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par

LATOUR Chloé

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Interventions augmentant la participation au dépistage du cancer colorectal par recherche de sang dans les selles : une revue systématique des études interventionnelles randomisées contrôlées.

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Président : Monsieur le Professeur Rémy SENAND

Directeur de thèse : Monsieur le Docteur Cédric RAT

Membres du Jury : Madame le Docteur Corinne POGU

Monsieur le Docteur Jean-Michel NGUYEN

PREFACE

Ce travail a débuté en raison de l'intérêt que j'ai porté à l'étude IDLN, une étude d'intervention ciblant la participation au dépistage du cancer colorectal, qui était en cours de mise en place à Nantes en 2014. Dans le contexte du changement de test de dépistage en France (le test au gaiac (gFOBT) laissant place au test immunologique), la mise en œuvre de cette étude a été repoussée et la possibilité pour moi de travailler sur les données de cette étude d'intervention a disparu. Je me suis alors orientée vers une revue systématique de la littérature cherchant à identifier des études de même nature, c'est-à-dire des études interventionnelles visant à augmenter la participation des patients au dépistage du cancer colorectal. Ce travail s'est attaché à respecter les recommandations internationales. Dans ce contexte, cette revue est rédigée en anglais. Je présente mes excuses dès lors que la rédaction en anglais n'est pas un format habituel, mais le choix des recommandations issues de la Cochrane Collaboration et la nature de ce travail de revue ont rapidement amené à travailler et à écrire en anglais. Ceci augmentait la cohérence interne du travail, assurant une meilleure adéquation des termes lus et rapportés, et une brièveté dans l'écriture. Cette thèse a aussi constitué mon premier exercice de rédaction d'un travail scientifique.

TABLE DES MATIERES

SERMENT MEDICAL

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

REMERCIEMENTS

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A mes « chefs », auprès desquelles j'apprends la médecine : Docteur Anne-Elisabeth Rocard, Docteur Dominique El Kouri, Docteur Isabelle Gueffet.

A Alice,
A Anne,
A Pierre-Vincent,
J'adresse ce travail et ce qui en moi l'a porté.

TABLE DES ABREVIATIONS

CI : Confidence interval

CRC: Colorectal cancer

CR: Colorectal

FS: Flexible sigmoïdoscopy

GP: General practitioner

gFOBT: Guaiac fecal occult blood test

FOBT: Fecal occult blood test

FIT: Fecal immunochemical blood test

OR: Odds-ratio

RCT: Randomized controlled trial

RR: Relative-risk

vs: versus

INCREASING PATIENT UPTAKE OF FECAL TESTS FOR BOWEL CANCER SCREENING: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED INTERVENTIONAL STUDIES.

ABSTRACT

Background. International guidelines promote screening by fecal tests in asymptomatic patients having an average-risk of bowel cancer. High participation rates have demonstrated an impact on mortality reduction. However, participation does not reach recommended rates in most countries. In various countries, policymakers have experimented interventions in order to improve participation rates. We conducted a systematic review of randomized controlled studies based on interventions aiming at increasing patient uptake of fecal tests for bowel cancer screening.

Methods. Systematic review of the literature, searching Pubmed, Embase, and the Cochrane Library database, based on the Cochrane's PRISMA-P 2015 guidelines. We identified randomized controlled studies reporting interventions aiming at increasing gFOBT or FIT completion in general population or subgroups of it. Risk of bias of included studies was assessed.

Results. This review identified 24 randomized controlled studies aiming at increasing patient uptake of fecal test for colorectal cancer screening. The following interventions increase patient uptake of fecal test for CRC screening: advance notification letter, (2 studies, 3% to 7%) postal mailing (5 studies, 3.9% to 10.5%) written reminders (2 studies, 15.6% to 24.5%) telephone contacts with a navigator or a medical assistant (4 studies, 6.2% to 47.1%). Other studies assessed whether patient counseling could be provided based on video or automatized informatics software. 3 interventions demonstrated the positive impact of GP involvement. One was based on a GP signed invitation letter, one focused on GP communication training. The third one concluded to the positive impact of mailing reminders to GPs but this study included only 6 GPs and the results were not adjusted on GP effect. Inconclusive results were found for studies comparing FIT vs FOBT, and those testing effectiveness of providing written information. Concerning phone-based intervention, text messages and reminders remain a type of intervention that was not tested alone.

Conclusion: While GPs may have a main role in bowel cancer screening by providing tests and information, we found only 2 interventions focusing on their practice. Further interventional studies based on simple and reproducible designs should be performed in order to improve bowel screening rates.

KEYWORDS

Colorectal cancer screening, FOBT, participation rates primary care intervention, systematic review.

INTRODUCTION

Bowel cancer is a worldwide problem, with an annual incidence of more than 1,3 million cases, representing almost 10% of the global cancer incidence. In 2012, bowel cancer was the third most common cancer in men (746,000 cases) and the second most common in women (614,000 cases). The annual mortality was over 500,000, corresponding to the fourth most common cause of death from cancer worldwide (1). Screening programs conducted by government agencies and scientific societies differ from a country to another (2). Performing colonoscopy or fecal tests are accepted strategies for colorectal-cancer screening among patients having an average-risk of bowel cancer. In most countries, guidelines are based on the following rules 1) individualized assessment of risk for colorectal cancer is needed for all adults, 2) starting from 50 years of age, and in high-risk population from 40 years of age, 3) by a stool-based test, flexible sigmoidoscopy, or optical colonoscopy, but always colonoscopy in high-risk patients, and 4) screening can be stopped for adults over 75 years or for adults with a life expectancy of less than 10 years. Most of national guidelines recommend to use gaiac fecal occult blood tests (gFOBT) or fecal immunochemical blood tests (FIT), flexible sigmoidoscopy, or colonoscopy(3)(4).

