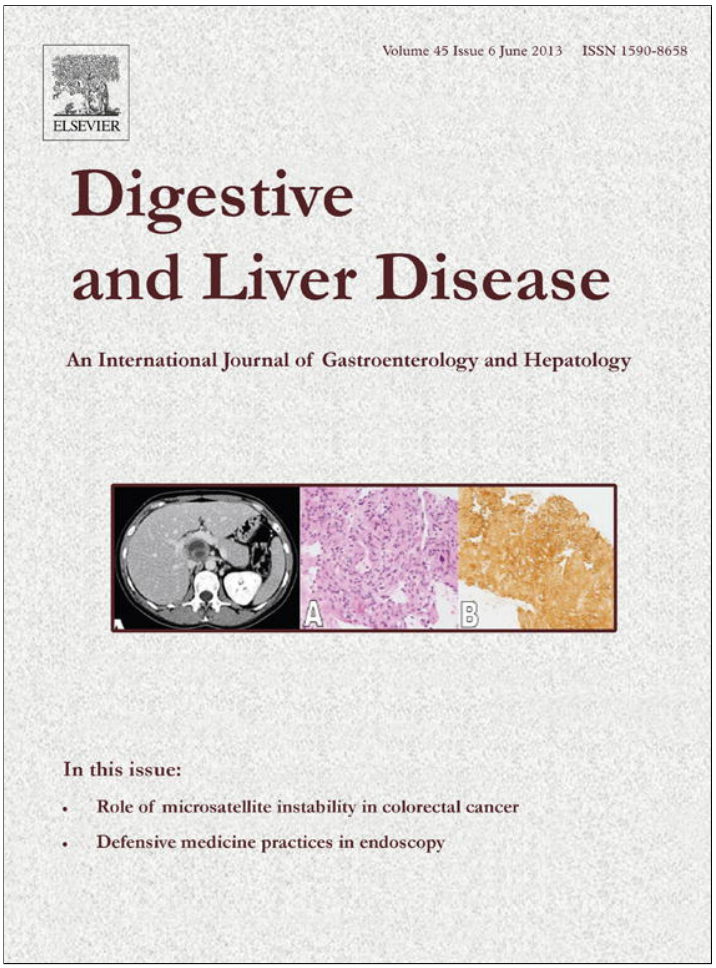

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Alimentary Tract

Harms of colonoscopy in a colorectal cancer screening programme with faecal occult blood test: A population-based cohort study

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ABSTRACT

Background and aims: To assess the harms of colonoscopy in a real world colorectal cancer screening programme with faecal occult blood test.
Methods: Retrospective cohort study of all colonoscopies performed in patients aged 50–74 for a positive guaiac-based faecal occult blood test between September 2003 and February 2010 within the screening programme in progress in Alsace (France). Adverse events were recorded through prospective voluntary reporting by gastroenterologists and retrospective postal surveys addressed to persons screened and their general practitioners.
Results: Of 10,277 colonoscopies, 250 adverse events were recorded, 48 (4.7‰, 95% CI 3.4–6.0) of them being moderate or severe, mainly 10 (1.0‰, 95% CI 0.4–1.6) perforations and 31 (3.0‰, 95% CI 2.0–4.1) bleeding. 91.7% of moderate and severe adverse events were the result of a therapeutic procedure. Of 103 serious adverse events, eight (7.8%) were considered preventable. Gastroenterologists reported 52.2% of moderate and severe adverse events. A mild adverse event or an incident was reported in up to 97.0‰ (95% CI 83.2–110.7) colonoscopies.
Conclusion: The harms of colonoscopy were underestimated in all randomized controlled trials on colorectal cancer screening with faecal occult blood test. They are greater in a real world programme, estimated at 7.5 major and 100 minor adverse events per 1000 colonoscopies.

1. Introduction

Colorectal cancer (CRC) is the second most common cause of death from malignant disease in Europe, resulting in 212,000 deaths in 2008 [1]. Four randomised controlled trials (RCTs) have demonstrated the efficacy of screening with guaiac-based faecal occult blood test (gFOBT) on CRC mortality [2–5]. Many countries, including France, have thus launched gFOBT-based CRC screening programmes [6]. However, the benefit of CRC screening is modest, estimated between 1.2 and 1.6 death avoided per 1000 persons invited in the three RCTs with biennial non rehydrated gFOBT [4,5,7]. Moreover, the harm of these programmes has been insufficiently evaluated [3,8–10].

