Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC
EUROPEAN JOURNAL OF CANCER

Review

Impact of colorectal cancer screening on cancer-specific mortality in Europe: A systematic review

Andrea Gini [a],[*], Erik E.L. Jansen [a], Nadine Zielonke [a],
Reinier G.S. Meester [a], Carlo Senore [b], Ahti Anttila [c], Nereo Segnan [b],
Dominika Novak Mlakar [d], Harry J. de Koning [a],
Iris Lansdorp-Vogelaar [a] on behalf of EU-TOPIA consortium

[a] *Erasmus MC, University Medical Center Rotterdam, Department of Public Health, Rotterdam, the Netherlands*
[b] *Epidemiology and Screening Unit-CPO, Città Della Salute e Della Scienza, University Hospital, Turin, Italy*
[c] *Finnish Cancer Registry, Helsinki, Finland*
[d] *National Institute for Public Health, Ljubljana, Slovenia*

Abstract **Background:** Populations differ with respect to their cancer risk and screening preferences, which may influence the performance of colorectal cancer (CRC) screening programs. This review aims to systematically compare the mortality effect of CRC screening across European regions.
Methods: Six databases including Embase, Medline, Web of Science, PubMed publisher, Google Scholar and Cochrane Library were searched for relevant studies published before March 2018. Bibliographic searches were conducted to select studies assessing the effect of various screening tests (guaiac fecal occult blood test [gFOBT]; flexible sigmoidoscopy [FS]; fecal immunochemical test [FIT] and colonoscopy) on CRC mortality in Europe (PROSPERO protocol: CRD42016042433). Abstract reviewing, data extraction and risk of bias assessment were conducted independently by two reviewers.
Results: A total of 18 studies were included; of which, 11 were related to gFOBT, 4 to FS, 2 to FIT and 1 to colonoscopy; 8 were randomised clinical trials, and 10, observational studies, and an approximately equal number of studies represented Northern, Western and Southern European regions. Among individuals invited to screening, CRC mortality reductions varied from 8% to 16% for gFOBT and from 21% to 30% for FS. When studies with a high risk of bias were considered, ranges were more extensive. The estimated effectiveness of gFOBT and FS screening appeared similar across different European regions.

 * *Corresponding author*: Mr. Andrea Gini, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands, Fax: +31(0)107038475.
 E-mail address: a.gini@erasmusmc.nl (A. Gini).

Conclusions: CRC mortality impact of inviting individuals with similar adopted screening strategies (gFOBT or FS) may be consistent across several European settings.

1. Introduction

Colorectal cancer (CRC) is the second and the third leading cause of cancer death among men and women in Europe, with more than 242,000 deaths estimated in 2018 [1]. The highest mortality rates were reported in Eastern Europe (Hungary and Slovakia), where CRC incidence rates have increased sharply in the last decades owing to changes in lifestyle factors [1,2]. Screening has the potential to reduce the burden of CRC, with the scientific literature suggesting a reduction in CRC mortality ranging from 18% to 57% (depending on the screening test investigated) [3]. In 2003, the European Council acknowledged the effectiveness of fecal occult blood test (FOBT) screening and recommended the implementation of organised CRC screening for men and women aged 50—74 years in the European countries [4].

However, CRC screening was not implemented homogenously across Europe. Existing organised programs differed in terms of target ages, screening interval and primary test [5]. In Finland, biennial guaiac FOBT (gFOBT) screening is offered to men and women aged 60—69 years [6,7], whereas in France and the United Kingdom (UK), biennial gFOBT is offered from the age of 50 to 74 years [8,9], and in the Netherlands, Spain, Slovenia, Ireland, Malta and Hungary, biennial fecal immunochemical test (FIT) screening is offered in various age ranges between 50 and 75 years [5,10—12]. CRC screening also varies within the countries, for instance, in Italy. There, 112 regional CRC screening programs were gradually implemented during 2003—2012, some offering the FIT and some offering flexible sigmoidoscopy (FS) [13].