A minimal participation to screening is required to ensure screening efficiency, and various participation thresholds have been established: 65 % (5), 75% (4). However participation rates in countries with organized screening programs remain low, ranging from 20% to 52% (6). While higher participation rates to screening programs have been found to reduce mortality (7) (8), increasing participation to bowel cancer screening is a major issue, and might reduce disparities in screening. Authors in previous publications have identifies over-representation of certain factors associated with a lower participation rate: female gender, younger participants, low level of education, lower income, ethnic minorities and not having a spouse were the most frequently reported barriers (9). On the one hand, providing evidence on these predictors would help policy makers and clinicians to concentrate their effort on the relevant population. On the other hand, identifying predictors associated with poor adherence to screening does not allow to elaborate recommendations for practice.

Identifying reproducible interventions that can be duplicated and developed in a wider context would be relevant for policymakers and clinicians aiming at increasing patient uptake of colorectal screening strategies. Screening implementation modalities differ between countries. Comparisons between a strategy based on colonoscopy and a strategy based on fecal blood test have shown a

better compliance to fecal blood test (10) (11) (12), so that French national guidelines recommend the use of fecal screening tests. However, there was a change in the French strategy for bowel cancer screening in 2015: gFOBT was replaced by FIT, and the postal mailing of screening kits to non-respondent patients was suspended, so that GPs are now the only providers of FIT kits (3). Policymakers insist that GPs should be involved in interventions aiming at increasing patient uptake of screening tests.

We identified the following key questions:

1) What type randomized controlled interventions have been performed, aiming at increasing patient uptake of fecal tests for bowel cancer screening, in asymptomatic patients having an average-risk of bowel cancer?

2) What was the impact of such interventions on patient screening test uptake?

3) What information should be provided with the test in order to increase patient uptake?

4) What material support would increase patient uptake?

5) What is the impact of reminders on patient uptake?

6) Are there studies specifically targeting GPs?

We conducted a systematic review of randomized controlled studies, searching interventions aiming at increasing patient uptake of fecal tests for bowel cancer screening.

METHOD

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13) (Table 1) and was registered with Prospero.

Table 1. PICO determinants of our review

Population	Intervention	Comparison	Outcomes	Study design
Main concept				
Asymptomatic patients having an average-risk of bowel cancer	All types of intervention designed in order to increase fecal test uptake	Type of intervention	Screening test uptake. Number of screened cancers	Randomized controlled trials
MESH terms/ synonyms				
Primary care patients	Mass screening, early detection of bowel cancer	Intervention	Patient compliance, patient participation.	Randomized controlled trials, clinical trials

Eligibility criteria

We referred to the following checklist to determine eligibility:

1. Does the article present primary data? We excluded the following type of studies: review article, commentary, protocol, but let a flag for later reference scan.

2. Does the article report a randomized controlled trial (RCT) or a cluster-randomized trial (CRCT)? We excluded studies if they were not RCT or CRCT.

3. Did the study include asymptomatic adults having an average risk of bowel cancer? We excluded the studies conducted on high-risk patients as well, or if no precision was provided for population of the study.

4. Was the eligible population recruited in a primary care setting?

Study identification and selection

We conducted a systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials, on September 1st 2015 (Text Box 1). We followed PRISMA 2015 guidelines (13), and searched studies written in the English or French language, with no date or location limits (see

appendices for search strategy). To find further find relevant studies, we also hand searched reference lists of systematic and narrative reviews identified during the initial search, and the reference list of the selected articles.

Abstracts and full texts were reviewed independently by two reviewers for inclusion. Discussions about inclusion or exclusion of these studies were resolved by consensus and a third senior reviewer was consulted to resolve any remaining disagreements.

Text Box 1. Search algorithms.

MEDLINE algorithm
Filters: Clinical Trial; Randomized Controlled Trial; Review; English; French ; ((("Patient Compliance"[Mesh]) OR "Patient Participation"[Mesh])) AND ((("Mass Screening"[Mesh] OR "Early Detection of Cancer"[Mesh])) AND colorectal cancer) ; Filters: Clinical Trial; Randomized Controlled Trial; Review; English; French

EMBASE algorithm
'patient compliance'/exp OR 'patient participation'/exp AND ('mass screening'/exp OR 'early diagnosis'/exp) AND 'colorectal cancer'/exp AND ('review]' OR 'clinical trial') AND ([english]/lim OR [french]/lim)

COCHRANE LIBRARY
systematic review of the CRC group publications

Data extraction

One reviewer extracted relevant data in a data collection form based on the Cochrane data collection form for reviews and RCTs (14) (Table 2). The studies were critically appraised for bias by 2 reviewers using the Cochrane Collaboration's tool for assessing risk of bias (15). These data were verified by a second reviewer, and discrepancies were resolved by consensus.

Data synthesis and analysis

We performed qualitative data synthesis, organizing the results by type of intervention, depending on whether the intervention focused on physician practice, patient information, or test modalities. We attempted to provide a quantitative synthesis for studies evaluating similar interventions, but this quantitative synthesis was limited because of the heterogeneity of the study designs, populations, and results. Using our critical appraisal of individual studies and the body of evidence

for each study design, we identified strengths and weaknesses of each study. We did not assess publication bias.

Table 2. Data collection form

General information

Title, authors, date and type of publication, country.

Eligibility

As described in the eligibility section of the method description

Methods

Aim, type and design of study, setting, start and end dates, type of intervention, target of the intervention, type of test (gFOBT, FIT), type of outcome measures, ethical approval.

Participants

General or group, age/sex/ethnicity/illness/co-morbidities, inclusion and exclusion criteria in the study, method of recruitment of participants, informed consent obtained, total randomized or total population at start of study, withdrawals and exclusions, clusters.

Outcomes

Outcome name and precise definition, time points measured/reported, imputation of missing data, statistical analysis performed, power.

Other

Funding sources, possible conflicts of interest

Risk of bias

Described as low/high/unclear by two independent investigators: selection bias (random sequence generation, allocation concealment), performance/detection bias (blinding), incomplete outcome data (attrition bias), reporting bias (selective outcome reporting), other bias.