Would the effectiveness of a CRC screening programme be measured by the reduction of all-cause or CRC specific mortality, both measures are obtained late after more than 10 years of follow up. Surrogate short term endpoints are necessary for an earlier estimation of the benefit-risk balance. We, and others, have demonstrated that participation and yield (i.e. benefit) obtained in RCTs are reproducible in the real-world through organized population-based programmes [11–13]. But, how about risk? Real-world data is needed. As stated by Sir Muir Gray "All screening programmes do harm, some do good as well".

Our aim was to assess the harms of colonoscopy in a real world CRC screening programme with gFOBT.

2. Methods

We retrospectively analysed the complications of all colonoscopies performed in a cohort of residents undergoing a colonoscopy for a positive gFOBT between September 2003 and February 2010 within the population-based CRC screening programme organized in Alsace, a region in eastern France.

2.1. gFOBT screening programme

Alsace (1.8 million inhabitants) is composed of two administrative areas, Haut-Rhin and Bas-Rhin. A gFOBT CRC screening

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programme was initiated in both areas, in September 2003 and December 2007 respectively, as part of the French national programme. Its design has been previously described [11]. Briefly, residents aged 50–74 (0.5 million persons) 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 (Hemoccult II). People with serious illness, recent CRC screening or high CRC risk were excluded. Faecal material was assessed from two samples from each of three consecutive stools. The test was defined as positive if at least one slide was positive. People with a positive gFOBT were referred for colonoscopy.

Colonoscopies were performed by all the certified endoscopists practicing in Alsace. As usual in France, they were performed by gastroenterologists and most (95%) under sedation/anaesthesia provided by an anaesthetist. Diagnostic colonoscopy was defined as colonoscopy without intervention or with cold biopsy whereas therapeutic colonoscopy corresponded to any procedure with polypectomy, regardless the technique. The result of each colonoscopy was classified according to the lesion with the worst prognosis. Cancer was defined as carcinoma invading at least the submucosa across the *muscularis mucosa*, advanced adenoma as an adenoma $\geq$10 mm or with a villous component >20% or with high-grade dysplasia, and advanced neoplasia as a cancer or an advanced adenoma.

2.2. Adverse events (AEs) recording

AEs of all initial colonoscopies were recorded; those of surveillance colonoscopies were excluded. AEs were searched using three sources: gastroenterologists were asked to voluntarily and prospectively report AEs, and three retrospective postal surveys were conducted in July 2007, April 2009 and March 2010 directed towards all people who had undergone a colonoscopy and their GPs. All received a mailed questionnaire with a pre-paid envelope for reply. The questionnaire asked for any colonoscopy-related AE and its consequences: medical consultation, hospital admission, repeat endoscopy, blood transfusion, surgery. The investigators reviewed all AEs with a phone call to the patient, the GP and/or the gastroenterologist. All colonoscopy reports and hospital charts concerning serious AEs were reviewed.

2.3. AEs classification

AEs were classified according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon and the National Institutes of Health (NIH) criteria (Fig. 1A) [14,15]. All events definitely, probably and possibly related to colonoscopy occurring within 30 days of the colonoscopy were taken into account, whereas events unlikely related were not [14]. An event that prevented completion of the planned procedure and/or resulted in admission to hospital, prolongation of existing hospital stay, another procedure needing sedation/anaesthesia, or subsequent medical consultation was considered an AE [14]. Unplanned events that did not interfere with completion of the planned procedure or change the plan of care were considered incidents [14]. Serious AEs were defined as any AE that resulted in death; was life-threatening; resulted in inpatient hospitalization or prolongation of existing hospitalization; resulted in a persistent or significant disability/incapacity; or based upon appropriate medical judgement, might jeopardize the subject's health and might require medical or surgical intervention to prevent one of the other outcomes listed in this definition [15]. Preventability of an AE was assessed using a six-point scale, ranging from no evidence (1) to virtually certain evidence of preventability (6). AEs were considered preventable for a score of four or more [16]. The judgement on causality, severity and preventability was made by the two first authors (BD and IG).

