European Journal of Epidemiology (2019) 34:163–172
https://doi.org/10.1007/s10654-018-0471-z

SCREENING

Contribution of the OC Sensor® immunoassay in comparison to the Hemoccult II® guaiac-test in organized colorectal cancer screening

Carole Vitellius[1,2] · Margot Laly[1] · Anne-Sophie Banaszuk[2] · Isabelle Deherce[2] · Nathanaëlle Cornet[1] · Sandrine Bertrais[2] · Patrick Saulnier[4] · François-Xavier Caroli-Bosc[1,2,3]

Received: 29 July 2018 / Accepted: 4 December 2018 / Published online: 8 December 2018

Abstract

Colorectal cancer (CRC) is a major cause of cancer-related death of worldwide with high incidence and mortality rate, accessible to a screening program in France, first with guaiac- based fecal occult blood test (g-FOBT) then with fecal immunochemical tests (FIT), since 2015, because of better accuracy. The aim of our study was to compare the characteristics of screen-detected lesions in two successive CRC screening campaigns, using two different tests (Hemoccult II® and OC Sensor®) in the department of Maine-et-Loire, and to precise the performance of these tests [participation rate, detection rates (DR), positive predictive value (PPV)]. Participants, invited by CAP SANTE 49, with polyps or cancer at the colonoscopy after a positive screening test between 01/01/2013 and 31/12/2016 were included. A guaiac-based fecal occult blood test (g-FOBT) was used from January 2013 to December 2014 and a FIT was used from June 2015 to December 2016). 2575 participants, 642 in g-FOBT group and 1933 in FIT group had lesions. Participation rate was not different between tests ($p=0.104$), whereas DR and PPV were statistically higher in FIT for all lesions (2.61, 95% CI [2.50–2.70] vs 0.93, 95% CI [0.90–1.00], $p<0.0001$ and 64.84, 95% CI [63.10–66.60], 50.00, 95% CI [47.30–52.70], $p<0.0001$ respectively). FIT detects more precancerous lesions (adenomas, $p<0.001$, and advanced adenomas, $p<0.001$) than g-FOBT but g-FOBT detects more serrated polyps ($p=0.025$). AAs were more in right colon in FIT than g-FOBT ($p=0.035$). No different participation rate was detected between FIT and g-FOBT but DR and PPV of all lesions was higher with FIT.

Keywords Colorectal cancer · Screening · Immunochemical test · Performance test

Introduction

Colorectal cancer (CRC) is the 3rd most common cancer in France with a projection by the French Institute for Public Health Surveillance of 44,000 new patients in 2017 and the 2nd cause of mortality with more 17,000 deaths to this date [1]. The European 5-year relative survival rate was 57% for the colon and 56% for the rectum in the EUROCARE-5 study [2]. All stages combined, the survival rate at 5 years is about 60% in France [3]. Given its considerable impact on population, CRC is a major cause of cancer-related death of worldwide. The mortality is higher in advanced stage of tumor and its discover at an early stage led to cure in 90%. It is possible to prevent the development of CRC by the earlier detection and removal of precursors lesions by colonoscopy. Colonoscopy is the most sensitive test for detection of CRC or adenoma but it is an expensive, invasive procedure and requires hospital attendance and administration of a bowel preparation that is often inconvenient and unpleasant for the patient. Three randomized trials in the 1990's from the USA, UK and Denmark showing that screening with guaiac-based fecal occult blood tests (g-FOBT) prevents death from CRC in average risk persons. Several studies have proved that g-FOBT can reduce mortality related to CRC up to 20%

✉ Carole Vitellius
Carole.Vitellius@chu-angers.fr

1 Service d'Hépato-gastro-entérologie, CHU Angers, 4, rue Larrey, 49933 Angers Cedex 09, France

2 HIFIH Laboratory, UNIV Angers, Université Bretagne Loire, Angers, France

3 CAP-Santé 49, Angers, France

4 MINT Laboratory, UNIV Angers, INSERM 1066, CNRS 6021, Université Bretagne Loire, Angers, France

[4–8]. Screening aims to detect cancerous or precancerous lesions before symptoms appear and when they are more likely to be curable. Established in France in 2002, in 23 pilot areas, the organized screening program for colorectal cancer was widespread throughout the country in December 2008. The test was proposed to the asymptomatic 50–74 years old people with any risk factors (medium risk population). The test consists of detecting every 2 years blood in the stool with fecal occult blood tests (FOBT) and to propose a colonoscopy if the test was positive, to search a lesion (polyp or cancer). They include guaiac based test and immunochemical tests.

Guaiac-based fecal occult blood tests (g-FOBT) were the first approach to CRC screening based on the pseudo peroxidase activity of the haem, which facilitates oxidation of guaiac when hydrogen peroxide is added [9]. The test consists of applying two fecal samples of three separate stools with a separate applicator stick in three separate cards. Test gives a qualitative result and at least one positive sample out of six collected samples defines an overall positive test. G-FOBT has a good clinical specificity but a low clinical sensitivity with a relatively high false negative rate for detecting CRC and adenomas. It is not specific for human blood and it is susceptible to interfere with some foods involving dietary restriction during fecal sample collection.

Fecal Immunochemical tests (FIT) have been used as screening test since the 2000's. The OC Sensor® test consisted of a single sampling tube, filled with stabilizing buffer, used with a fecal probe. OC Sensor® test is using monoclonal or polyclonal antibodies against blood protein (more often human globin). Reading system is automatic and gives quantitative result. Four population-based randomized controlled trials and a meta-analysis comparing FIT to g-FOBT have found an absolute increase in participation ranging from 5.4 to 16.2% [7, 8, 10, 11]. A recent meta-analysis of 19 studies reported the sensitivity and specificity of FIT for the detection of CRC in average-risk asymptomatic populations with an overall pooled sensitivity and specificity of FIT for CRC were 79% (95% CI 69–86%) and 94% (95% CI 92–95%), with an overall accuracy of 95% (95% CI 93–97%) [12]. This test could decrease in CRC mortality [10, 11]. As shown in a French study in 2007, FIT increase 1.5–2 times the number of cancers detected and 3–4 times the number of adenomas found and decrease the number of false positive results 1.5-fold [13]. Since June 2015, FIT have been generalized in France and OC Sensor® test (FIT) replaced Hemoccult II® test (g-FOBT) in French screening campaigns [14].