Data analysis

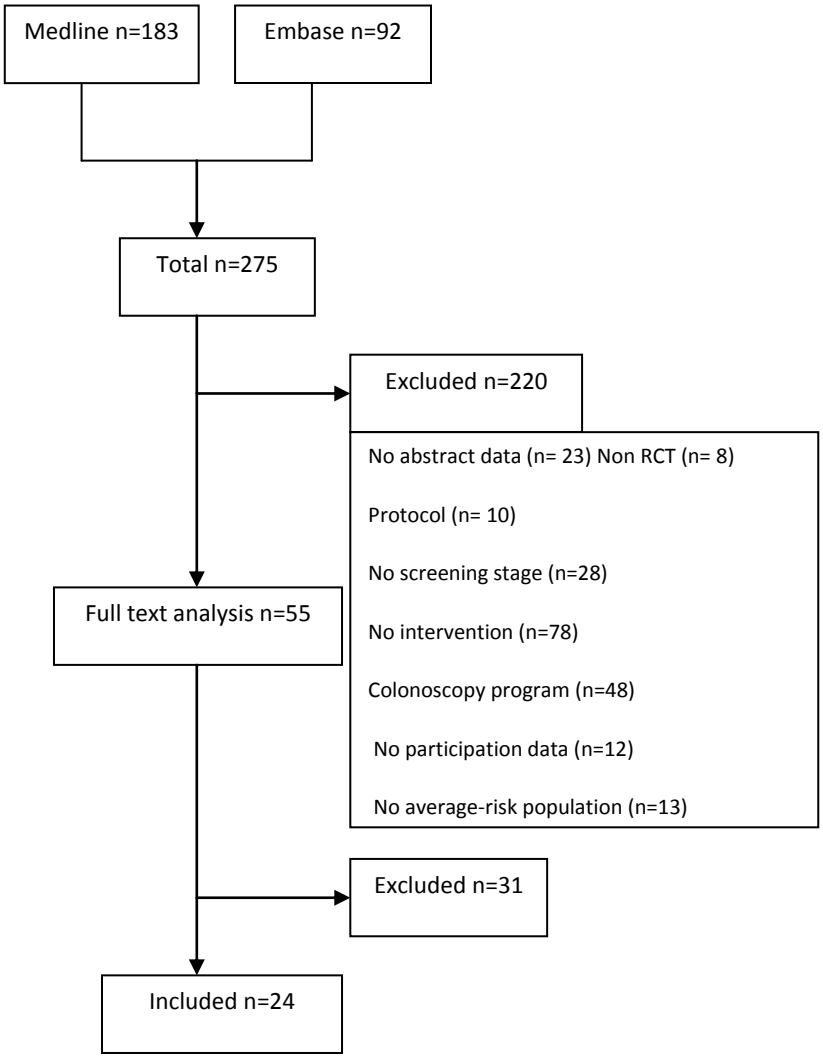
Main outcome, time point of the measure, comparison between groups or modification made towards the baseline.

RESULTS

Study selection

We reviewed 275 abstracts and 55 full texts, including 24 studies (Figure 1). When we identified multiple reports from the same authors investigating the same population or model, we included only the most recent study.

Figure 1. Flowchart of the study selection process



Study characteristics

The trials varied in their design, including in the unit of randomization (GP or patient) and the population targeted by the intervention (clinician or patient). The main characteristics of the studies are reported in Table 3. The interventions reported in the included studies focused either on test modalities (6 studies), on patient information (16 studies), or on physician practice (2 studies) (Table 3). Ten studies were based on complex interventions (16–25). We decided to report them in multiple categories where relevant.

For each study, we analyzed the following risks of bias: selection bias, performance bias and detection bias, attrition bias, reporting bias. These biases were classified in three categories (low, moderate, high), according to the PRISMA-P guidelines (Annex 2).

Table 3. Studies description

Author, year, setting	Sample	Design	Outcome/ delay	Intervention
Aubin-Auger, 2015, France	45 GPs	Cluster RCT	PR within 7 m.	Implementation of a training course focused on communication skills among GPs
Baker, 2014, USA	450	RCT	PR within 6 m	1: Mailing an FIT kit. 2: Telephone and text reminders. 3: For non-respondents within 3 months, personal navigator contact
Myers, 2014, USA	764	RCT	PR within 6 m.	Preference-based tailored navigation on CRC
Neter, 2014, Israel	29 833	RCT	PR at 2 and 6 m.	Use of the II (implementation intentions). 1: instruction leaflet was sent to participants. 2: the leaflet contained suggestions for overcoming common problems that individuals face in attempting to perform FOBT, and an encouragement
Tinmouth, 2014, Canada	3 594	RCT	PR at 6 m.	Addition of a gFOBT kit to a second mailed invitation

Green, 2013, USA	4 675	4 arms RCT	PR at 12 and 24 m.	Use of a stepped-intensity intervention. 1: usual care: information letter and FOBT kit mailing. 2: automated care: in addition, a study database registry tracked when screening was due and automatically generated mailings. Non-respondents received a reminder letter. 3: assisted care: in addition, telephone assistance from a MA to complete screening. 4: navigated care: in addition, support from a nurse on questions or requests for an FOBT alternative. MA contacted navigated patients who did not request such alternative.
Birkenfled, 2011, Israel	16 132	RCT	PR	Use of FIT
Hewitson, 2011, UK	1 288	4 arms RCT	PR within 20 w.	Use of educational letters. 1: GP's endorsement letter, 2: enhanced procedural instruction leaflet. 3: GP's letter plus leaflet, 4: control. An FOBT kit was sent a week after the first mailed letter.
Levi, 2011, Israel	12 537	RCT	PR + CRC DR	Use of FIT
Giorgi Rossi, 2011, Italy	4 219	RCT	PR within 9 m.	Direct kit-mailing
Van Roon, 2011, Netherlands	5 000	RCT	PR within 8 m.	Use of a mailed prior notification letter
Gimeno-Garcia, 2009, Spain	158	RCT	PR within 12 m.	Video-based educational intervention
Lee, 2009, USA	775	RCT	PR within 6 m.	Use of a mailed educational reminder
Hol, 2009, Netherlands	15 011	RCT	PR within 12 m.	Use of FIT, and patient mailed reminders
Cole, 2007, Australia	2 400	4 arms RCT	PR within 2 w.	Use of 3 different mailed information: risk, advocacy, prior notification
MACS group, 2006, Australia	1 333	RCT	PR	Use of choice between different screening tests (FIT, colonoscopy, Flexible sigmoidoscopy plus FIT)

