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Colorectal cancer screening with the addition of flexible sigmoidoscopy to guaiac-based faecal occult blood testing: A French population-based controlled study (Wintzenheim trial)

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ABSTRACT

Objective: To assess the feasibility, participation and neoplasia yield of adding a flexible sigmoidoscopy (FS) once in a lifetime to a colorectal cancer screening programme with guaiac-based faecal occult blood test (gFOBT).

Methods: A total of 4771 average risk residents aged 50–74 of a canton of the Haut-Rhin, a French administrative area, were invited every other year to participate in an organised screening programme with gFOBT. Of them, those aged 55–64 (1824 people) were, in addition, invited once by mail to visit their general practitioner (GP) for a screening with FS performed by a gastroenterologist.

Results: In all, 2717 people (56.9%) (95% confidence interval (CI) 55.5–58.4) were screened with one or other of the two tests or with both tests. Compliance was 56.7% (55.3–58.1) with gFOBT and 20.9% (19.1–22.8) with FS. Both tests were performed by 20.2% (18.4–22.1) of people. Compliance with FS was 1.9% in people who had not complied with gFOBT and 31.9% in people who complied. The latter was $\geqslant$50% in patients of 26 motivated GPs. The detection rate for advanced neoplasia was 17.7 per 1000 people screened (12.7–22.6) with the combined procedure, more than three times higher than that with gFOBT alone.

Conclusion: A population-based screening programme with the addition of FS to gFOBT is feasible and safe through an organisation involving GPs. The performances of the two screening tools are complementary: high compliance – low yield for gFOBT and vice versa for FS. The addition of a single FS screening in people aged 55–64 to an organised programme with biennial gFOBT in people aged 50–74 is a colorectal cancer screening option that deserves further exploration.

1. Introduction

Colorectal cancer (CRC) is the second most common cause of death from malignant disease in France and resulted in 16,865 deaths in 2005.[1] Data from cancer registries and EUROCARE-3 and -4 indicate that from the mid 1990s to early 2000 the incidence of CRC increased slightly for both sexes in France whereas mortality from CRC decreased and

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5-year relative survival improved.[1,2] In 2002, France initiated an organised population-based CRC screening programme with a biennial guaiac-based faecal occult blood test (gFOBT). The results of the first round in the administrative district of the Haut-Rhin in eastern France have been published.[3] gFOBT is simple, easy to perform, inexpensive and the only screening tool with high quality evidence obtained from randomised controlled trials (RCTs) demonstrating its efficacy to reduce CRC mortality.[4–7] However, gFOBT is not perfect. The main disadvantages are its low sensitivity[8,9] and the requirement for frequent testing, which may limit compliance and thereby effectiveness.

Indirect evidence suggests that endoscopic screening may be far more effective than FOBT screening, but results from RCTs are still awaited.[10–13] Moreover, the benefit of flexible sigmoidoscopy (FS) screening is long lasting, persisting for up to 10 years[14] or even 16 years.[15]

In theory, the combination of FOBT and FS should be more effective than either test alone since the two tests are complementary. Two thirds of interval cancers missed by screening with gFOBT in the British and Danish trials were situated within the reach of FS.[5,6] Three RCTs showed that the yield for advanced neoplasia was significantly higher (4–5-fold) with the combination than with FOBT alone.[16–18] They all assessed a once only screening with FOBT and not a programme with repeat FOBT testing. The effectiveness of the combined strategy in reducing CRC mortality has never been directly studied in a RCT, and in France, screening neither with FS alone nor with the FOBT – FS combination has been assessed.

The aim of this study was to assess the feasibility, participation rate and neoplasia yield of adding an FS once in a lifetime for people aged 55-64 years to an organised CRC screening programme with biennial gFOBT.

2. Methods

2.1. Study population

This trial was performed in the canton of Wintzenheim (18,620 inhabitants), an administrative district in the Haut-Rhin (710,000 inhabitants). All residents of this canton aged 50–74 were invited, as were all residents of Haut-Rhin, to participate in a biennial gFOBT screening programme.[3] In addition, an FS was proposed to all those aged 55–64 who had a negative gFOBT or who had not complied with gFOBT.

