanced adenoma: adenoma >1 cm in size or with high-grade dysplasia or intramucosal carcinoma or with villous component (>20%).

[b]Adenoma morphology was classified according to Paris classification.

Several reasons may explain this difference in FIT sensitivity for right-sided versus left-sided advanced adenomas. First, the sensitivity of fecal occult blood tests has been shown to be significantly higher for adenomas with advanced histology, larger size, and pedunculated shape (15, 17). In our study, distal advanced adenomas were mainly pedunculated shaped, in contrast with proximal advanced adenomas, that were mainly sessile or flat lesions. Second, a lower sensitivity for right sided adenomas could be also related to a longer bowel passage and to a different stool consistency (14).

However, colorectal cancer screening aims to reduce colorectal cancer mortality by detecting colorectal cancer at earlier stages and by detecting precancerous lesions with high malignancy potential (3). Several adenoma factors have been related to the risk of progressing to colorectal cancer (22, 28) and developing metachronous neoplasia. FIT sensitivity increases according to the adenoma risk of colorectal cancer progression and metachronous neoplasia development (23, 29–31). Previous studies have clearly demonstrated that the probability of a positive test increases with the presence of advanced adenomas or high-risk adenomas (according to the American guidelines; refs. 13–17). However, no study has evaluated the sensitivity of FIT to detect adenomas on the basis of European guidelines classification, so far. Our study has shown that FIT detects 44.9% to 46.9% patients with high-risk adenomas in one round. In contrast, the lower detection rate of low-risk lesions might be seen as an advantage of FIT colorectal cancer screening, because it would reduce the number of individuals needed to scope with a consequent saving in costs and minimization of potential colonoscopy-related complications.

Our study has several limitations. First, we have limited our analysis to patients in whom adenomas were detected. We have previously analyzed FIT diagnostic accuracy for colorectal cancer and advanced neoplasia detection (7, 8). The aim of this analysis was to determine which adenomas characteristics were related to a positive FIT result. For this reason, we have delimited the analysis to patients with

adenomas. The second limitation of our study is that we have only considered one FIT determination. However, in our experience, performing 2 tests does not enhance the accuracy to detect advanced neoplasia (7, 8). In fact, the most accepted FIT colorectal cancer screening strategy is based on a FIT determination with a 100 ng Hb/mL threshold (19). The third limitation of our analysis is that we considered colonoscopy as the gold standard for detecting adenomas. It is widely known that colonoscopy sensitivity for adenomas is variable, depending mainly in technical issues (31, 32). Several associations have produced clinical guidelines to improve colonoscopy quality and to reduce risks associated with colonoscopy in colorectal cancer screening setting (20, 31, 32). Our endoscopists have adhered to Spanish and European guidelines for the quality of colonoscopy (20). It is relevant that cecal intubation rate exceeds 97% and the adenoma detection rate reaches 38% (7, 8). Finally, we have determined that several individual characteristics (sex, colorectal cancer familial history, age, previous colonoscopy, bowel cleansing, or cecal intubation) were not related to a positive FIT result in the individuals with adenomas on colonoscopy. We must remember that individuals with a colorectal cancer or a normal colonoscopy were excluded, so these results must be evaluated just as an internal analysis to control bias.

However, our analysis has some strengths. First, it is based on 2 prospective cross-sectional diagnostic tests studies that included 1,317 asymptomatic individuals that performed a colonoscopy as a colorectal cancer screening method. We have used a semiquantitative automated FIT to determine the fecal hemoglobin and the colonoscopy was performed blind to the result. Finally, we collected data from each adenoma: size, location, morphology, and histology, as well as the total amount of adenomas. These data have allowed us to differentiate between the different variables associated with a positive FIT result.

In conclusion, we have determined that FIT sensitivity for adenomas increases with the risk of progression to colorectal cancer and developing metachronous neoplasia. FIT has a low sensitivity for detecting advanced adenomas limited to proximal colon. Finally, we have identified 4 variables independently related to a positive FIT determination. These factors should be considered in the context of the development of new biomarkers for colorectal cancer screening.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Cubiella, I. Castro, V. Hernandez, C. González-Mao, C. Rivera, F. Iglesias, L. Cid, S. Soto, L. de-Castro, P. Vega, J.A. Hermo, R. Macenlle, A. Martínez, D. Martínez-Ares, P. Estevez, E. Cid, L. Bujanda

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Cubiella, I. Castro, V. Hernandez, I. Portillo