The aim of our study was to compare the screen-detected lesions in two successive screening colorectal cancer campaigns in the department of Main-et-Loire in France, using the two different tests (Hemoccult II® and OC Sensor®) from 2013 to 2016 and compare the performance of these tests.

Patients and methods

All participants to colorectal cancer screening campaign invited by CAP SANTE 49, the departmental analysis center that organizes CRC screening in Maine-et-Loire who have a positive test between 01/01/2013 and 31/12/2016 were screened. Only participants with removed polyp or cancer at the colonoscopy after a positive screening test were included in our study.

We also get data from CAP SANTE 49 database about all individuals invited to participate in CRC- screening between 01/01/2013 and 31/12/2016.

Participants with a positive test from CAP SANTE 49 database, who have refused or have a contraindication to colonoscopy were excluded from the analysis.

Hemoccult II® was used from 01/01/2013 to 31/12/2014 in the first campaign in our study and OC Sensor® test was used in the second campaign from 01/06/2015 to 31/12/2016. No invitation was sent from 01/11/2014 to 01/06/2015. Hemoccult II® was realized from three stool samples and the result was positive from one sample positive and OC Sensor® was realized from one stool sample and the result was positive if the rate was higher than 150 ng Hemoglobin/ml buffer.

Gastroenterologists and pathologists have sent a copy of results of colonoscopy and histopathological results of the samples to CAP SANTE 49. Thanks to their registry, informations about participants were collected about their age (birthday), gender and date of positive test. Data from the colonoscopy were collected as date of colonoscopy, quality of preparation (insufficient, average, good), if the exam was complete or not, localization (rectum, left, transversal and right colon) and size of lesions. Lesions were considered as distal when lesion was localized in rectum, sigmoid or descending colon or a left colectomy, rectal resection or sigmoidectomy were realized. And they were categorized at proximal when lesion was in transverse or right colon. Polyp size was recording by endoscopists and not by pathologists although in several studies macroscopic evaluation by endoscopist was neither reproducible nor reliable in comparison with pathologist evaluation [15].

Histological data were collected from CAP SANTE 49 or histopathological departments of Maine-et-Loire in Centre de Pathologie de l'Ouest or Angers University Hospital. Only data about the 3 most pejoratives lesions per colonoscopy were analyzed. Histological analysis of the type of polyp (tubular adenoma, tubulovillous or villous adenoma, serrated adenoma, hyperplastic polyp and others), dysplasia (low or high-grade) and the presence of carcinoma were collected. All lesions were counted separately (i.e., one subject can be counted as more as adenomas or advanced adenomas or invasive cancers was detected).

If a cancer was diagnosed, other data were collected: date of resection, differentiation (low—moderately—well-differentiated), staging tumoral according to the AJCC classification [16], anterior participation to screening CRC campaign and date of the last screening test result. The criterion for diagnosing cancer, in accordance with the international classification, was an invasion of malignant cells beyond the muscularis mucosa. Intramucosal carcinoma and carcinoma in situ were classified as adenoma with high grade dysplasia [17].

Advanced adenoma (AA) was defined by size ≥ 10 mm, tubulovillous or villous adenoma, or high grade dysplasia (including In Situ Carcinomas). [17].

Advanced neoplasia (AN) was an advanced adenoma or a colorectal cancer.

Collection data was retrospectively performed to 1/05/2017.

Data analysis

The participation rate was calculated as the ratio of number of persons returning the screening test to the number of individuals invited during the corresponding screening campaign. Detection rate was calculated as the number of persons with a lesion at colonoscopy relative to the number of participants in CRC screening. The positive predictive value (PPV) was the proportion of true positives (persons with a lesion at colonoscopy) relative to the total number of patients who were screened positive and underwent colonoscopy. Detection rate and PPV are expressed as percentages with 95% confidence intervals (95% CI) for PPV. In our study, colonoscopy was only performed to subjects with a positive test. So, sensitivity and specificity of each test could not be directly estimated.

Characteristics of subjects were expressed as mean ± standard deviation or frequency (%). Continuous variables were compared between groups (FIT vs g-FOBT) using the Student *t* test. Categorical variables were compared between groups using the Chi square test or the Fisher's exact test where appropriate.

All statistical analyses were performed using IBM SPSS version 24 for Windows.

Results

In overall 391 932 individuals were invited to participate in CRC screening campaigns between 01/01/2013 and 31/12/2016; 188 815 received an invitation for g-FOBT-based CRC screening (2013–2014) and 203 117 for a FIT-based CRC screening (2015–2016). 143 408 individuals performed a screening test, 69 326 did a Hemoccult® test (g-FOBT) and 74 082 an OC Sensor® test (FIT). Main characteristics are presented in the Flow chart (Fig. 1).

4565 participants had a positive screening test: 1346 g-FOBT (1.9%) and 3219 FIT (4.3%) ($p < 0.0001$).