2.2. gFOBT screening

The design of the gFOBT screening programme has been previously described.[3] Briefly, residents aged 50–74 were invited by mail every other year to participate. A first letter invited them to visit their general practitioner (GP) for CRC screening. Three recall letters were mailed to all those who had not complied. The second recall letter was mailed along with the gFOBT itself. People with serious illness, recent CRC screening or high CRC risk were excluded. The gFOBT (Haemoccult II) was used without dietary restriction and was processed without rehydration. The test was defined as positive as soon as one slide was positive. People with a positive gFOBT were referred for colonoscopy.

2.3. FS screening invitation

A first letter was mailed at the beginning of the study to all residents aged 55–64 of the canton informing them about the trial. Then, all of them who had a negative gFOBT or had not complied with gFOBT were invited once by mail to visit their GP for FS screening. There was no recall letter. A leaflet explaining the FS procedure and the advantages and risks of adding FS to gFOBT accompanied the invitation letter. The gFOBT screening was to be performed before the FS screening. GPs were instructed to exclude from screening with FS any person with a positive gFOBT, recent digestive symptoms, recent (<5 years) colonoscopy or FS procedure, high CRC risk or serious illness. GPs were asked to try to convince eligible people to participate and to complete a questionnaire about socio-demographic characteristics and family history of CRC. The FS appointment was obtained by phone either by the GP or by the enrolled person. Written informed consent was obtained from each subject by the GP. In all, 110 GPs were involved in the study. This study was approved by the ethics committee of the University of Strasbourg.

2.4. FS procedure

Bowel preparation was limited to a single 130 ml sodium phosphate enema (Normacol®) administered by a nurse in the endoscopy suite immediately before the FS procedure. Before the examination, participants were asked to complete a questionnaire administered by a nurse asking about their knowledge about the FS procedure, its reputation and their possible fear of the examination. FS procedures were performed without sedation in a single hospital endoscopy unit by 10 senior gastroenterologists practicing in the area. The FS was undertaken with an Olympus 100 cm upper videoendoscope (GIFQ 160). The aim was to advance the endoscope to the extent that it could be achieved without causing undue pain. If the bowel preparation was inadequate, a second enema was administered in the endoscopy suite and a second examination was performed immediately thereafter. Polyps <10 mm detected during the FS were either removed or biopsied without removal at the discretion of the endoscopist. Polyps and specimens were sent for histological examination. As a screening test, FS was called positive when referral to colonoscopy was indicated, i.e. for people with polyps $\geqslant$10 mm or any neoplasia at FS and people who had a polyp that could not be biopsied or a polyp and inadequate bowel preparation. The result of each endoscopic procedure, either FS or colonoscopy, was classified according to the lesion with the worst prognosis.

The endoscopist recorded on a standard form information about adequacy of bowel preparation (rated on a 10 point scale), reach of the scope, technical adequacy and duration of the examination, characteristics of detected lesions and occurrence of immediate adverse effects. FS examination was considered technically inadequate if the depth of insertion was <40 cm or the visual inspection limited to <90% of the mucosal surface due to inadequate bowel preparation with no detection of a polyp or mass. Immediately after the examination participants were asked to answer a questionnaire administrated by a nurse asking about their discomfort

with the bowel preparation, the degree of discomfort experienced, the degree of pain expected and experienced and their satisfaction with the FS examination (all rated on a four-level scale). The same questionnaire was administrated by phone 4–6 weeks after the examination along with questions about the occurrence of any adverse effect.

2.5. Pathologic classification

Dysplasia was classified according to the revised Vienna classification of gastrointestinal epithelial neoplasia.[19] *In situ* and intramucosal carcinomas (categories 4.2 and 4.4 in the revised Vienna classification and Tis in the tumour-node-metastasis (TNM) classification) were classified as high grade dysplasia.[19,20] Advanced adenoma was defined as an adenoma $\geqslant$10 mm or with villous elements >20% or with high grade dysplasia. Cancer was defined as carcinoma invading at least the submucosa across the *muscularis mucosa* (category 5 in the revised Vienna classification)[19] and was classified according to the TNM classification.[20]

2.6. Statistical methods

The χ^2 test was used to test for statistical significance by comparisons of proportions. The significance threshold was set at 0.05.