Cole, 2003, Australia	1 818	RCT	PR	Use of FIT with spatula and FIT with brush (simpler stool sample)
Hughes, 2005, Australia	3 358	RCT	PR	Use of FIT
Federici, 2005, Italy	7 332	Cluster RCT	PR + CRC DR	Use of FIT
Miller, 2005, USA	204	RCT	PR within 30 d.	Use of a computer-assisted intervention and a nurse counseling intervention
Vinker, 2002, Israel	2 315	4 arms RCT	PR	1: use of a reminder note to the physician. 2: patients received either a reminder letter or a phone call. One month later the non respondents received a follow-up reminder using the same method (the 4th arm if a control group)
Ore, 2001, Israel	2 000	RCT	PR within 5 m.	Direct kit-mailing
Mant, 1992, UK	1 588	4 arms RCT	PR	1: mailed kit. 2: mailed kit with an invitation for a health check. 3: invitation to a health check, test offered at the health check. 4: just invited for the health check.
Myers, 1991	2 201	RCT	PR within 90 d.	Use of a booklet, telephone reminders and health education messages framed in "loss" terms as compared to those framed in "gain" terms.

PR : participation rate

CRC DR : CRC detection rate

d. days, w. weeks, m. months, y. years

MA: medical assistant

Interventions and their related impact on patient uptake of screening tests

. Use of FIT vs gFOBt

4 studies (published between 2003 and 2010) included a total of 25000 patients and concluded that FIT was associated with higher patient uptake of screening test than gFOBT. *Cole et al. 2003* (26) compared use of FIT with a brush, FIT with a spatula and gFOBT in a 3-arm design study, involving 1 818 patients. It showed significant improvement of compliance with brush-FIT vs gFOBT (RR 1.27, p 0.01), and no significant difference between spatula-FIT and gFOBT (RR 1.65, p>0.05). *Hughes et al*. (27) in sample of 3 358 patients reported 38.7 % test uptake in FIT arm and 30.2 % in gFOBT arm, OR 1.88, 95 % CI 1.59-2.22, p< 0.001. *Federici* (28) conducted a study on a sample of 7 320 patients. 35.8 % patients completed the FIT vs 30.4 % the gFOBT (RR 1.2, 95% CI 1.02-1.44). CRC detection rate was 29.3% among positive tests in the FIT arm, vs 19.7% in the gFOBT arm. *Hol* (20) tested the impact of an intervention based on 1) mailing an FOBT kit, 2) mailing a reminder in a sample of 15 011 patients. Both groups (gFOBT and FIT) received mailed kits and mailed reminders. The overall participation was 48.0 % (CI 47.1-48.7). In total 49.5% patients attended gFOBT (CI 95 % 48.1-50.9) and 61.5 % attended FIT (CI 95 % 60.1-62.9).

2 studies published in 2010 and 2011 included a total of 27000 patients and concluded that FIT was not associated with higher compliance. *Birkenfeld* (29) compared the effectiveness of FIT vs gFOBT in a sample of 16 132 patients. Results showed no significant difference between both arms, with 23.1 % test uptake in control group vs 24.6 % in the intervention group (OR 0.996, CI 0.46-2.17, p 0.99). *Levi* (30) conducted a FIT-gFOBT comparison-based study on 12 537 patients and showed a significant improvement in the FOBT arm (28.8% vs 25.9 %, p < 0.001).

. Prior notification letter

2 studies reported the impact of an advance notification letter on patient uptake of screening tests. In a RCT implying 5 000 patients, *Van Roon* (31) evaluated the impact of mailing an information letter in order to inform the patients that they should perform a fecal occult blood test. The main result was a significant increase of patient test uptake in the intervention group (64.4% vs 61.1%, p= 0.019). In a RCT involving 2400 patients, *Cole* (2007) (21) had also demonstrated that sending an prior notification letter before the standard invitation increased patient participation 2 weeks later (RR 1.38).

. Postal mailing of FOBT kits

5 studies reported that mailing FOBT kits to patients increased patient uptake. *Mant* (1992) (24) reported an interventional study involving 1203 participants. Patients were provided a FOBT kit either 1) by postal mail kit only, or 2) by postal mail, associated with an invitation letter for a health check, or 3) during a health check consultation (so that the kit was not mailed to the patients). The overall test uptake was higher in the groups were the kit was mailed to the patients (25.5 % and 31.7 % in the first two groups, vs 20.6% in the group who did not receive the screening test by postal mail). *Ore (2001)* (32) performed a RCT in 1940 patients, and concluded to a higher uptake in the mailed kit group (19.9% vs 15.9%, p= 0.02). *Giorgi Rossi* (2011) (33) compared a direct mailing of the gFOBT kit vs a standard letter invitation to pick a kit to the primary care clinic (3196 patients). The participation rate were 14.6% in the mailing kit group and 10.7 % in the control group (RR 1.36, 95 CI 1.16-1.60, p<0.05). In a study involving 4 219 patients, *Green (2013)* (18) compared an automated care procedure (postal invitation letter followed by postal mailing of FOBT kits to the patients and postal reminders) to usual care procedure were patients had their FOBT kit in a care centre, before or after a physician discussion. Patient uptake was higher in the group who received the kits by postal mail (50.8% vs 26.3%, p<0.001). *Tinmouth (2015)* (34) tested the impact of mailing a gFOBT kit with a second invitation letter to non-respondent patients of an initial mailed invitation, in a sample of 3594 patients. The test completion was 20.1 % in the intervention arm vs 9.6 % in the control arm (OR 2.1, 95 % CI 1.6-2.6; p< 0.0001).