2.4. Statistical methods

We calculated the incidence of complications per 1000 colonoscopies and 95% confidence intervals (95% CI) using the binomial distribution. The Chi^2 test was used to test for statistical significance by comparisons of proportions. All statistical tests were 2-sided. The significance threshold was set at 0.05. Backward logistic regressions were used to study the association between incidence of serious AEs and risk factors of interest, including endoscopist, age, sex, type of colonoscopy, and colonoscopy yield, and for therapeutic colonoscopies only, size of largest polypectomy and number of polypectomies.

(A)

	NIH	ASGE	Our proposal
Procedure aborted	-	mild	minor
Postprocedure medical consultation	-	mild	minor
Unplanned endotracheal intubation	-	mild	minor
Unplanned hospital admission or prolongation of hospital stay			
1 night	serious	mild	minor
2 – 3 nights	serious	mild	major
4 – 10 nights	serious	moderate	major
> 10 nights	serious	severe	major
Intensive Care Unit admission for 1 night	serious	moderate	major
Intensive Care Unit admission for > 1 night	serious	severe	major
Life threatening adverse event	serious	-	major
Transfusion	serious	moderate	major
Repeat endoscopy / interventional radiology or treatment for integument injuries	serious	moderate	major
Surgery	serious	severe	major
Permanent disability	serious	severe	major
Death	serious	fatal	major

(B)

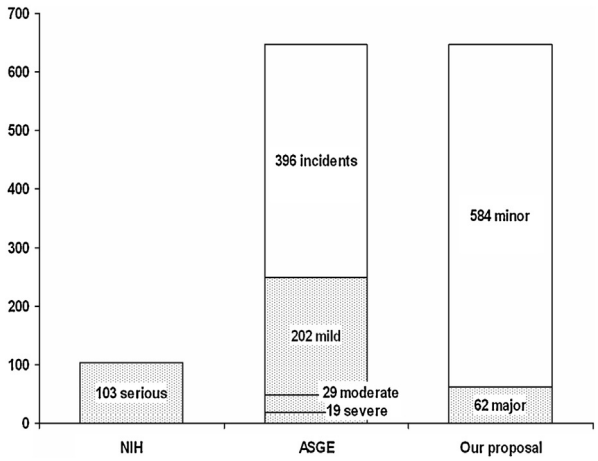

Fig. 1. (A) Classifications of adverse events according to National Institutes of Health (NIH) criteria and American Society for Gastrointestinal Endoscopy (ASGE) lexicon. We propose to define major adverse events as moderate and severe adverse events according to ASGE lexicon with the addition of life threatening events (such as deep vein thromboses) and adverse events leading to unplanned hospital admission >1 night and (B) present series.

Table 1
Classification of complications and their severity according to National Institutes of Health (NIH) criteria and American Society for Gastrointestinal Endoscopy (ASGE) lexicon.

	Diagnostic colonoscopies $n = 5288$ Number (‰) [95% CI]	Therapeutic colonoscopies $n = 4989$ Number (‰) [95% CI]	All colonoscopies $n = 10,277$ Number (‰) [95% CI]
Incidents (ASGE)	188 (35.6) [30.6–40.5]	208 (41.7) [36.1–47.2]	396 (38.5) [34.8–42.3]
Adverse events (ASGE)	79 (14.9) [11.7–18.2]	171 (34.3) [29.2–39.3]	250 (24.3) [21.3–27.3]
Mild	75 (14.2) [11.0–17.4]	127 (25.5) [21.1–29.8]	202 (19.7) [17.0–22.3]
Moderate	0 (0) [0–0]	29 (5.8) [3.7–7.9]	29 (2.8) [1.8–3.8]
Severe	4 (0.8) [0.0–1.5]	15 (3.0) [1.5–4.5]	19 (1.8) [1.0–2.7]
Moderate and severe adverse events (ASGE)	4 (0.8) [0.0–1.5]	44 (8.8) [6.2–11.4]	48 (4.7) [3.4–6.0]
Bleeding	0 (0) [0–0]	31 (6.2) [4.0–8.4]	31 (3.0) [2.0–4.1]
Perforation	2 (0.4) [0–0.9]	8 (1.6) [0.5–2.7]	10 (1.0) [0.4–1.6]
Other complications	2 (0.4) [0–0.9]	5 (1.0) [0.1–1.9]	7 (0.7) [0.2–1.2]
Serious adverse events (NIH)	11 (2.1) [0.9–3.3]	92 (18.4) [14.7–22.2]	103 (10.0) [8.1–11.9]