3. Results

3.1. Participation

The first round of the biennial gFOBT screening programme had started in the canton in June 2004 and the second round in June 2006. Recruitment for the FS examinations took place between July 2006 and June 2007. Fig. 1 details participant numbers throughout the study. In all, 628 people (11.6%) were excluded from the screening programme with gFOBT: 406 for recent CRC screening, 201 for high CRC risk and 21 for serious illness. Seventy seven people (4.1%) were excluded from the FS trial: nine for recent $\leqslant$5 years FS, 11 for recent digestive symptoms, 10 for serious illness and 47 people were under guardianship and could not sign informed consent. In all, 2704 average risk people (56.7%) (95% confidence interval (CI) 55.3–58.1) had performed a gFOBT and 382 (20.9%) (19.1–22.8) an FS (Table 1). Among 1824 eligible people aged 55–64, 369 (20.2%) (18.4–22.1) had both procedures performed. The median delay between gFOBT and FS was 297 days. A total of 806 people (44.2%) (41.9–46.5) had gFOBT only and 13 (0.7%) (0.3–1.1) had an FS procedure only. The compliance with gFOBT was higher in women (59.7%) (57.7–61.6) than in men (53.5%) (51.5–55.5) ($p < 0.001$) (Table 1) but not significantly different between the older age group (60–64) and the younger (55–59). The compliance with FS was higher in men

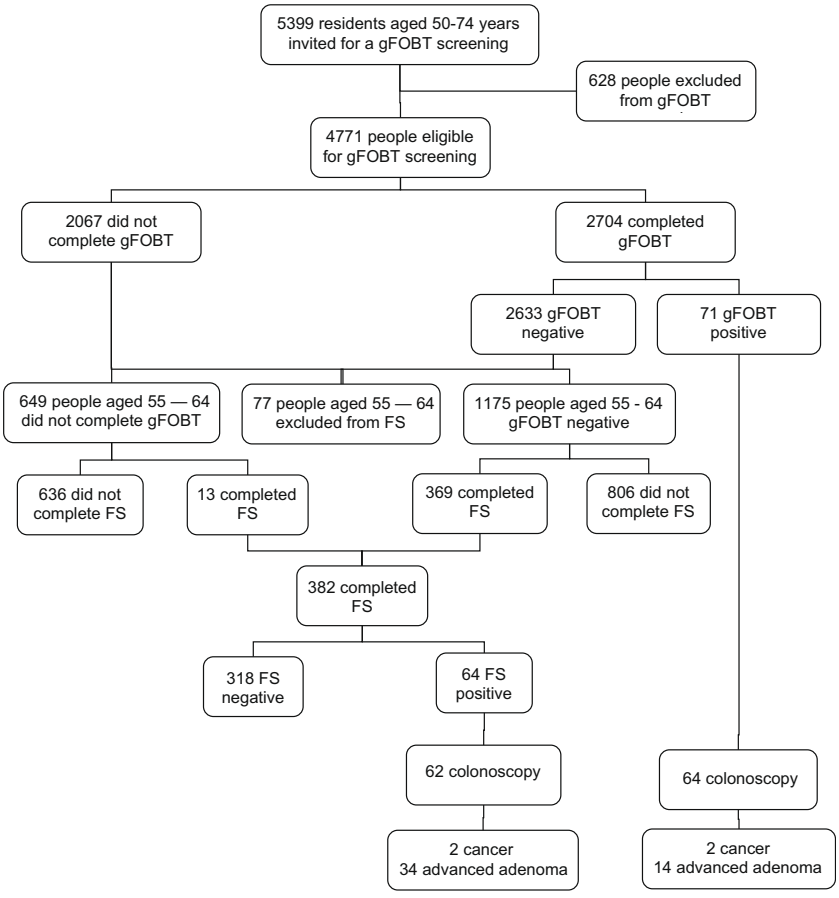

Fig. 1 – Flow diagram of the trial. FS flexible sigmoidoscopy, gFOBT guaiac-based faecal occult blood test.