Among participants who were screened positive, 93.5% (4266 of 4565) patients underwent a colonoscopy. Colonoscopy rate was 95.5% for g-FOBT-based campaign with 1285 colonoscopy realized and 92.6% for FIT-based campaign with 2981 colonoscopy realized ($p = 0.51$). There was 2.3-fold supplementary realized colonoscopy after a positive FIT. 10 patients in g-FOBT group and 23 in FIT group refused or had contraindication for colonoscopy. Furthermore, 51 patients in g-FOBT group and 215 in FIT group did not undergo further exploration after positive test; these patients were excluded of the study (61 and 238 respectively). Among them 55 had an incomplete colonoscopy, 7 (1.1%) in the g-FOBT group and 48 (2.4%) in the FIT group.

2575 subjects had screen-detected colorectal lesion: 642 in g-FOBT group (47.7% of patients who had been screened positive) and 1933 in FIT group (60.0% of patients who had been screened positive) ($p < 0.0001$). Mean age of patients at test was 62.1 ± 7.1 for g-FOBT group and 62.7 ± 6.9 for FIT group, $p = 0.061$. For each screening campaign, there was a higher proportion of men than women among patients with screen-detected lesions: 60.7% (390) versus 39.3% (252) in the g-FOBT group and 63.2% (1221) versus 36.8% (712) in the FIT group but no difference between campaign ($p = 0.273$). 138 subjects have already participated to screening colorectal campaign before in g-FOBT group and 442 in FIT ($p = 0.471$).

In these subjects, colonoscopy was performed within 90.5 ± 3 days after the test reading in g-FOBT group and within 100.8 ± 1.3 days in FIT group with a significantly longer time in FIT group ($p < 0.001$).

Screen detected lesions

1863 participants had adenomas: 1416 in FIT group and 447 in g-FOBT group of which 219 with advanced adenomas (AA) in g-FOBT and 924 in FIT, 506 had hyperplasics polyps: 319 in FIT versus 187 in g-FOBT, 23 had other polyps: 21 in FIT and 2 in g-FOBT, 121 had serrated polyps: 82 in FIT and 39 in g-FOBT, 45 had in situ carcinomas: 33 in FIT and 12 in g-FOBT and 285 had colorectal cancer: 222 in FIT and 63 in g-FOBT.

The detection rate for any type of colorectal lesions was significantly higher in FIT group than in g-FOBT (2.61%, 95% CI [2.50–2.70] in FIT vs 0.93%, 95% CI [0.928–0.932] in g-FOBT, $p < 0.0001$) (Table 1). Positive predicative value (PPV) was significantly higher in FIT (64.84, 95% CI [63.10–66.60]) versus in g-FOBT (50.00%, 95% CI [47.30–52.70], $p < 0.0001$), significant differences

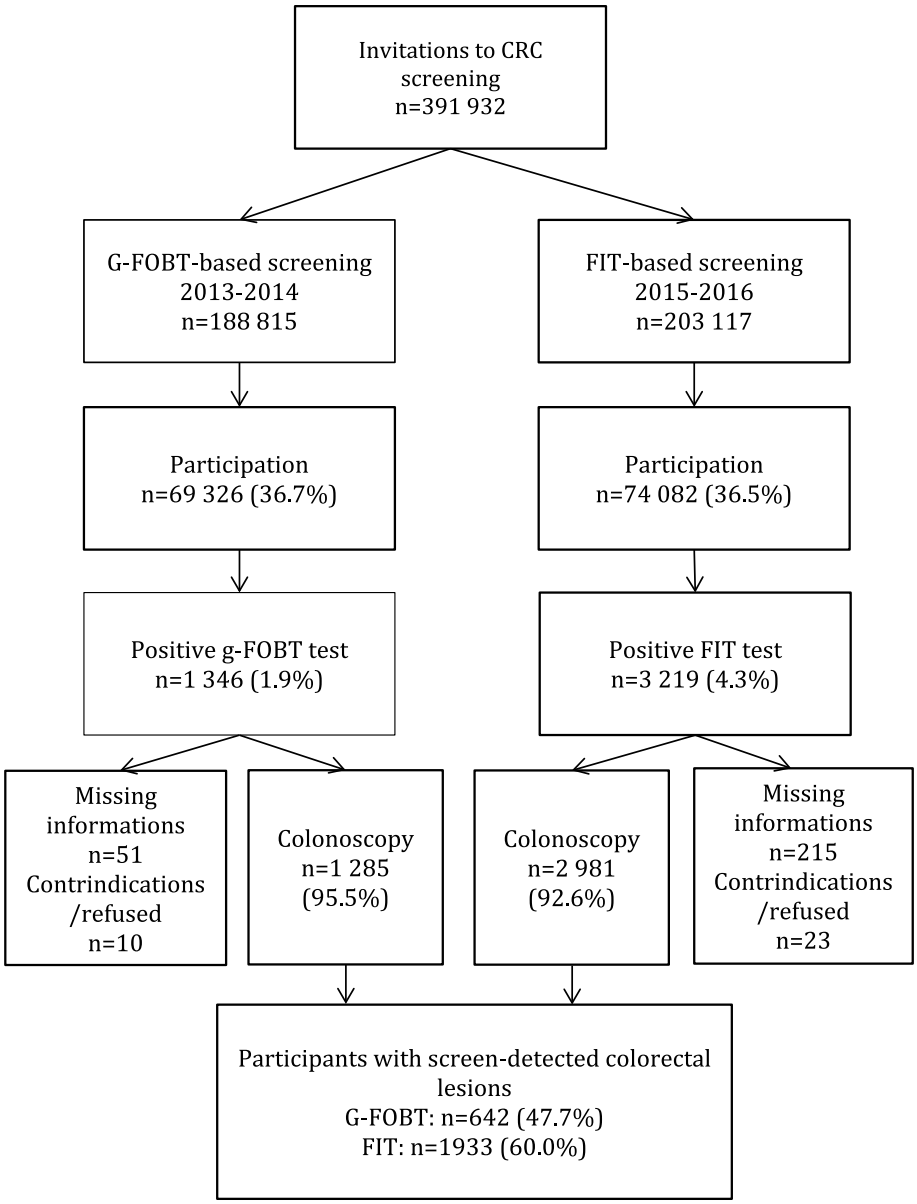

Fig. 1 Flow chart of the study

in favor of FIT were also found for advanced lesions (AA, CRC and AN) (Table 1).