3. Results

3.1. Colonoscopies and yield

Depending on administrative area and screening round, 45.0–54.3% of people invited were screened. A total of 10,277 colonoscopies were performed by 113 gastroenterologists in 10,024 persons (mean age 62.7 years; SD 7.0). Age and sex distribution of people having undergone a colonoscopy is presented in Appendix A. The rate of therapeutic colonoscopies was 48.5%. The positive predictive value was 6.3% for cancer, 29.8% for advanced neoplasia and 43.6% for neoplasia. The estimated false-positive rate was 2.8% for cancer and 2.3% for advanced neoplasia.

3.2. Sources of information

Of 1523 GPs, 72.8% answered the postal surveys and gave information about 6256 (60.9%) colonoscopies. A total of 6645 people answered the surveys concerning 6840 (66.6%) colonoscopies. The median delay between surveys and colonoscopies was 11.4 months (IQR 6.2–22.7).

3.3. Adverse events (Fig. 1B)

Overall and according to the ASGE lexicon, 250 (24.3‰ colonoscopies) AEs were recorded in 249 patients. They were classed as mild ($n = 202$, 80.8%), moderate ($n = 29$, 11.6%) and severe ($n = 19$, 7.6%) (Table 1). The rate of moderate and severe AEs was 4.7‰ (95% CI 3.4–6.0), 8.8‰ for therapeutic and 0.8‰ for diagnostic colonoscopies ($p < 0.001$) (Table 1). No death occurred. 103 AEs (10.0‰, 95% CI 8.1–11.9) were serious according to the NIH classification (Table 2) [17–22].

During the study period, 3.0% of gFOBTs were positive and 90.4% of people having a positive gFOBT had a colonoscopy so the rate of moderate and severe AEs was 0.13 per 1000 gFOBTs. When limiting our analysis to the three first rounds of the screening programme in the Haut-Rhin, 236,599 persons were invited, 134,153 (56.7%) completed at least one FOBT and 7675 (5.7%) had a positive test. A total of 7090 colonoscopies were performed in 6907 persons. 24 moderate and severe AEs were recorded, that is a rate of 3.4 (95% CI 2.0–4.7) per 1000 colonoscopies and 0.18 (95% CI 0.11–0.25) per 1000 persons screened. One moderate or severe AE was encountered for 13.2 cancers and 62.3 advanced neoplasia detected.

In univariate analysis, the rate of moderate and severe AEs increased significantly with colonoscopy yield: 0.7‰ without neoplasia, 5.8‰ with non-advanced neoplasia and 11.7‰ with advanced neoplasia ($p < 0.001$). Logistic regression analyses (Table 3) showed that polypectomy and advanced neoplasia were associated with higher odds of serious AEs. Endoscopist, age and sex were not significant factors. Large polypectomy was the strongest risk factor for a serious AE in patients having a therapeutic colonoscopy.

The rate of moderate and severe AEs did not vary according to the delay between postal surveys and colonoscopies, but varied depending on the type and number of sources of information. It reached 5.4‰ (95% CI 3.2–7.6) in the subset of 4277 colonoscopies with three sources available. In this subset, it was 2.8‰ when considering the GP or the gastroenterologist as only source and 5.1‰ with the patient as only source ($p < 0.001$). In this subset, the GPs and gastroenterologists had reported 52.2% of moderate and severe AEs and the patients 95.7%.