Table 1 – Overall participation and diagnostic yield (most advanced lesions) of the three screening strategies: guaiac-based faecal occult blood test (gFOBT) in people aged 50–74, flexible sigmoidoscopy (FS) in people aged 55–64 and combined screening strategy with gFOBT in people aged 50–74 and/or FS in people aged 55–64.

	gFOBT			FS			Combined strategy		
	50–74			55–64			gFOBT 50–74 and/or FS 55–64		
	Men	Women	All	Men	Women	All	Men	Women	All
Eligible people	2320	2451	4771	896	928	1824	2320	2451	4771
Screened (%)	1241 (53.5)	1463 (59.7)	2704 (56.7)	213 (23.8)	169 (18.2)	382 (20.9)	1251 (53.9)	1466 (59.8)	2717 (56.9)
Positive test (%)	40 (3.2)	31 (2.1)	71 (2.6)	47 (22.1)	17 (10.1)	64 (16.8)	87 (7.0)	48 (3.3)	135 (5.0)
Colonoscopy (%)	36 (2.9)	28 (1.9)	64 (2.4)	45 (21.1)	17 (10.1)	62 (16.2)	81 (6.5)	45 (3.1)	126 (4.6)
Adenoma									
Any	16	10	26	40	17	57	56	27	83
(Per 1000 screened)	(12.9)	(6.8)	(9.6)	(187.8)	(100.6)	(149.2)	(44.8)	(18.4)	(30.5)
Advanced	7	5	12	25	7	32	32	12	44
(Per 1000 screened)	(5.6)	(3.4)	(4.4)	(117.3)	(41.4)	(83.8)	(25.6)	(8.2)	(16.2)
⩾10 mm	5	5	10	14	2	16	19	7	26
(Per 1000 screened)	(4.0)	(3.4)	(3.7)	(65.7)	(11.8)	(41.9)	(15.2)	(4.8)	(9.6)
Cancer	1	1	2	2	0	2	3	1	4
(Per 1000 screened)	(0.8)	(0.7)	(0.7)	(9.4)	(0)	(5.2)	(2.4)	(0.7)	(1.5)
Advanced neoplasia	8	6	14	27	7	34	35	13	48
(Per 1000 screened)	(6.4)	(4.1)	(5.2)	(126.8)	(41.4)	(89.0)	(28.0)	(8.9)	(17.7)
[Per 1000 eligible]	[3.4]	[2.4]	[2.9]	[30.1]	[7.5]	[18.6]	[15.1]	[5.3]	[10.1]
Proximal advanced neopl.	3	0	3	3	1	4	6	1	7
(Per 1000 screened)	(2.4)	(0)	(1.1)	(14.1)	(5.9)	(10.5)	(4.8)	(0.7)	(2.6)
Number colo/1 adv. neopl.[a]	4.5	4.7	4.6	1.7	2.4	1.8	2.3	3.5	2.6

a Number colo/1 adv. neopl. Number of colonoscopies to be performed to detect one advanced neoplasia.

(23.8%) (21.0–26.6) than in women (18.2%) (15.7–20.7) ($p < 0.01$) and in the older age group (26.2%) (23.0–29.5) than in the younger (17.6%) (15.3–19.8) ($p < 0.001$). Compliance with FS was 1.9% in people who had not complied with gFOBT and 31.9% in people having complied. The latter was ⩾50% in patients of a group of 26 GPs.

3.2. *Flexible sigmoidoscopy procedures*

Of 382 FS procedures, 340 (89.0%) were adequate, without difference between men and women. The quality of bowel preparation was rated ⩾8/10 in 74.5% of cases. A second enema was necessary in 19.7% of cases. The median depth of insertion was 60 cm and it was ⩾50 cm in 80.7% of cases, significantly more often in men (85.4%) than in women (73.4%) ($p < 0.01$). The examination was completed to the descending colon in 75.7% of cases and to the splenic flexure or beyond in 52.4% of cases. The median duration of FS examination was 7 min 42 s. No pathology specimens were removed in 288 people (75.4%) who were discharged. A further 30 people (7.9%) were discharged after pathological analysis of samples with non-significant pathology or hyperplasic polyps. In all, 159 polyps were detected during FS in 94 people. Of them, 61 (38.4%) were removed; a tissue specimen was removed in 59 (37.1%) and the other were neither removed nor biopsied. In all, 64 (16.8%) people were referred for colonoscopy. The reason for referral was a cancer or a polyp ⩾1 cm in 14 cases, the pathological diagnosis of an adenoma in 38 cases, the detection of a polyp during an incomplete examination in 6 cases and the detection of a polyp without pathological assessment in 6 cases.