5193 lesions were detected: 1283 with g-FOBT and 3910 with FIT. We had collected data from 4532 lesions (only data about the 3 most pejoratives lesions per colonoscopy were analyzed).

There was a significant difference in the type of lesions ($p < 0.001$) between the two campaigns with more hyperplasic polyps ($p < 0.0001$), more adenomas ($p < 0.0001$), more advanced adenomas ($p < 0.001$) and less serrated polyps ($p = 0.025$) in FIT group as compared to g-FOBT group.

There was a difference of localization of lesions ($p = 0.003$) with more lesions in rectum in g-FOBT (17.9% and 13.9% in FIT, $p < 0.001$) and left colon in FIT (53.6% and 49.1% in g-FOBT, $p = 0.010$). There was no difference in right colon (33.0% in g-FOBT and 32.4% in FIT, $p = 0.73$).

Hyperplasic polyps

877 polyps were detected: 329 in g-FOBT and 548 in FIT. FIT detected more hyperplasic polyps than g-FOBT ($p < 0.0001$). No difference of sex with 58.3% men in FOBT and 60.2% in FIT ($p = 0.674$) and age (61.05 ± 7.01 in FOBT and 62.00 ± 6.73 in FIT, $p = 0.382$) of participants. Hyperplasic polyps were significantly more in rectum in g-FOBT group (39.9% and 31.9% in FIT, $p = 0.035$) and in left colon in FIT group (52.0% and 43.1% in g-FOBT, $p = 0.025$). There was no difference in size of polyps (4.25 ± 1.70 in g-FOBT and 4.35 ± 2.49 in FIT, $p = 0.706$).

Table 1 Test performance of g-FOBT (Hemoccult II®) versus FIT (OC Sensor®)

	g-FOBT		FIT		*p* values
	n	%	n	%	
Participation rate	69,326	36.72	74,082	36.47	0.105
FOBT positive patient	1346	1.94	3219	4.35	< 0.0001
Completed screening	1285	95.84	2981	92.98	0.0003
Detection rate[a]					
Any lesion	642	0.93	1933	2.61	< 0.0001
AA	219	0.32	924	1.25	< 0.0001
CRC	63	0.09	222	0.30	< 0.0001
AA or CRC	282	0.41	1146	1.55	< 0.0001
PPV + CI 95%[b]					
Any lesion	642	50.0 [47.0–53.0]	1933	64.84 [63.0–66.0]	< 0.0001
AA	219	17.0 [15.0–19.0]	924	31.0 [29.0–33.0]	< 0.0001
CRC	63	4.90 [4.0–6.0]	222	7.45 [7.0–8.0]	0.002
AA or CRC	282	21.9 [20.0–24.0]	1146	38.44 [37.0–40.0]	< 0.0001

AA advanced adenomas, *CRC* ColoRectal Cancer, *PPV* positive predictive value, *CI 95%* confidence interval at 95%

[a]Detection rate: percentage of individuals with lesions relative to the total number of participants in CRC screening campaigns

[b]Positive predictive value: percentage of individuals with lesions relative to the number of participants who screened positive and underwent colonoscopy or CTC

Tubular and/or villous adenomas

3035 adenomas were detected: 685 in g-FOBT and 2350 in FIT. FIT detected more tubulovillous and villous adenomas than g-FOBT ($p < 0.0001$). No difference of sex ($p = 0.451$) was found in participants but participants in FIT were older ($p = 0.048$). Sizes were available for 466 adenomas in g-FOBT and for 1921 adenomas in FIT. There was a significantly difference ($p = 0.015$) with bigger polyps in FIT group (10.11 mm ± 7.57 vs 9.16 mm ± 7.44). No difference of localization ($p = 0.487$) and no difference in dysplasia ($p = 0.088$) (Table 2).

Advanced adenomas and in situ carcinomas

1443 advanced adenomas were detected: 264 in g-FOBT and 1193 in FIT.

There was significantly more AA diagnosed by FIT versus g-FOBT ($p < 0.0001$), with more AA at right in FIT

Table 2 Characteristics of adenomas in g-FOBT and FIT groups

	g-FOBT	FIT	*p* value
Adenomas	58.8% (n = 685)	69.8%(n = 2350)	< 0.0001
Age	62.29 ± 7.18	63.04 ± 6.90	0.048
Gender			
Male	63.1% (n = 282)	65.0% (n = 921)	0.451
Female	36.9% (n = 165)	35.0% (n = 495)	
Localization of adenomas			0.487
Rectum	10.2% (n = 70)	9.6% (n = 226)	
Left colon	52.7% (n = 361)	54.8% (n = 1287)	
Transverse and right colon	36.8% (n = 252)	34.4% (n = 808)	
Unknown	0.3% (n = 2)	1.2% (n = 29)	
Dysplasia			0.088
No	89.8% (n = 615)	87.3% (n = 2052)	
High grade	10.1% (n = 69)	12.5% (n = 293)	
Unknown	0.1% (n = 1)	0.2% (n = 5)	
Size	9.16 ± 7.44	10.11 ± 7.57	0.015

($p=0.035$). No sex difference was found ($p=0.546$) and participants in FIT with AA were older ($p=0.028$) (Table 3).

45 in situ carcinomas were detected: 12 in g-FOBT and 33 in FIT.