. Presentation and content of written information provided with the invitation messages

Myers (1991) (25) reported that providing either a gain or a loss framed message in booklets sent with invitation letters had no impact on patient uptake of screening tests. *Myers 1991* (25) assessed a complex and intensity-stepped intervention. In this study, a total of 2,201 men and women aged 50-74 were randomly allocated to a gain or a loss framed information booklet. The content of self-held screening booklets reported: a list of colorectal cancer risk factors, a summary of the steps to follow in doing FOBT, and a section with either 3 gain-framed statements or 3 loss-framed statements (so that 2 different versions of the booklets were created). There was no significant difference between the group who received loss-framed messages (40 %) and the group who received gain-framed messages (36 %, p> 0.05). The Australian *MACS group* study (35) aimed to determine if a letting the patient choose between different screening tests (FOBT, colonoscopy, flexible sigmoidoscopy, CTC) could lead to an improvement of screening adherence (1333 eligible patients). Participation for FOBT was 27.4% in the intervention group having choice with screening,

compared to 18.6% in the control arm (p 0 .03). In the intervention arm, patients having choice between the tests, most people chose FOBT (66%). *Cole (2007)* (21) assessed the impact of 1) providing enhanced awareness of risk of CRC, and 2) combining invitation with advocacy messages from individuals. In this study, 1800 people aged 50-74 were randomly allocated to the following groups: Control, Risk, Advocacy. Providing enhanced awareness of risk of CRC and combining invitation with advocacy messages had no significant impact on participation.

Hewitson (2011) (19) reported that leaflet containing information on FOBT increased patient uptake of 6%. *Neter (2014)* (17) also reported a slight but significant impact of framing information using an implementation intention technique. In this study, leaflets provided with the test kit contained an "if-then" condition and planned instructions of when, where, and how to do the test. Patient uptake was higher in the intervention arm (71.4% vs 67.9%, p=0.0001).

. Written and telephone reminders

Lee (2009) (36) assessed the impact of sending an educational patient reminder by postal mail 10 days after providing the FOBT kits, in 775 patients having an average-risk of CRC, recruited in a veteran center. The main result was a significant increase of tests uptake (64.4% vs 48.8 %, OR 1.94, 95 % CI 1.45-2.60 p<0.001). *Green (2013)* (18) performed a stepped-intensity navigation intervention. A total of 2340 patients were randomly allocated either to 1) a usual care group, or 2) a "usual care plus automated interventions" group with postal mailing of FOBT kits and mailed reminder letters. Patient participation was higher in the group with automated postal reminders (50.8% in the automated group vs 26.3% in the usual care group). *Baker (2014)* (16) reported the impact of a multimodal design intervention conducted in a population of 450 patients, based on 1) mailing a FIT kit to eligible patients, 2) using telephone and text message reminders, and 3) adding a phone contact with a personal navigator for patients who were not compliant within 3 months. Patient participation to screening before the end of the 3rd month was higher in the intervention arm (73.8% vs 26.7%, p<0.001). There was no significant difference in participation between patients who received text messages and those who did not (44.3% vs 43.7%, p>0.99).

. Telephone contacts with a navigator, medical assistant or nurse

Myers (1991) (25) performed a stepped-intensity navigation intervention. In this study, 601 patients were randomly allocated to a usual care group. The screening strategy in this usual care group was based on an advance letter, a mailed screening kit, and a postal reminder letter. A total of 450 patients were allocated to another group: they had a reminder phone call at 30 days if no tests were

returned. Patient uptake was higher in the second group (37% vs 27%, p<0.001). Myers also created a third group of 450 patients in order to assess the impact of a telephone call giving instructions in testing (instruction call), provided to patients within a week of screening kit mailing. The screening follow-up in this third group associated advance letter, a mailed screening kit, an instruction call, and a reminder phone call. The instruction phone call had a positive impact on patient participation: test uptake was measured at 48%.

Green (2013) (18) performed a stepped-intensity navigation intervention. A total of 3494 patients were randomized between 1) a usual care group, 2) a "usual care plus automated interventions" group with postal mailing of FOBT kits and mailed reminder letters, and 3) an "assisted care" group with telephone assistance. Patient participation was higher in the group with telephone calls than in the group with mailed reminders alone (57.5% vs 50.8%, p< 0.05).

Baker (2014) (16) reported the impact of a multimodal design intervention conducted in a population of 450 patients, based on 1) mailing a FIT kit to eligible patients, 2) using telephone and text message reminders, and 3) adding a phone contact with a personal navigator for patients who were not compliant within 3 months. Patient participation to screening was higher in the intervention arm. Patient participation within 3 months was higher in the group with telephone reminders and text messages (73.8% vs 26.7%, p<0.001). An 8.4% participation increase was observed after the contact of non-compliant patients with a navigator.

Myers (2014) (37) assessed the impact of a follow-up by a navigator, in a study involving 764 patients. All patients received a mailed CRC screening informational booklet, a personalized letter that included a contact telephone number to schedule a colonoscopy appointment, and a FIT kit. In the interventional arm, a trained navigator called each participant to 1) review the mailed materials, 2) reassess screening preference, 3) discuss concerns or barriers to test performance, 4) help to develop a plan to complete the preferred screening test, and 5) arrange a follow-up call. If the navigator found that the participant's screening test preference had changed from baseline, new screening materials related to the current preferred test were sent. All patients received a reminder letter was mailed at 45 days post randomization to those who had not returned the FIT kit. The main result was a significant increase of patient participation within 6 months in the intervention arm (21.5% vs 15.3%; p=0.001).

. Videos and computers

Gimeno-Garcia (2009) (38) reported a video-based educational intervention, performed in 158 patients. A significant improvement of FOBT uptake within 2 weeks was observed (69.9% vs 54.4%, p = 0.035). *Miller (2005)* (22) had also compared the impact of counseling provided by automatized

informatics software to counseling provided by a nurse. The study included 204 patients. There was no significant difference in patient uptake of screening tests between the two groups (62% vs 63%, p = 0.42).

. Intervention requiring GP involvement

Hewitson et al. (19) assessed the impact of sending a GP-signed invitation letter to the patient. The main result was a significant increase of patient participation in the groups who were provided a GP-signed letter (+5.8%). *Aubin-Auger* (39) reported the impact of a GP training focused on communication skills. The study was based on a clustered randomized controlled design implying 45 GPs. The main result was a significant increase of patient participation in the intervention arm (36.7% ± 20.3 vs 24.5% ±10.1; p = 0.03). *Vinker* (23) reported the impact of mailing reminders to GPs, comparing to patient-reminders by phone call or mailed reminders. The study included 6 GPs and 2,315 patients. The main result was a significant increase of patient participation associated with sending reminders to GPs (14.3% vs 1.2%; p<0.0001).