3.3. *Diagnostic yield of FS screening*

The results of FS examinations are listed in Table 2. Of 64 people referred for colonoscopy, 62 (96.9%) had the examination. The most advanced lesions detected at FS and/or colonoscopy were two (0.5%) cancers, 32 (8.4%) advanced adenomas and 25 (6.5%) non-advanced adenomas (Table 1). The two cancers were a rectal cancer stage pT1N0M0 and a sigmoid colon cancer stage pT3N1M0. The detection rate for advanced neoplasia was 89.0 per 1000 people screened (60.4–117.6) (Table 1). It was threefold higher in men (126.8) than in women (41.4) ($p < 0.01$), not significantly different between the older age group and the younger. The diagnostic yield of FS screening was not significantly different between people having had a single or two previous negative gFOBTs (Table 3). Adopting any ⩾5 mm polyp as a threshold would reduce the rate of referral for colonoscopy by 35% from 16.2% to 10.5% and the detection rate for advanced neoplasia by 23.5% from 8.9% to 6.8%. Likewise, adopting any advanced neoplasia as a threshold would reduce the rate of referral for colonoscopy by 50% from 16.2% to 8.1% and the detection rate for advanced neoplasia by 26.5% from 8.9% to 6.5%.

3.4. *Diagnostic yield of gFOBT screening*

Of 2704 people aged 50–74 who completed a gFOBT, 71 (2.6%) had a positive result. Of them 64 (90.1%) had a colonoscopy. The most advanced lesions detected were two (0.07%) cancers, 12 (0.4%) advanced adenomas and 14 (0.5%) non-advanced adenomas (Table 1). The detection rate for advanced

Table 2 – Most advanced lesions detected at flexible sigmoidoscopy.

	Men	Women	Total
Screened	213	169	382
Polyps	68 (31.9%)	26 (15.4%)	94 (24.6%)
Adenoma			
Any	32 (15.0%)	15 (8.9%)	47 (12.3%)
Advanced	16 (7.5%)	6 (3.6%)	22 (5.8%)
⩾10 mm	9 (4.2%)	1 (0.6%)	10 (2.6%)
Cancer	2 (0.9%)	0 (0%)	2 (0.5%)
Advanced neoplasia	18 (8.5%)	6 (3.6%)	24 (6.3%)

Table 3 – Most advanced lesions detected at flexible sigmoidoscopy (FS) and/or colonoscopy according to the number of previous guaiac-based faecal occult blood test (gFOBT) performed.

Previous gFOBT	None	One negative	Two negative
Screened	13	179	190
FS positive	3 (23.1%)	31 (17.3%)	30 (15.8%)
Colonoscopy performed	3 (100%)	30 (96.8%)	29 (96.7%)
Adenoma			
Any	3 (23.1%)	27 (15.1%)	27 (14.2%)
Advanced	2 (15.4%)	17 (9.5%)	13 (6.8%)
⩾10 mm	1 (7.7%)	7 (3.9%)	8 (4.2%)
Cancer	0 (0%)	1 (0.6%)	1 (0.5%)
Advanced neoplasia	2 (15.4%)	18 (10.1%)	14 (7.4%)

neoplasia was 5.2 per 1000 people screened (2.5–7.9), not significantly different between men and women.

3.5. *Comparison between gFOBT and FS screening*

In the 55–64 years age group, compliance with gFOBT was more than threefold higher than that with FS (Table 4). The positivity rate was eight times higher with FS than with gFOBT. The detection rate for advanced neoplasia was more than 20 times higher in the FS group than in the gFOBT group.

3.6. *Participation and diagnostic yield of the combined strategy*

In all, 2717 (56.9%) (55.5–58.4) people were screened with one or other of the two tests or with both tests (Table 1). The positivity rate and the number of colonoscopies performed with the combined strategy were twofold higher than those with the gFOBT only screening strategy. The detection rate for advanced neoplasia was 17.7 per 1000 people screened (12.7–22.6), 3.5 times higher with the combined strategy than with the gFOBT strategy. The number of colonoscopies to perform to detect one advanced neoplasia was 4.6 for gFOBT screening, 1.8 for FS screening and 2.6 for the combined screening strategy.