Nevertheless, there was no significantly difference of in situ carcinoma between the groups ($p=0.759$). The sex of individuals with in situ carcinoma was significantly different between FOBT and FIT ($p=0.009$) with 83.3% men in g-FOBT and 39.4% men in FIT. No difference of age ($p=0.880$). No difference of localization ($p=0.882$).

144 serrated polyps were detected: 47 in FOBT and 97 in FIT. There were statistically less serrated polyps in FIT group than in g-FOBT ($p=0.025$). There was no difference of the sex (48.7% men in g-FOBT and 54.9% men in FIT, $p=0.526$), age of subjects (63.03 ± 6.21 years in g-FOBT and 61.43 ± 6.88 in FIT, $p=0.220$), adenomas size (data available for 66% (n=31) polyps in g-FOBT measuring 7.42 ± 4.70 mm and 67% (n=65) in FIT measuring 8.38 ± 4.62 mm, $p=0.343$), localization (76.6% in right colon, 21.3% in left colon and 2.1% in rectum in g-FOBT and 71.1% in right colon, 23.7% in left colon and 3.1% in rectum in FIT, $p=0.933$). Only one polyp was in high grade of dysplasia in FIT ($p=1$).

Invasive cancers

288 invasive cancers were diagnosed: 64 in g-FOBT and 224 in FIT. The detection rate for CRC was significantly higher in FIT group (0.30%) versus g-FOBT (0.09%) ($p<0.0001$). There were 64 invasive cancer diagnosed after a g-FOBT: 62 adenocarcinomas, 1 lymphoma and 1 neuro-endocrine carcinoma, and 224 after a FIT: 222 adenocarcinomas and 2 neuroendocrine carcinomas, no difference between the campaign ($p=0.215$). Sex repartition was not different between the groups (40 and 145 cancers in men; 23 and 77 cancers in women respectively for g-FOBT and FIT) ($p=0.789$). No difference in the age of participants ($p=0.972$). CRC localization ($p=0.610$), differentiation ($p=0.615$) and stage ($p=0.117$) of cancer were not statistically different between the two screening campaigns (Table 4).

Among the 222 individuals with CRC diagnosed after a positive FIT, 120 (54.1%) individuals with 121 CRC

Table 3 Characteristics of Advanced adenomas and In Situ Carcinoma in g-FOBT and FIT groups

	g-FOBT	FIT	*p* value
Advanced adenomas (AA)[a]	22.7% (n=264)	35.4% (n=1193)	<0.0001
Age	62.02 ± 7.17	63.16 ± 6.81	0.028
Gender			
Male	66.7% (n=146)	64.5% (n=596)	0.546
Female	33.3% (n=73)	35.5% (n=328)	
Localization of AA			0.104
Rectum	13.3% (n=35)	12.2% (n=144)	0.594
Left colon	68.6% (n=181)	64.2% (n=758)	0.123
Transverse and right colon	17.4% (n=46)	23.6% (n=279)	0.035
Unknown	0.7% (n=2)	1.0% (n=12)	
In situ carcinomas (ISC)[a]	1.6% (n=12)	1.3% (n=33)	0.759
Age	63.08 ± 6.00	63.45 ± 7.62	0.880
Gender			0.09
Male	83.3% (n=10)	39.4% (n=13)	
Female	16.7% (n=2)	60.6% (n=20)	
Localization of ISC			0.882
Rectum	16.7% (n=2)	18.2% (n=6)	
Left colon	66.6% (n=8)	69.7% (n=23)	
Transverse and right colon	16.7% (n=2)	12.1% (n=4)	

AA advanced adenoma, *ISC* in situ carcinoma

AA size ≥ 10 mm, villous component or high-grade dysplasia

Serrated polyps

[a]Percentage of all polyps diagnosed

Table 4 Characteristics of Invasive cancers in g-FOBT and FIT groups

	g-FOBT	FIT	*p* value
Invasive cancer	9.7% (n=64)	11.6% (n=224)	0.315
Age at diagnosis	64.59 ± 6.66	64.55 ± 6.36	0.972
Gender			0.789
Male	63.5% (n=40)	65.3% (n=145)	
Female	36.5% (n=23)	34.7% (n=77)	
Localization			0.610
Rectum	25.0% (n=16)	28.1% (n=63)	
Left colon	45.3% (n=29)	48.2% (n=108)	
Transverse and right colon	29.7% (n=19)	23.7% (n=53)	
Subdivision of cancers			0.215
Adenocarcinoma	96.9% (n=62)	99.1% (n=222)	
Lymphoma	1.6% (n=1)	0.0% (n=0)	
Neuroendocrine carcinomas	1.6% (n=1)	0.9% (n=2)	
Differentiation for ADK			0.615
Well	38.1% (n=24)	37.1% (n=83)	
Intermediate	55.6% (n=35)	53.6% (n=120)	
Low	3.2% (n=2)	2.7% (n=6)	
Unknown	2	15	
Subdivision in stages			0.117
0–1	39.1% (n=25)	39.3% (n=88)	
2	21.9% (n=14)	23.7% (n=53)	
3	26.6% (n=17)	26.3% (n=59)	
4	9.4% (n=6)	8.5% (n=19)	
Unknown	2	5	

NA non applicable, *ADK* adenocarcinoma

had participated to previous campaign and had realized a g-FOBT test 2 years before. There was no statistical difference of their sex (65.8% men in g-FOBT and 64.7% in FIT, $p=0.860$) and their age (64.18 ± 11.32 years in g-FOBT and 62.84 ± 13.10 in FIT, $p=0.414$). There was no difference in localization of cancer (24.0% in rectum, 49.6% in left colon and 26.4% in right colon in g-FOBT and 33.0% in rectum, 46.6% in left colon and 20.4% in right colon, $p=0.275$), in the stage ($p=0.527$) and in differenciation ($p=0.866$) of CRC at screening between these groups.