Serious AEs resulted in hospitalization in 98 cases: overnight admission ($n = 45$), stay of two or three days ($n = 20$) and stay >3 days ($n = 33$) (mean 4.1 days; SD 6.2). Eight (7.8%) serious AEs were

Table 2
Serious adverse events (National Institutes of Health criteria).

	Our series $n = 10,277$ colonoscopies Number (‰) [95% CI]	Literature ‰ range (ref)
Bleeding	64 (6.2) [4.7–7.7]	0.3–6.4 (17)
Perforation	10 (1.0) [0.4–1.6]	0.1–3.0 (17,18)
Post-polypectomy syndrome	5 (0.5) [0.1–0.9]	0.03–1.0 (17)
Abdominal pain	9 (0.9) [0.3–1.4]	–
Diverticulitis	1 (0.1) [0.0–0.3]	0.2–0.8 (17,19)
Cardiovascular events	8 (0.8) [0.2–1.3]	0.8–20.0 (20,21)
Infectious complications	4 (0.4) [0.0–0.8]	–
Acute urinary retention	2 (0.2) [0.0–0.5]	–
Total	103 (10.0) [8.1–11.9]	2.0–9.5 (19,22)

Table 3
Logistic regression analyses of risk factors for serious adverse events (National Institutes of Health criteria).

Variable	Odds ratio (95% CI)	p Value
All colonoscopies		
Type of colonoscopy		
Diagnostic	1.0	
Therapeutic	3.36 (1.49–7.61)	0.004
Colonoscopy yield		
No neoplasia	1.0	
Non advanced neoplasia	2.13 (0.83–5.46)	0.1
Advanced neoplasia	5.45 (2.48–11.99)	<0.0001
Therapeutic colonoscopies		
Number of polypectomies		
One	1.0	
Several	1.65 (1.02–2.68)	0.04
Size of largest polypectomy		
<10 mm	1.0	
10–19 mm	7.29 (2.34–22.70)	0.0006
>19 mm	24.03 (7.50–77.02)	<0.0001

Table 4
Incidents reported (American Society for Gastrointestinal Endoscopy lexicon).

Incident	Number (incidence ‰) [95% CI]
Abdominal pain	107 (10.4) [8.4–12.4]
Abdominal discomfort	99 (9.6) [7.7–11.5]
Diarrhoea/constipation	47 (4.6) [3.3–5.9]
Bloating	62 (6.0) [4.5–7.5]
Self-limited bleeding	28 (2.7) [1.7–3.7]
Miscellaneous	53 (5.2) [3.8–6.5]
Total	396 (38.5) [34.8–42.3]

considered preventable: one deep vein thrombosis in a patient on anticoagulant therapy and seven haemorrhages.

3.4. Perforations

Ten perforations, all severe and treated surgically, were recorded that is a rate of 1.0‰ colonoscopies (95% CI 0.4–1.6), 0.4‰ for diagnostic and 1.6‰ for therapeutic colonoscopies (Table 1). Seven perforations were caused by polypectomy and four occurred during a second colonoscopy performed by an "expert" for a large polyp which a first endoscopist had been unable to remove. All polyps were large measuring 15–30 mm. Two perforations were caused by mechanical disruption of the sigmoid colon wall due to the progression of the colonoscope and one by barotrauma, situated in the caecum.

3.5. Haemorrhage

In all, 97 haemorrhages were recorded, 28 were classified as an incident and 69 as an AE. Severity was moderate in 25 (36.2%) and severe in six (8.7%), giving a 3.0‰ (95% CI 2.0–4.1) rate of moderate or severe haemorrhages, 0‰ for diagnostic and 6.2‰ for therapeutic colonoscopies (Table 1). Bleeding was immediate after polypectomy and treated successfully during colonoscopy in 24 cases leading to an overnight admission for surveillance. It was delayed in 27 (39.1%) cases (mean delay 4 days, SD 3). It required blood transfusion in 13 cases, iterative endoscopy in 29 (with an endoscopic treatment in 17), intensive care unit admission in four and surgical treatment in two.