3.7. *Participants' experience*

Of 380 people who answered the questionnaire before the FS examination, 23.0% reported moderate or severe anxiety about the discomfort and 24.9% about the result of the examination. Of 382 people who answered the questionnaire 4–6

Table 4 – Participation and diagnostic yield (most advanced lesions) of guaiac-based faecal occult blood test (gFOBT) and flexible sigmoidoscopy (FS) screening strategies in 1824 people aged 55–64.

	gFOBT	FS
Screened	1182 (64.8%)	382 (20.9%)
Positive test	25 (2.1%)	64 (16.8%)
Colonoscopy performed	24 (96.0%)	62 (96.9%)
Adenoma		
Any	10 (8.5[a])	57 (149.2[a])
Advanced	4 (3.4[a])	32 (83.8[a])
⩾10 mm	3 (2.5[a])	16 (4.2[a])
Cancer	1 (0.8[a])	2 (5.2[a])
Advanced neoplasia	5 (4.2[a])	34 (89.0[a])
Proximal advanced neoplasia	1 (0.8[a])	4 (10.5[a])

a Detection rate per 1000 people screened.

weeks after the examination, 5.8% reported discomfort and 1.3% great discomfort. 86.9% reported that they had experienced no pain or only mild pain during the FS examination, and 2.1% described the pain as unbearable. The FS was less painful than expected in 53.0% and more painful than expected in 8.7% of people. More women than men reported pain (17.9% versus 8.9%, $p < 0.01$) or a more painful than expected FS (13.6% versus 4.7%, $p < 0.01$). 97.1% were glad that they had the FS examination and 97.6% were ready to have it again. Of 369 people who had both tests, 89.2% said that they would, if asked to be screened again, have both tests, 7.3% would have gFOBT only, 3.3% would have FS only and 0.3% would refuse both tests.

3.8. *Adverse events of FS procedures*

There was no serious adverse event. Three (0.8%) people had a vasovagal reaction and one of them required an atropine injection. One person developed self-limited bleeding following polypectomy. The most frequent complaints after the procedure were abdominal pain (12.8%) and flatulence (12.0%).

4. Discussion

Our results show that the GP-based combined strategy is feasible and safe, producing, despite moderate compliance with FS, an advanced neoplasia yield more than threefold higher than that with gFOBT alone.

Though 56.7% of the invited people had a gFOBT, 20.9% had the FS performed; and 20.2% had both procedures. The latter rate is situated at the lowest end of the 20–51% range of participation observed in Europe.[13,16–18,21,22] Reasons for such a difference in participation rates between gFOBT and FS screening in our study are numerous. The 56.7% participation rate with gFOBT was obtained with a promotional campaign targeting the general public and after three reminders, one of them with direct mailing of the gFOBT kit. The participation after the first invitation letter was of the same magnitude with gFOBT as with FS in the screening programme in the Haut-Rhin: 26.9% in the first round[3] and 19.9% in the second round (personal data). On the contrary, the study with FS was conducted within a short period (1 year), without any reminder or promotional campaign. Though gFOBT is an established non-invasive test with the highest level evidence of efficacy on CRC mortality, FS is invasive with incompletely established evidence. Compliance with FS was penalised by the written informed consent procedure which was a restraint for both GPs and invited people. For busy GPs, selection of eligible people and filling in the questionnaire also created an extra workload. There had been no previous experience with organised FS screening in France where the perception of FS could be better. Gastroenterologists are partly responsible for the image of FS because they consider it to be an incomplete exam (N.B. misleading comparison with the single breast mammogram), pain control was not a priority until recently and FS is not financially advantageous for gastroenterologists in France.