DISCUSSION

Principal findings

This review identified 24 randomized controlled studies aiming at increasing patient uptake of fecal test for colorectal cancer screening. The following interventions increase patient uptake of fecal test for CRC screening: advance notification letter, (2 studies, 3% to 7% (31,21)) postal mailing (5 studies, 3.9% to 10.5% (24,32,33,18,34)) written reminders (2 studies, 15.6% to 24.5% (25,35)) telephone contacts with a navigator or a medical assistant (4 studies, 6.2% to 47.1% (18,25,16,37)). Other studies assessed whether patient counseling could be provided based on video or automatized informatics software (38,22). 3 interventions demonstrated the positive impact of GP involvement (19,39,23). One was based on an invitation letter signed by a GP, one focused on GP communication training. The third one concluded to the positive impact of mailing reminders to GPs but this study included only 6 GPs and the results were not adjusted on GP effect. Inconclusive results were found for studies comparing FIT vs FOBT, and those testing effectiveness of providing written information. Concerning phone-based intervention, text messages and reminders remain a type of intervention that was not tested alone.

Strengths and weaknesses

Quality of the evidence

Risk of bias has been evaluated on the basis of the PRISMA-P guidelines (13). General evaluation showed lacks in methodology and quality report for most studies. None of the study was blind. Lost-to-follow-up and randomization were barely described: it is clearly reported in eight studies (30–32,18,35,36,22,39). Only nine studies reported a power calculation (26,28,20,31,35,19,38,22,39). Confidence Interval and Odds Ratio were missing in one study (23). Selective reporting was estimated as moderate or high for 6 studies (29,21,24,32,38,23). Funding sources was missing in 8 studies (28–30,24,25,19,17,16). This led to heterogeneous level of evidence, and therefore high degree of heterogeneity in our analysis in this review.

Most studies focused on an average-risk population aged from 50 to 74. Five studies included specific populations (24,35,19,36,22) and the related reason was unclear in 4 studies (24,35,19,22). Only one study focused on non-responders (34), although they should be considered as of major interest.

Potential biases in the reviewing process

The main bias of this review might be the lack of grey literature leading to a publication bias. Interventions leading to non-conclusive results might have not been accepted for publication so that the review probably selected interventions reporting significant results. The selection and inclusion process based on two reviewers prevent from a selection bias, and using PRISMA-P guidelines prevents from reporting and attrition bias. No funding source has been necessary to lead this review, and no conflict of interest is to declare.

Discussing the results with international literature

Bowel screening in France has switched from gFOBT to FIT in 2015. *Vart et al*. (40) focused on comparing FIT and gFOBT in a systematic review and meta-analyses. Without focusing on further interventional-based studies, they reported factors that can improve CRC screening test uptake: simplicity of the tests, absence of dietary restrictions, fewer stool manipulation and simplified procedures of technical manipulation of the tests kits. Seven studies were included in the meta-analysis, assessing higher participation rates in FIT group. Contrary to our review, *Birkenfeld* (29) article was not included. The studies performed by *Hoffman et al. 2010, and Van Rossum et al*. 2008 were included in their review, while they were excluded in our review due to selection and population exclusion criteria (Annex 3). Even if 8 studies performed during the 2003-2010 period had shown a higher compliance in patients who were provided FIT, the results were not confirmed by the two most recent studies performed in a large sample (29,30). A reasonable explanation of these conflicting results might be that the first studies were performed in patients who were asked to respect dietary restrictions before test uptake, while dietary restrictions were not asked in the two last studies. Irrespective of these considerations, a conclusion might be that the promotion of FIT screening should be reaffirmed, mainly due to the enhanced sensibility and specificity of this test, rather than on uptake issues.

On the one hand, this review provides evidence for various modalities that can be widely implemented: prior notification letter, postal mailing of screening tests, and written reminders. All of these methods show low to moderate improvement rates. On the other hand, our review concluded that telephone contacts and involvement of navigators led to higher uptake of screening tests, despite heavy designs and apparent difficulty of applicability in usual care setting. These results are consistent with the conclusions of *Naylor et al. (41)* who focused on interventions decreasing racial and ethnic disparities toward CRC care and prevention. Naylor included 33 studies targeting African-American patients, Hispanic patients, Asian patients and other minorities' individuals. Navigation

interventions and multi-modal education interventions, including specific actions such as language-adapted education materials in some heavy designs, showed an improvement of compliance to CRC screening in these specific populations. However, all these interventions require recruiting navigators and appear difficult to generalize in a national context for the whole population having an average risk of bowel cancer. Several designs seem to be far from the setting of a regular primary care organization, questioning the applicability of the research findings. Navigation-based designs imply several calls and long interviews with patients. The question arises as to the scheduling of these complex and long follow-up processes. Navigation designs based on nurses or medical assistants in a primary care setting would require a lot of time, and would lead to elevated costs.

This review suggests alternative solutions based on video or computer-based information. However, it is questionable whether such information modalities may convince a patient with no concern for bowel cancer screening beforehand. In the corresponding studies (38,22), the high participation rate observed in the control group (60%) suggests that the patients who agreed to participate to these studies were not representative of the general population: because of the type of intervention, patient's compliance might mainly illustrate a recruitment bias.

GPs training or change of exercise are effective. Such training should be encouraged, but appears to be really difficult to set up and generalize, because of the complexity of such implementation in ordinary work setting. Furthermore, development of specific communication skills by medical and paramedical staff is not always fully developed, especially in European health and scientific societies nowadays.