3.6. Other gastrointestinal adverse events

Four postpolypectomy syndromes (transmural burn and localized peritonitis without perforation) and one diverticulitis were managed conservatively. One focal peritonitis was caused by endoscopic tattooing of a polyp cancer with India ink and was treated surgically. Nine people suffered abdominal pain after colonoscopy and were admitted for one night for surveillance.

3.7. Other adverse events

Eight (0.8‰, 95% CI 0.2–1.3) serious cardiovascular complications were encountered: one myocardial infarction, one pulmonary embolism, one hypertension and two dysrhythmia. Three deep vein thromboses occurred, one of them in a patient on anticoagulant therapy.

3.8. Mild adverse events and incidents

Overall, 396 (38.5‰) incidents were recorded (Table 4), so that the rate of mild AEs and incidents was 58.1‰ (95% CI 53.6–62.6). Among people who answered the patient's survey, this rate reached 97.0‰ (95% CI 83.2–110.7) in the subset of 1784 people interviewed within six months after their colonoscopy, and was significantly higher than in those interviewed later (80.2‰, 95% CI 72.5–87.8) ($p = 0.03$).

4. Discussion

4.1. Main findings

The harm caused by colonoscopies was estimated in our programme at 10.0 serious AEs and 24.3 AEs per 1000 colonoscopies depending on the classification adopted. Most were mild, so the rate of moderate and severe AEs was 4.7 per 1000 colonoscopies. In contrast, mild AEs and incidents were frequent, reported in up to 97.0‰ of procedures. There was a strong correlation between harm and colonoscopy yield: 91.7% of moderate and severe AEs resulted from therapeutic procedures and their frequency increased from 0.7‰ procedures displaying no neoplasia to 11.7‰ procedures displaying advanced neoplasia. Most were considered not preventable. Our bleeding rate was 3.0‰ for moderate and severe bleedings, high rate related to the high large polyp burden of gFOBT positive patients [11]. It was 6.2‰ therapeutic colonoscopies, within acceptable limits set at less than 10‰ by some guidelines [23,24]. Likewise, our 1.0‰ rate of perforation was within limits set at less than 1‰ [23,24]. Of these perforations, 70% were caused by large polypectomies and almost inevitable.

4.2. Comparison with other studies

Whereas our complication rates were similar to those reported in recent series and reviews (Table 2), the harm caused by colonoscopies was greater in our population-based gFOBT CRC screening programme than in RCTs [17–22]. The latter reported 0–4.7 AEs per 1000 colonoscopies [2,3,25–27] and we found 10.0 serious AEs and 24.3 AEs per 1000 colonoscopies [14,15]. Why such a difference? Mainly because the NIH and ASGE classifications overestimate clinically significant AEs while RCTs underestimated them for several reasons: lack of standards for defining, classifying, searching and recording complications; non-negligible number of gFOBT positive people not explored by colonoscopy (28.1% in the Nottingham trial); and performance of colonoscopies by few experts.

4.2.1. AEs nomenclature (Fig. 1A and B)

The ASGE lexicon proposes a standardized nomenclature for AEs, but some criteria are open to criticism [14]. One of the criteria to differentiate incidents from AEs, i.e. a post procedure medical consultation, is subjective as it depends on the patient and health system (accessibility of GP or gastroenterologist, cost and reimbursement of consultation fee). In our study, this criterion was the only one involved in classifying 136 events (54.4%) as AEs. Besides, a hospital admission >3 nights is one of the criteria to classify AEs as moderate, whereas we would consider >1 night more suited. Finally, deep vein thrombosis is classified as mild AE, but should probably be considered as moderate because it is life threatening and requires a lengthy treatment. Applying these modifications, 14 AEs would be classified moderate instead of mild, giving a total of 62 (6.0‰, 95% CI 4.5–7.5) major AEs in our whole study and 32 (7.5‰, 95% CI 4.9–10.1) major AEs in the subset of 4277 colonoscopies with three sources of information available. The concept of serious AE is useful as it is used in all research studies and allows comparisons between different disciplines [15]. However, 23.3% of our AEs were classified serious only because of an overnight admission for surveillance after a bleeding successfully managed during colonoscopy. We would prefer calling these AEs minor. Considering the limitations of existing classifications and placing our priority on comparison with RCTs, we created a group of major AEs as defined

above and focused our results on the 7.5‰ rate derived from the subset of colonoscopies with three sources available.