Among the 63 individuals with CRC diagnosed by g-FOBT, 40 (64.1%), with 41 CRC, had participated at the last campaign with 23 men and 17 women, without significant difference ($p=0.193$). There was no difference in differenciation ($p=0.899$), localization ($p=0.269$) or stage of tumors ($p=0.101$).

Advanced neoplasias

1745 advanced neoplasias (advanced adenomas and invasive colorectal cancers) were diagnosed: 328 in 282 individuals in g-FOBT and 1417 in 1146 individuals in FIT group. There was no difference between the groups of the sex of participants (66.0% men in g-FOBT and 64.7% in FIT, $p=0.682$), the age (62.59 ± 7.13 years in g-FOBT and 63.43 ± 6.75 years in FIT, $p=0.066$) localization of lesions (15.5% in rectum, 64.0% in left colon and 19.8% in right colon in g-FOBT and 14.6% in rectum, 61.1% in left colon and 23.4% in right colon, $p=0.359$).

Discussion and conclusion

Screening by FOBTs has been shown in randomized trials to reduce colorectal cancer (CRC) incidence and mortality [5–8]. Two meta-analysis have evaluated sensitivity and specificity of g-FOBT [18, 19]. First meta-analysis from Rosman and Korsten found a pooled sensitivity of g-FOBT for CRC of 36% (CI 95%, 25–47%) and a pooled specificity of 96% (CI 95%, 94–97%) without verification bias [18]. In the second one, the sensitivity was 47% (CI 95%, 37–58%) and specificity was 93% (CI 95%, 91–95%) [19]. More recently, FITs have been developed and have a higher specificity 94% (CI 95%, 92–95%) for human blood than g-FOBTs, hence removing any need for dietary restriction and have a higher sensitivity (79%, CI 95%, 69–86%) [12]. However, the effectiveness of any screening program depends not only on the diagnostic performance of the screening but also on the compliance and general acceptance of the test by the public. The participation rate with g-FOBT in France is low and has never exceeded 30%, far away from the 45% acceptable, even further from the 65% recommended by European standards [20]. In our study, sensitivity and specificity of each test could not be directly estimated but the participation rate was calculated.

The participation rate remains low with FIT (36.5%) and no difference has been highlighted versus g-FOBT (36.7%) in our study. In according to French Public Health, the participation rate in Maine-et-Loire was 38% with g-FOBT in 2013–2014 and 41.3% with FIT in 2015–2016 as in Holland and Italy that have found higher participation rate with FIT [21, 22]. Moreover, these data are superior in comparison with national average rate at 29.4% in the national registries data of the 2015–2016 campaign [20]. This low participation rate with FIT could explain by two mainly reasons. Invitations to participate at CRC screening with FIT test began belatedly (01/06/2015), so a part of the population had been invited late, and had probably not yet performed the test at the end of 2016, decreasing the participation rate in FIT group. It can also be explained by the fact that the FIT tests were not delivered with the second dunning letters contrary to g-FOBT. However, this action would allow an increase of the participation rate of 10%. It has been shown that when the FIT is mailed after the medical free-offer phase to non-participants at this phase, the participation rate increased from 28 to 45% [23] to achieve the 45% recommended by European Union experts [23]. Interestingly, these results were comparable regardless of the age group studied [23].

Colonoscopy rate was higher after a positive test in g-FOBT group (92.6% in FIT vs 95.5% in g-FOBT), but individuals invited late in FIT group may not have realized their colonoscopy at the collection data date. Other screening studies have shown an equal number of colonoscopy realized between the two tests [21, 24] and when comparing FIT and g-FOBT at similar colonoscopy referral rates, it should get quite clear that FIT outperforms g-FOBT in every regard. Moreover the FIT positivity rate was more than twice as high compared to the g-FOBT (respectively 4.35% and 1.94%) responsible for an increase of up to 2.3 fold in colonoscopy in our study, nevertheless PPV was significantly higher in FIT compared to g-FOBT. In consequence, the delay between test and colonoscopy was significantly higher in FIT. If colonoscopy follow up was performed before 10 months after the test, colorectal cancer risk and advanced stage disease will not increase [25]. Although the number of colonoscopies was higher with FIT, this potential drawback could easily be solved by elevating the FIT cutoff a bit.

Whatever the lesion (polyp, advanced adenoma or invasive cancer), detection rates and predictive positive values were significantly higher with FIT, as reported in several studies [13, 26–28]. Compared to g-FOBT, and based on our data, FIT can detect more AA and more invasive cancer than g-FOBT. This increase of detection rate was not explained by a most important first participation in FIT group, contrary to 2 studies that reported an increase detection rate of lesions in population who had never been

screened before, creating a bias [13, 24]. In our study, only 22.9% of the subjects in FIT group participated for the first time in screening campaign. So it is a very important finding and FIT could decrease incidence of colorectal cancer in the future by removing advanced adenomas before their transformation in carcinoma.

Colorectal cancer detection rate was statistically higher in FIT group compared to g-FOBT group (0.09 and 0.30; $p < 0.05$). Majority of studies reported no difference in localization or stage of cancers diagnosed after FIT or g-FOBT in the literature [21, 29–33]. One study, in French screening conditions, has compared g-FOBT (Hemoccult II®) and another FIT (MAGSTREAM®) for detection of colonic lesions according to lesion type and localization. The authors found a gain in sensitivity restricted in rectal cancer in early stage (there were no difference depending on localization in advanced adenomas) [13]. In other meta-analysis, FIT and g-FOBT have a higher sensitivity to detect CRC in distal than proximal colon [34, 35].In our study, we have not found better accuracy for the diagnostic of rectal, distal or proximal colon cancer or for diagnosis of CRC at early stage by FIT compared to g-FOBT. Nevertheless FIT has a higher detection rate and PPV for colorectal cancer than g-FOBT.