Camilloni et al. (42) report a systematic review and meta-analysis on interventions leading to increase participation in organized screening programs of cervical, breast and CR cancers. A wide heterogeneity of the sources is also described, 20 studies are included for CRC screening, with RCTs, experimental studies and before and after studies. Included RCTs focusing on CRC are*: Lee, Myers 1991, Myers 1994, Stokamer 2005, Cole 2007, Hewitson 2011, Nichols 1986, Pye 1988, Hart 1997, Gimeno-garcia 2009, Church 2004, Giorigi Rossi 2011, Mant 1992 (26,24,33,25,19,36,38).* The RCTs lead by *Myers 1994, Stokamer 2005, Church 2004, Nichols 1986 and Pye 1988* were not included in our review because of exclusion criteria identified in the selection phase (annex 3). According to our own results, effective interventions reported in *Camilloni* review (42) for cervical, breast and colorectal cancers are postal and telephone reminders with a modest improvement associated with mailed reminders, mailed invitation letter signed by GPs, scheduled appointments and mailing kits

among non responders (all significant outcome). In the same way, *Sabatino et al*. (43) conducted a systematic review as well on the effectiveness of 11 interventions to increase screening for cervical, breast and colon cancers, without specifically targeting FOBT completion in that section of the review. The review also aims at adding recommendations for the general practice. They reported that one-on-one education improves participation rates for CRC screening tests, as well as reminder information, with high strength, and the need to reduce structural barriers was reaffirmed.

Various interventions based on telephone or one-on-one counselling have been conducted for other health problems: chronic diseases (asthma, chronic bronchitis, diabetes) or as prevention strategies (exercise, smoking, nutrition, vaccination). The impact of such interventions was demonstrated for chronic disease management, but authors reported the difficulty to modify patient behaviors in prevention. *Butler et al.* (44) included 53 GPs in a RCT testing the effect of a behavioural counselling training. Effectiveness was measured on the proportion of patients reporting change in behaviours including smoking, alcohol use, exercise, and healthy eating. There was no effect at three months (OR 1.12, 95% CI 0.90-1.39), suggesting that in respect of behavioural change, complex studies should be conducted so as to reinforce counselling programs. *Mehring et al*. (45) conducted an interventional RCT, assessing the effectiveness of automated web-based coaching program in addition to accompanied telephone counselling in smoking cessation on 168 primary care patients. The telephone counselling was reached by GPs. The main outcome fails at establishing a difference between the intervention arm and the control arm: OR 0.86, 95% CI 0.25-3.0; p=0.816. *Hilberink et al.* (46) conducted a cluster-randomized controlled trial including 68 general practices, randomly assigned to the intervention arm, implying GPs-counselling, or usual care arm. The main outcome, defined as smoking cessation, was not higher in the intervention group: OR 2.3, 95% CI 0.9-6.0.

Implications for future practice and research

We found only one RCT focusing on non-responders (34). Further research should probably aim at increasing patient uptake in these non-compliant patients. Only 3 studies focused on GPs involvement. A hypothesis is that general practitioners might provide personalized counseling so that GP-based intervention can increase patient uptake. We deplore that the only study experimenting the mailing of reminders to GPs was of poor quality, based only on 6 GPs, without integrating the cluster effect in the analysis.

Comparison of patient uptake, depending on FIT or gFOBT tests might lead to pool the data in a meta-analysis.

CONCLUSION

All the studies included in this systematic review suggest a wide panel of possible actions that can be conducted in order to increase CRC participation rates, which can be easily provided in a primary-care setting, particularly patient navigation, patient education an GPs' based interventions. On the latter type of target, it should be interesting for researchers to refine and specify the research, in order to increase CRC prevention among general population.

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TABLE DES ANNEXES

Annex 1. Risk of bias assessment

Study	Selection bias	Performance and detection bias	Attrition bias	Reporting bias
Aubin-Auger, 2015, France	low	low	low	low
Baker, 2014, USA	moderate	low	moderate	Low
Myers, 2014, USA	low	moderate	low	Low
Neter, 2014, Israel	moderate	high	moderate	Low
Tinmouth, 2014, Canada	moderate	moderate	low	Low
Green, 2013, USA	low	moderate	low	low
Bikrkenfled, 2011, Israel	low	moderate	moderate	moderate
Hewitson, 2011, UK	low	moderate	moderate	low
Levi, 2011, Israel	moderate	moderate	moderate	low
Giorigi Rossi, 2011, Italy	low	moderate	low	low
Van Roon, 2011, Netherlands	low	moderate	low	low
Gimeno-Garcia, 2009, Spain	moderate	moderate	moderate	high
Lee, 2009, USA	low	low	low	low
Hol, 2009, Netherlands	low	moderate	low	low
Cole, 2007, Australia	moderate	moderate	high	moderate
MACS group, 2006, Australia	low	moderate	low	low
Cole, 2003, Australia	low	moderate	moderate	low
Hughes, 2005, Australia	moderate	moderate	moderate	low
Federici, 2005, Italy	moderate	moderate	moderate	low
Miller, 2005, USA	low	low	low	low
Vinker, 2002, Israel	moderate	moderate	high	high
Ore, 2001, Israel	moderate	moderate	low	high
Mant, 1992, UK	moderate	moderate	high	high
Myers, 1991	moderate	moderate	high	low

Methods report: poorly reported in 4 studies: Rossi et al., Mant et al., Hughes et al., Vinker et al.

Fundings report: poorly Poorly report in 8 studies: Baker et al., Neter et al., Birkenfeld et al.,
Federici et al., Mant et al., Myers et al., Hewitson et al., Levi et al.