4.2.2. Sources of information

Depending on the type and number of information sources, our rate of moderate and severe AEs varied from 3.1‰ (gastroenterologist alone) to 5.4‰ (three sources). The gastroenterologists, often unaware of delayed complications, had reported 52.2% of them. Others have shown that studies that rely on voluntary reporting underestimate actual complication rates [28]. AEs are more prevalent provided they are actively looked for in the patient population [28,29]. Patients were not contacted in RCTs. In our opinion, a patient survey should be routine practice for quality assessment in any CRC screening programme.

4.2.3. Endoscopic competence and technique

In the four RCTs, the colonoscopies were performed by a very limited number of expert endoscopists, an information not published before except for the Minnesota trial [2–5]. In the Nottingham and Funen trials almost all colonoscopies were performed by one expert surgeon [3,4]. In our study, colonoscopies were performed by all certified community gastroenterologists practicing in the area. A difference in endoscopic competence is plausible to explain our higher AEs rate, but again, it is impossible to compare AEs rates between programmes without common rules for their measurement. Colonoscopy technique greatly evolved since the eighties–nineties, years of the RCTs, towards more comfort, safety and ability to remove large lesions so that complication rates can hardly be compared. On one hand, AEs could be expected to be more prevalent today with increased risks of cardiopulmonary AEs related to sedation and of gastrointestinal AEs related to endoscopic mucosal resection of large neoplasia. On the other hand, recent haemostasis and suture techniques allow endoscopic management of complications. However, all perforations and two haemorrhages were managed surgically in our study, providing evidence that improvements in endoscopic management of complications reported by some experienced centres are not widely available in the real world. In addition, the RCTs did not report rates of referral for surgery for large polyps, hampering any comparison.

4.2.4. Generalizability

Our findings question the generalizability of results of RCTs concerning the harms of colonoscopy in a gFOBT screening programme and suggest that their low rates of AEs can hardly be reproduced in the real world. Of four RCTs and one controlled trial, four reported their major AEs (the Funen trial did not) [2,25–27]. None specified the classification used, the way AEs were searched, and AEs other than major gastrointestinal events. The Nottingham trial is the only that can be compared [4,26]. The colonoscopy rates of the Minnesota (28% and 38%) and Göteborg (0.8%) trials are too different of those of usual gFOBT screening programmes to be compared [2,5]. The Burgundy trial did not encounter a single AE but reported severe AEs only and relied on endoscopists' reports only [27]. Our rate of 7.5‰ major AEs was not significantly different of that of 4.7‰ reported by the Nottingham trial, which was underestimated [4,26]. The only other real world data available to date come from the National Health Service (NHS) Programme where the same ASGE lexicon gave a rate of moderate and severe AEs of 2.6‰, significantly lower than ours [30]. Again, this could be explained by differences in measurement methods or in endoscopic competence. Only a few accredited endoscopists were involved in the NHS Programme.

4.2.5. Preventability

Few serious AEs (7.8%) were considered preventable. We found a similar 10% rate in a previous study [31]. Some AEs are preventable with the help of a quality improvement programme, e.g. with proper management of anticoagulant and antiplatelet therapy, but most seem to be almost inevitable. Even, the judgement on preventability of bleeding after polypectomy of a large pedunculated polyp is rather subjective and one can question whether a detachable snare should be systematically used. Their use is not mandated in the ASGE guidelines [23]. Besides, one could consider that our rate of preventable AEs is underestimated as some AEs related to removal of large polyps could have been avoided if the endoscopists had adopted an alternative approach such as referral to an expert for endoscopic removal or to a surgeon for surgical removal.