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References

1. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893–917.
2. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev 2011;33:88–100.
3. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570–95.
4. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas Á, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697–706.
5. Terhaar sive Droste JS1, Oort FA, van der Hulst RW, van Heukelem HA, Loffeld RJ, van Turenhout ST, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011;20:272–80.
6. Oort FA, van Turenhout ST, Coupé VM, van Heukelem HA, Loffeld RJ, Terhaar sive Droste JS, et al. Double sampling of a faecal immunochemical test is not superior to single sampling for detection of colorectal neoplasia: a colonoscopy controlled prospective cohort study. BMC Cancer 2011, 11:434.
7. Castro I, Cubiella J, Rivera C, González-Mao C, Vega P, Soto S, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. Int J Cancer 2014;134:367–75
8. Hernandez V, Cubiella J, Gonzalez-Mao C, Iglesias F, Rivera C, Iglesias MB, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20:1038–47.
9. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287–97.

10. de Wijkerslooth TR, Stoop EM, Bossuyt PM, Meijer GA, van Ballegooijen M, van Roon AH , et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570–8.
11. Cubiella J, Salve M, Díaz-Ondina M, Vega P, Alves MT, Iglesias F, et al. Diagnostic accuracy of faecal immunochemical test for colorectal cancer in symptomatic patients: comparison with NICE and SIGN referral criteria. Colorectal Dis 2014 Jan 24. doi: 10.1111/codi.12569.
12. Crotta S, Segnan N, Paganin S, Dagnes B, Rosset R, Senore C. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. Clin Gastroenterol Hepatol 2012;10:633–8.
13. Haug U, Kuntz KM, Knudsen AB, Hundt S, Brenner H. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. Br J Cancer 2011;104:1779–85.
14. Haug U, Knudsen AB, Brenner H, Kuntz KM. Is fecal occult blood testing more sensitive for left- versus right-sided colorectal neoplasia? A systematic literature review. Expert Rev Mol Diagn 2011;11:605–16.
15. Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, et al. Identification of colorectal adenomas by a quantitative immunochemical faecal occult blood screening test depends on adenoma characteristics, development threshold used and number of tests performed. Aliment Pharmacol Ther 2009;29:906–17.
16. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Sakaguchi K, et al. Sensitivity of Immunochemical Fecal Occult Blood Test to Small Colorectal Adenomas. Am J Gastroenterol 2007;102:2259–64.
17. Ciatto S, Martinelli F, Castiglione G, Mantellini P, Rubeca T, Grazzini G, et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer 2007;96:218–21.
18. Cubiella J, Hernández V, Castro I, González-Mao C, Rivera C, Iglesias F, et al. Diagnostic accuracy of fecal immunochemical test in average and high risk colorectal cancer screening. Gut 2012;61(Suppl 3):A183.
19. Salas D. Implantación del cribado de cáncer de colon y recto en España [cited 2013 Dec 1]. Available from: http://www.programascancerdemama.org/images/archivos/06_LSalas_ImplantacionCCCR.pdf.
20. Jover R, Herráiz M, Alarcón O, Brullet E, Bujanda L, Bustamante M, et al. Clinical practice guidelines: quality of colonoscopy in colorectal cancer screening. Endoscopy 2012;44:444–51.
21. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3–43.
22. Muto T, Bussey HJR MB. The evolution of cancer of the colon and rectum. Cancer 1975;36:2251–70.
23. Atkin WS, Valori R, Kuipers EJ, Hoff G, Senore C, Segnan N, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Colonoscopic surveillance following adenoma removal. Endoscopy 2012;44:SE151–63.
24. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375:1624–33.
25. Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial–SCORE. J Natl Cancer Inst 2011;103:1310–22.
26. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169–74.
27. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:659–69.
28. Shinya H, Wolff WI. Morphology, anatomic distribution and cancer potential of colonic polyps. Ann. Surg 1979;190:679–83.
29. Winawer S, Zauber A, Fletcher R, Stillman JS, O'brien MJ, Levin B, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer. CA Cancer J Clin 2006;56:143–59.
30. Segnan N, Patrick J, von KL (eds). European guidelines for quality assurance in colorectal cancer screening and diagnosis. Brussels: European Commission, 2011. First Edit. (Segnan N, Patrick J, von KL ed.). Luxembourg: Luxembourg: Publications Office of the European Union; 2010 [cited 2011 Feb 2]. Available from: http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en_GB/-/EUR/ViewPublication-Start?PublicationKey=ND3210390.
31. Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002;97:1296–308.
32. Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795–803.