Our results suggest that, when a lesson is learned from our pilot study (i.e. with reminders and promotional campaign and without written consent and extra workload), a $\geqslant$30% compliance rate with FS screening should be in all probability within reach in France. This rate will probably never reach the Northern Europe rates or the gFOBT rate, but it can be enhanced as demonstrated by 26 motivated GPs who had $\geqslant$50% participation rates. As was previously demonstrated by several studies, a clear recommendation from physicians is strongly correlated with patient participation in CRC screening.[23] In France, GPs play an essential role in convincing people to participate in gFOBT screening.[24,25] Moreover, with the concept of an FS once in a lifetime between 55 and 64, GPs would have about 10 years to convince their patients to participate. Our pilot study should contribute to restoring the image of FS since tolerance was good. People who had a FS can be expected to spread the word, leading to improved acceptability of FS screening in our area. Moreover, the performance of FS by trained nurses should facilitate the implementation of an FS screening programme and even increase the compliance.[26,27]

The major concern about combining FOBT with FS is the added complexity of the dual strategy and the negative effect this may have on overall participation in screening. An assessment of this effect will be forthcoming when the participation rate during the next third round of the ongoing gFOBT screening programme is known. Nevertheless, any negative effect can be expected to be quite minimal, since only 0.3% of people who had the FS procedure stated that, if asked again, they would refuse both tests.

Tolerance of the FS procedure was excellent, slightly better than that in United Kingdom (UK) flexiscope trial: only 2.1% (versus 2.7%) of people described the pain they experienced as unbearable, 87.3% (versus 79.8%) of participants experienced no pain or only mild pain and 97.7% were satisfied and ready to undergo again.[10] Reasons for such a difference might be related to the extreme attention focused on pain control in our study and to the use of an upper video-endoscope instead of a standard sigmoidoscope. We agree with Farraye et al. that screening FS is better tolerated using an upper endoscope.[28]

As in other trials, the advanced neoplasia yield was much higher with the combined strategy than with the gFOBT only strategy.[16–18,21] However, one must admit that our gFOBT detection rate was calculated after two screening rounds and that a five-round programme should result in a higher detection rate. The latter will only be available at the end of 2014. In our trial, where almost all participants had one or even two previous negative gFOBTs, the FS screening procedure gave a high rate of cancer detection (5.2 per 1000 people screened), of the same magnitude or even higher than that in FS only trials (from 2.9 to 5.4).[10–13] This result underscores the low sensitivity of gFOBT screening and the interest of adding FS to enhance yield. The high yield of FS screening in our study may be explained by the fact that the incidence of CRC in Haut-Rhin is one of the highest in Europe (www.arer68.fr) but also by the use of an upper endoscope. In our study, the splenic flexure or beyond was reached in 52.4% of cases, when it was in 8% only with a 60 cm sigmoidoscope in the study of Painter et al.[29] The upper endoscope is longer, thinner and floppier than the standard sigmoidoscope and

thus should allow a deeper intubation with minimal discomfort.[29]

The number of colonoscopies to be performed to detect one advanced neoplasia was 4.6 for gFOBT screening, 1.8 for FS screening and 2.6 for the combined screening strategy. This ratio is a good indicator of the benefit-risk ratio of a CRC screening strategy. It reflects both the yield of the screening strategy and its actual cost in terms of potential adverse events and resources' requirement. This ratio is favourable in both screening strategies with FOBT and FS. On the contrary, it is prohibitive with colonoscopy: it was 17.7 in the 50–66 year age group without family history of CRC in the Polish trial.[30]

We adopted any adenoma or any $\geqslant$1 cm polyp at FS as criteria for colonoscopy. This corresponds to standard practice in France established after a meta-analysis showed that any distal adenoma, including diminutive adenoma, is associated with an increased prevalence of synchronous proximal neoplasia.[31] These criteria resulted in a high colonoscopy referral rate of 16.8%, close to the 19.5% and 16.2% rates of the NORCCAP and PLCO trials.[11,13] Adopting any advanced neoplasia as a criterion should reduce the rate to 8.1%, close to the 7.8% of the SCORE trial.[12] In any case, criteria for colonoscopy in an organised screening programme should be determined according to the colonoscopic capabilities of the health system. The present criteria for colonoscopy resulted in an acceptable overall 5.0% colonoscopy referral rate with the combined strategy.