4.3. Strengths and limitations of the study

The population-based setting, with direct interviews of persons screened, is the main strength of our study, the first designed to assess the harms of colonoscopy in a real-world FOBT CRC screening programme. Our study is not without limitations. A third of people did not answer the patients' survey and we could not analyse hospitalization claims for the period, so that one cannot rule out that AEs were missed. Despite this, a reliable estimate of the actual rate of major AEs could be derived from the subset of 4277 procedures with three sources of information available that is 7.5‰. The median delay between postal surveys and colonoscopies was long, nearly a year. Since the rate of moderate and severe AEs did not differ according to this delay we may estimate that very few were missed. In contrast, the rate of mild AEs and incidents increased with shorter delays, so that 97.0‰ probably underestimates the actual rate. Others found that phone interviews conducted 30 days after colonoscopy allowed detecting minor complications in up to 34% of colonoscopies [32]. Finally, we did not assess all the harm of CRC screening with gFOBT: false negative results (interval cancers), AEs of surveillance colonoscopies and treatment, mis- and over-diagnosis, over-treatment, over-surveillance, anxiety and other inequalities generated by the screening programme.

4.4. Future research

Future research should be directed at measuring the whole range of AEs of real-world CRC screening programmes and searching means to minimize them. The overall harm of CRC screening has not been correctly assessed yet [8,10]. At a time when many countries are planning for widespread CRC screening programmes, there is an urgent need for an international consensus on standardized indicators for the assessment of the benefit-risk balance of screening strategies and programmes. The definition of AEs and a classification of their severity should be standardized along with the minimal procedure for their search through an international multidisciplinary multisociety consensus.

5. Conclusion

The harms of colonoscopy were underestimated in all RCTs on gFOBT CRC screening. They are greater in our real-world programme than in all RCTs but the British. The invited population should be informed that the complication rate of colonoscopy is around 7.5‰ major and 100‰ minor AEs. These results reinforce the imperious necessity for any screening programme to incorporate a rigorous quality assurance programme for all steps of the process designed to evaluate and minimize harm. One must acknowledge that the French programme lacks quality standards for colonoscopy such as those of the British programme or the ASGE [23,24]. Our results do not question the benefit of gFOBT screening, but indicate that the price to be paid is higher in the real world than stated in most RCT reports so that its benefit-risk ratio is more balanced than usually appreciated. When applying to 100,000 people

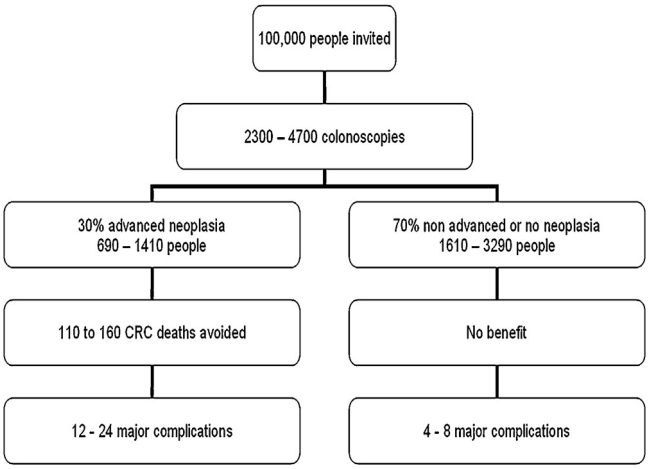

Fig. 2. Flow diagram of a colorectal cancer screening programme with biennial guaiac-based faecal occult blood test concerning people aged 50–74 years after six or seven rounds.

the results of the three trials similar to our programme, that is a 2.3–4.7% cumulative rate of colonoscopies and an absolute reduction of 1.1–1.6 CRC death per 1000 persons invited, along with our AEs rate, we would expect to avoid after six or seven rounds 110–160 deaths from CRC at the cost of 16–32 major AEs [4,7,27]. A finer analysis shows that people having a colonoscopy split into two groups: a group of 30% with advanced neoplasia who most likely would receive all the benefits of screening at the cost of 12–24 major AEs; and another group of 70% without advanced neoplasia who would suffer 4–8 major AEs without any benefit (Fig. 2).

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Conflict of interest

No competing interests to declare.

List of abbreviations

AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; CRC, colorectal cancer; gFOBT, guaiac based faecal occult blood test; GP, general practitioner; NHS, National Health Service; NIH, National Institutes of Health; RCT, randomized controlled trial.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2013.01.006.

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