More adenomas were diagnosed by FIT than g-FOBT, and adenomas with a higher risk on malignant transformation (more villous and tubulovillous lesions). G-FOBT had poor sensitivity to screen advanced neoplasia (advanced adenomas and CRC) [36, 37]. FIT permitted to screen 4 times more advanced neoplasias. In our study, FIT detected more lesions (polyps, AA, invasive cancer) in rectum or left colon than g-FOBT in particularly hyperplasics polyps. Interestingly, we have found that there were more advanced adenomas in right colon in FIT. As FIT detects more AA at right and invasive CRC, interval cancers could be decreased in future, as reported by Portillo et al. [38], because proximal localization or right-sided colon seem to be a risk factor when developing an interval cancer (OR 0.28, 95% CI 0.20–0.40, $p < 0.0001$). Moreover FIT are better at detecting the immediate precursors to CRC (advanced adenomas) suggesting that, unlike g-FOBT they may have an impact on CRC incidence.

Serrated polyps can represent 9% of all ones after 50 years [39]. We now know that serrated polyps had potential for dysplasia and malignant transformation, and can represent 15% up to 30% of all CRC [40, 41], because of a specific epigenetic malignant pathway [42], particularly in interval cancer. In our study, more serrated polyps were found with g-FOBT (4.03%) than FIT (2.88%) but the most of them were not degenerated, except 1 polyp in FIT group in high-grade dysplasia. Our results are in line with different studies that did not find association between FIT and detection of serrated adenomas because of proximal localization and non-hemorrhagic nature [43–45].

Our study compares for the first time two tests used in colorectal cancer screening in real life in a French department. Many participants were included and many datas have been collected, so our analysis was realized about high number of lesions. This study had also several drawbacks. This is a retrospective study, monocenter (one department).There was a lot of missing information regarding the lesion's size. 661 lesions were not collected after colonoscopy for anatomopathological analysis and could create a bias in polyp analysis but lesions more pejorative were a priori analyzed.

In our study, distribution of the FIT by the general practitioner during the medical-offer phase does not allow to increase participation rates if the mailing of the tests is deleted during reminders. Recently, the mailing phase of the screening test has been partially restored in France for subjects who had already participated in a CRC screening campaign in the previous 6 years. Given the results of our study it is likely that this measure is insufficient. However, the detection rate of polyps, advanced adenomas or cancers was higher than g-FOBT and advanced adenomas were more often found in right colon with FIT. This could decrease interval cancer in the future as suggested by Wieten et al. [46].

References

1. Jéhannin-Ligier K, Dantony E, Bossard N, Molinié F, Defossez G, Daubisse-Marliac L, Delafosse P,, Remontet L, Uhry Z. Projection de l'incidence et de la mortalité par cancer en France métropolitaine en 2017. Rapport technique. Saint-Maurice: Santé publique France; 2017 [cited 2018 June 21]. http://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Projection-de-l-incidence-et-de-la-mortalite-en-France-metropolitaine-en-2017-Rapport-technique.
2. Holleczek B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999–2007—results from the EUROCARE-5 study. Eur J Cancer. 1990;2015(51):2158–68.
3. Cowppli-Bony A, Uhry Z, Remontet L, Guizard A-V, Voirin N, Monnereau A, Bouvier A-M, Colonna M, Bossard N, Woronoff A-S, Grosclaude P. Survie des personnes atteintes de cancer en France métropolitaine, 1989–2013. Partie 1—Tumeurs solides. Saint-Maurice: Institut de veille sanitaire; 2016 [cited 2018 June 21]. http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-chroniques-et-traumatismes/2016/Survie-des-personnes-atteintes-de-cancer-en-France-metropolitaine-1989-2013-Partie-1-tumeurs-solides.
4. Selby JV. Effect of fecal occult blood testing on mortality from colorectal cancer: a case–control study. Ann Intern Med. 1993;118:1.
5. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348:1472–7.

6. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348:1467–71.
7. Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. Gastroenterology. 2004;126:1674–80.
8. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328:1365–71.
9. Tinmouth J, Lansdorp-Vogelaar I, Allison JE. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. Gut. 2015;64:1327–37.
10. Chiu H-M, Chen SL-S, Yen AM-F, Chiu SY-H, Fann JC-Y, Lee Y-C, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer. 2015;121:3221–9.
11. Zorzi M, Fedeli U, Schievano E, Bovo E, Guzzinati S, Baracco S, et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut. 2015;64:784–90.
12. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med. 2014;160:171.
13. Guittet L, Bouvier V, Mariotte N, Vallee JP, Levillain R, Tichet J, et al. Comparison of a guaiac and an immunochemical faecal occult blood test for the detection of colonic lesions according to lesion type and location. Br J Cancer. 2009;100:1230–5.
14. HAS. Place des tests immunologiques de recherche de sang occulte dans les selles (iFOBT)dans le programme de dépistage organisé du cancer colorectal en france. 2008 [cited 2018 Jun 21]. https://www.has-sante.fr/portail/upload/docs/application/pdf/2008-12/rapport_-_place_des_tests_immunologiques_de_recherche_de_sang_occulte_dans_les_selles_ifobt.pdf.
15. Chaptini L, Chaaya A, Depalma F, Hunter K, Peikin S, Laine L. Variation in polyp size estimation among endoscopists and impact on surveillance intervals. Gastrointest Endosc. 2014;80:652–9.
16. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471–4.
17. Winawer SJ, Zauber AG, Fletcher RH, 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 Society. Gastroenterology. 2006;130:1872–85.
18. Rosman AS, Korsten MA. Effect of verification bias on the sensitivity of fecal occult blood testing: a meta-analysis. J Gen Intern Med. 2010;25:1211–21.
19. Launois R, Le Moine J-G, Uzzan B, Fiestas Navarrete LI, Benamouzig R. Systematic review and bivariate/HSROC random-effect meta-analysis of immunochemical and guaiac-based fecal occult blood tests for colorectal cancer screening. Eur J Gastroenterol Hepatol. 2014;26:978–89.
20. Taux de participation au programme de dépistage organisé du cancer colorectal 2015–2016/Indicateurs d'évaluation/Evaluation du programme de dépistage du cancer colorectal/Evaluation des programmes de dépistage des cancers/Cancers/Maladies chroniques et traumatismes/Dossiers thématiques/Accueil [cited 2018 June 21]. http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Cancers/Evaluation-des-programmes-de-depistage-des-cancers/Evaluation-du-programme-de-depistage-du-cancer-colorectal/Indicateurs-d-evaluation/Taux-de-participation-au-programme-de-depistage-organise-du-cancer-colorectal-2015-2016.
21. van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135:82–90.
22. Federici A, Giorgi Rossi P, Borgia P, Bartolozzi F, Farchi S, Gausticchi G. The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial. J Med Screen. 2005;12:83–8.
23. Piette C, Durand G, Bretagne J-F, Faivre J. Additional mailing phase for FIT after a medical offer phase: the best way to improve compliance with colorectal cancer screening in France. Dig Liver Dis. 2017;49:308–11.
24. Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. Am J Med. 2003;115:111–4.
25. Corley DA, Jensen CD, Quinn VP, Doubeni CA, Zauber AG, Lee JK, et al. Association between time to colonoscopy after a positive fecal test result and risk of colorectal cancer and cancer stage at diagnosis. JAMA. 2017;317:1631–41.
26. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med. 1996;334:155–9.
27. de Wijkerslooth TR, Stoop EM, Bossuyt PM, Meijer GA, van Ballegooijen M, van Roon AHC, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol. 2012;107:1570–8.
28. Castiglione G, Zappa M, Grazzini G, Mazzotta A, Biagini M, Salvadori P, et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. Br J Cancer. 1996;74:141–4.
29. Guittet L, Bouvier V, Mariotte N, Vallee JP, Arsène D, Boutreux S, et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. Gut. 2007;56:210–4.
30. Levi Z, Birkenfeld S, Vilkin A, Bar-Chana M, Lifshitz I, Chared M, et al. A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate. A prospective, controlled, feasibility study. Int J Cancer. 2011;128:2415–24.
31. Nakama H, Kamijo N, Abdul Fattah AS, Zhang B. Validity of immunological faecal occult blood screening for colorectal cancer: a follow up study. J Med Screen. 1996;3:63–5.
32. Robinson MH, Marks CG, Farrands PA, Thomas WM, Hardcastle JD. Population screening for colorectal cancer: comparison between guaiac and immunological faecal occult blood tests. Br J Surg. 1994;81:448–51.
33. Petrelli N, Michalek AM, Freedman A, Baroni M, Mink I, Rodriguez-Bigas M. Immunochemical versus guaiac occult blood stool tests: results of a community-based screening program. Surg Oncol. 1994;3:27–36.
34. 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.
35. Hirai HW, Tsoi KKF, Chan JYC, Wong SH, Ching JYL, Wong MCS, et al. Systematic review with meta-analysis: faecal occult blood tests show lower colorectal cancer detection rates in the proximal colon in colonoscopy-verified diagnostic studies. Aliment Pharmacol Ther. 2016;43:755–64.
36. Graser A, Stieber P, Nagel D, Schäfer C, Horst D, Becker CR, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut. 2009;58:241–8.

37. Jouve JL, Remontet L, Dancourt V, Lejeune C, Benhamiche AM, Faivre J, et al. Estimation of screening test (Hemoccult) sensitivity in colorectal cancer mass screening. Br J Cancer. 2001;84:1477–81.
38. Portillo I, Arana-Arri E, Idigoras I, Bilbao I, Martínez-Indart L, Bujanda L, et al. Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain). World J Gastroenterol. 2017;23:2731–42.
39. Abdeljawad K, Vemulapalli KC, Kahi CJ, Cummings OW, Snover DC, Rex DK. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. Gastrointest Endosc. 2015;81:517–24.
40. East JE, Atkin WS, Bateman AC, Clark SK, Dolwani S, Ket SN, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut. 2017;66:1181–96.
41. Rex DK, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012;107:1315–29 **(quiz 1314, 1330)**.
42. Ma MX, Bourke MJ. Sessile serrated adenomas: how to detect, characterize and resect. Gut Liver. 2017;11:747–60.
43. Zorzi M, Senore C, Da Re F, Barca A, Bonelli LA, Cannizzaro R, et al. Detection rate and predictive factors of sessile serrated polyps in an organised colorectal cancer screening programme with immunochemical faecal occult blood test: the EQuIPE study (Evaluating Quality Indicators of the Performance of Endoscopy). Gut. 2017;66:1233–40.
44. Chang L-C, Shun C-T, Hsu W-F, Tu C-H, Tsai P-Y, Lin B-R, et al. Fecal immunochemical test detects sessile serrated adenomas and polyps with a low level of sensitivity. Clin Gastroenterol Hepatol. 2017;15(872–9):e1.
45. Heigh RI, Yab TC, Taylor WR, Hussain FTN, Smyrk TC, Mahoney DW, et al. Detection of colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). PLoS ONE. 2014;9:e85659.
46. Wieten E, Schreuders EH, Grobbee EJ, Nieboer D, Bramer WM, Lansdorp-Vogelaar I, et al. Incidence of faecal occult blood test interval cancers in population-based colorectal cancer screening: a systematic review and meta-analysis. Gut. 2018. https://doi.org/10.1136/gutjnl-2017-315340.