What is the near future of mass CRC screening programmes? Most countries implement FOBT-based programmes because FOBT is simple, cost-effective and has the highest quality evidence of efficacy to reduce CRC mortality.[4–7] gFOBT has been or will probably soon be replaced by quantitative immunochemical FOBTs (iFOBT) which offer higher participation rates and allow the choice of the positivity rate associated with an ideal balance between sensitivity and specificity.[32,33] This however doubles the positivity rate to around 5% without enhancement of the same magnitude of the diagnostic yield. Two RCTs showed that the advanced neoplasia detection rate was 3–4 times higher after screening with FS than with iFOBT.[18,34] Our results support the addition of FS to FOBT. The two tests are complementary: high compliance – low yield for gFOBT and vice versa for FS. In France, compliance with gFOBT screening is satisfactory (participation rates from 31.1% to 54.3%) but its yield remains low (cancer detection rates between 1.7 and 3.0 per 1000 people screened) (www.invs.sante.fr). However, compliance with gFOBT deteriorates with time.[35] A 4.3% decrease in crude participation rate was observed between the first and the second rounds in the Haut-Rhin (personal data) and such a decrease was observed in almost all French pilot areas (www.invs.sante.fr). The effectiveness of a FOBT CRC screening programme depends on adherence with frequent repeat testing every other year. People who do not comply with repeat testing should be encouraged to have FS screening.

The objective of an organised screening programme is to reduce CRC mortality in the greatest number of the population at the lowest cost. The adjunction of FS to FOBT, either gFOBT or iFOBT, is in our opinion a good option: FOBT screening is the way to offer a minimal but effective screening to the greatest number of people and FS screening is the way to offer the opportunity of a better protection or an alternative to FOBT to those who want it. The advantage is to combine a cancer detection test that primarily detects cancer early according to the recent American joint guideline and a cancer prevention test that can detect cancer early and also can detect adenomatous polyps, thus providing a greater potential for prevention through polypectomy.[36] Moreover, a cost-effectiveness analysis showed that the combination was the most cost-effective of all screening options[37] and a mathematical model suggested that 21% more CRC deaths would be prevented if FS was added to an FOBT screening programme.[38]

Some might consider CRC screening with FS obsolete when analysing time trends that reveal during last decades a steady increase in the proportion of proximal cancers in most Western countries (the explanations seem to be multifactorial, reduction in distal CRC incidence, ageing, lifestyle modifications...).[39–41] Such is not the case. The efficacy of FS screening to reduce distal CRC mortality has been demonstrated by several case control and cohort studies, the magnitude of the reduction remains to be determined by the results of RCTs.[14,42–46] Thus, when it is now well established that distal CRC is preventable, the question whether proximal CRC is preventable remains unanswered. Indeed, several recent studies have questioned the effectiveness of colonoscopy in reducing proximal CRC mortality.[47–49] The possible explanations for this lack of effectiveness are numerous: proximal neoplasia may be more likely to be either missed or fast-growing than distal neoplasia.

The strength of our study is that it is the first assessing CRC screening with the addition of FS to gFOBT in an ongoing population-based organised biennial gFOBT programme in average risk people instead of a once only combined procedure screening. This study had some limitations. The study population was small and FS exams were performed in a single hospital endoscopy unit. Both feasibility and acceptability of the combined strategy have to be confirmed on a larger scale with performance of FS exams in all existing facilities, either private or public, to get close to 'real world' conditions. However, the size of the study population was enough to demonstrate with adequate statistical power the considerable increase in diagnostic yield between the gFOBT and combined strategies.

5. Conclusion

It is probably too early to conclude that a single FS screening in people aged 55–64 is worth adding to an organised programme with biennial gFOBT in people aged 50–74. There are still two steps to pass. First, we have to wait for the results of RCTs on FS screening, but no doubt that they will demonstrate the efficacy of FS screening to reduce CRC mortality. Second, our results with the combined screening strategy have yet to be confirmed with a longer follow up and a cost-effectiveness analysis on a large population-based scale. It is the authors' conviction that the combined screening strategy is a right track that deserves further exploration.

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Conflict of interest statement

The upper video-endoscope was lent by Olympus France. Forceps were provided by Boston-Scientific France. Enemas were provided by Norgine Pharma. A grant was received from SKD France. B.D., I.G. and P.P. are employees of ADECA Alsace, the association in charge of the organised screening programme in the Haut-Rhin.

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