Annex 2. Table of main outcome

Study	Main outcome
Patients targeted interventions	
Use of FIT	
Cole, 2003	bFIT RR 1.27 p 0.010, sFIT RR 1.65p>0.05
Hughes, 2005	IA 38.7% CA 30.2% OR 1.88 CI 1.59-2.22 p<0.001
Federici, 2005	IA 35.8% CA 30.4% RR 1.2 CI 1.02-1.44
Hol, 2009	IA 61.5% CA 49.5%OR 2 CI 1.3-3.2 p<0.05
Birkenfeld, 2011	IA 23.1% CA 24.6% OR 0,996 CI 0.45-2.17 p 0.990
Levi, 2011	IA 25.9% CA 28.8% p<0.001 in favor of FOBT arm
Prior notification letter	
Van Roon, 2011	IA 64.4% CA 61.1% p 0.019
Cole 2007	RR 1.23 CI 1.06-1.43
Postal mailing of FOBT kits	
Mant, 1992	CA 25.5 % IA (mail) 31.7 % (health check) 20.6%
Ore, 2001	IA 19.9% CA 15.9% p 0.02
Giorgi Rossi, 2011	IA 14.6% CA 10.7% RR 1.36 CI 1.16-1.60
Green, 2013	IA (navigated gr.) 65.9 % CA 25.8 % p<0.05 (1 y.)
Tinmouth, 2014	IA 20.1 % CA 9.6 % OR 2.1, 95 % CI 1.6-2.6; p< 0.0001
Written information and invitation messages	
Myers, 1991	*
MACS gr., 2006	IA 18.6% CA 27.4% p 0.03
Cole 2007	RR 1.23 CI 1.06-1.43
Hewitson, 2011	Letter group AD 5.8% leaflet group AD 6.0%
Neter, 2014	IA 71.4% CA 67.9% OR 1.17 CI 1.11-1.23 p< 0.0001
Written and telephone reminders	
Lee, 2009	IA 64.6% CA 48.4% OR 1.94 CI 1.45-2.60 p<0.001
Green, 2013	IA (navigated gr.) 65.9 % CA 25.8 % p<0.05 (1 y.)
Baker, 2014	IA 82.2% CA 37.3% p<0.001
Telephone contact with navigator/med assistant or nurse	
Myers, 1991	*
Green, 2013	IA (navigated gr.) 65.9 % CA 25.8 % p<0.05 (1 y.)
Baker, 2014	IA 82.2% CA 37.3% p<0.001
Myers, 2014	IA 21.5% CA 15.3% p 0.01
Video or computer-based interventions	
Gimeno-Garcia, 2009	IA : 69.9% CA 54.4% p 0.035
Miller, 2005	IA 62% CA 63% p 0.42
GPs targeted interventions	
Hewitson, 2011	Letter group AD 5.8% leaflet group AD 6.0%
Aubin Auger, 2015	PR per GP : IA 36.7 CA 25.5% p 0.03
Vinker, 2002	IA 25.4% CA 9.2% p 0.01

intervention not secifically tested in that section
outcome in favor of this intervention
several arms of intervention, not all proved in favor of the intervention
intervention has not proved effectiveness

AD : Absolute difference
PR : participation rate
IA : intervention arm
CA : control arm
CI : confidence interval
CRC DR : CRC detection rate
gr. : group y. : year
*CA 27.4 %, IA group 1 37.1%, group 2 37.3,% group 3 48.1% p<0.001
bFIT : brush FIT / sFIT : spatula FIT

Annex 3. Excluded studies

Aragones et al. A randomized controlled trial of a multilevel intervention to increase colorectal cancer screening among latino immigrants in a primary care facility. J Gen Intern Med. 2010 Jun;25(6):564-7

Braun et al. Testing a culturally appropriate, theory-based intervention to improve colorectal cancer screening among Native Hawaiians. Prev Med. 2005 Jun;40(6):619-27

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Vu, le Président du Jury,

(tampon et signature)

Vu, le Directeur de Thèse,

(tampon et signature)

Vu, le Doyen de la Faculté,

(tampon et signature)

NOM : LATOUR PRENOM : Chloé

TITRE: Interventions augmentant la participation au dépistage du cancer colorectal par recherche de sang dans les selles : une revue systématique des études interventionnelles randomisées contrôlées.

RESUME

Rationnel : En population générale, les recommandations internationales promeuvent le dépistage du cancer colorectal par recherche de sang dans les selles. Il est établi que des taux de participation élevés ont un impact direct sur la mortalité. Pourtant, ces taux de participation n'atteignent pas les seuils recommandés dans la plupart des pays. C'est pourquoi de nombreuses études ont été conduites dans le but d'améliorer la participation. Nous avons réalisé une revue systématique de la littérature des études interventionnelles randomisées contrôlées visant à augmenter les taux de participation au dépistage du cancer colorectal par recherche de sang dans les selles.

Méthode : Cette revue systématique de la littérature a été réalisée à partir des banques de données de la Cochrane Library, Pubmed et Embase, en suivant les recommandations du PRISMA-P réédité en 2015 par la Collaboration Cochrane. La revue porte sur les études interventionnelles contrôlées randomisées réalisées en population générale, visant à améliorer le taux de participation au dépistage du cancer colorectal. Nous rapportons les limites et biais des études incluses dans la revue.

Résultats : Nous avons identifié 24 études qui répondaient aux critères d'inclusion. Les interventions qui améliorent les taux de participation au dépistage du cancer colorectal sont les suivantes : envoi d'une lettre d'information précédant la réalisation du test (2 études, amélioration des taux de 3 % à 7 %), envoi postal du test (5 études, amélioration de 3.9 % à 10.5 %), rappels écrits (2 études, amélioration de 15.6 % à 24.5 %), contact téléphonique auprès d'un conseiller (4 études, amélioration de 6.2 % à 47.1 %). 2 études portaient sur l'effet d'un conseil réalisé sur support vidéo ou informatique. 3 études ont démontré l'effet positif de l'implication du médecin généraliste. L'une étudiait l'effet de l'envoi d'une lettre signée par le praticien, une autre proposait une formation en méthodes de communication du médecin. La troisième concluait à un effet positif de rappels réalisés auprès du praticien, mais cette étude incluait 6 médecins, et les résultats n'étaient pas ajustés sur l'effet lié au praticien. Des résultats non significatifs ont été mis en évidence pour les études comparant les tests (FIT vs gFOBT), et celles basées sur la délivrance d'information écrite au patient. Les interventions téléphoniques, par envoi de messages-texte ou de rappels n'ont pas été testés seuls.

Conclusion : Bien que le médecin généraliste ait un rôle central dans le cadre de la prévention du cancer colorectal, dans la délivrance des tests et de l'information, nous n'avons identifié que deux études axées sur leur activité. Il serait intéressant de mener d'autres études interventionnelles d'élaboration simple, et reproductibles, afin d'améliorer la participation au dépistage du cancer colorectal.

MOTS-CLES

Dépistage au cancer colorectal, FOBT, taux de participation, soin primaire, revue systématique.