CRC screening implementation, performance and its geographical differences are currently monitored [14]. The first European Guidelines on quality assurance in CRC screening and diagnosis have been published, making standards and recommendations to improve CRC screening programmes (especially in quality assurance and the management of detected lesions) [15]. The European Parliament has encouraged member states to invest more in reducing screening inequalities and stimulating early cancer diagnosis. To assist each country in reaching these goals, the European Commission funded the EU-TOPIA project (EU Framework Programme, Horizon 2020—634753). EU-TOPIA will systematically evaluate the harms and benefits of existing screening programs for CRC in all European countries and identify ways to improve health outcomes and reduce screening inequalities of European Union (EU) citizens. As a first step, and to assess the appropriateness of various chosen screening policies, EU-TOPIA will review the evidence of the effectiveness of alternative screening strategies across European countries.

In this study, we systematically reviewed the literature on the effectiveness of screening in Europe, focussing on geographical disparities in the effectiveness of screening.

2. Methods

We performed a systematic literature review following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [16]. This study was registered as part of a planned review, and its protocol was published on 6th July 2016 in PROSPERO (International Prospective Register of Systematic Reviews, CRD42016042433) [17].

2.1. Literature search

Systematic bibliographic searches were conducted on the databases Embase, Medline Ovid, Web of Science, PubMed publisher, Google Scholar and Cochrane Library to identify potentially relevant studies. All databases were searched from inception to 1st April 2016 (subsequently updated to 1st March 2018). The computer-assisted searches were designed and performed by a research librarian using controlled keywords to assess concepts related to screening, CRC and mortality among European countries (Appendix Tables 1a and 1b). In addition, the search was augmented with a list of relevant, recently published, articles. All references were managed using Thomson Reuters Endnote X7.1, and duplicates were removed.

2.2. Study selection, data extraction and quality assessment

Two investigators independently reviewed the titles and abstracts of all references identified by the literature search. A list of potential studies was retrieved considering the PICOS (population, intervention, control, outcome and study design) criteria defined in the study protocol (Table 1) [17]. Inclusion criteria were defined to select relevant studies investigating the reduction in

Table 1
Inclusion and exclusion criteria.

Category	Inclusion	Exclusion
Population	People invited to/ participating in organised mass screening for colorectal cancer	
Interventions	Organised screening for colorectal cancer (e.g. FS, gFOBT, FIT, colonoscopy)	
Controls	People not invited for/ participating organised screening or people participating in opportunistic screening only	
Outcomes	Change in mortality due to colorectal cancer screening (colorectal cancer mortality reduction)	
Study design	Randomised controlled trials and observational studies, such as prospective and retrospective controlled cohort studies.	Study designs that do not directly assess the effect of screening. Systematic reviews, meta-analyses, modelling/ simulation studies, non-original research studies (e.g. editorials, letters) and abstracts only.
Language	English	

gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy.

CRC mortality due to screening and focussing on populations invited to organised CRC screening programmes. To avoid exclusion of relevant references, studies that only reported CRC incidence reductions in the abstract were initially not excluded. Eligible articles were then reviewed in depth, and an additional selection was made applying the following eligibility criteria proposed by Elmunzer et al [3]: (i) studies in which data or patients were duplicated in other manuscripts; (ii) studies in which data were not reported for at least 5 years of follow-up; (iii) studies in which the total number of events and participants were not reported for each study group or (iv) studies that assessed only the effect on CRC incidence. From each included article, the following data were extracted: first author; year of publication; country where the study was conducted; study design; screening modality; screening target population; follow-up information; sample size of the study and the reported estimates (with the corresponding 95% confidence intervals [95% CIs]) of the CRC screening effect on cancer-specific mortality (as per the underlying cause of death from the hospital or mortality registry, depending on the study). Information on adjustment for demographic differences between participants and non-participants in screening was also extracted [18]. For

each included study, the conflict of interest was reviewed and reported in Appendix Table 2. Eligible articles were divided based on European areas (Northern, Western, Southern and Eastern Europe) following the classification provided by EUROVOC Multilingual Thesaurus of the European Union [19]. To assess quality and bias, the studies were evaluated using validated evaluation tools. Randomised controlled trials (RCTs) were evaluated using the Cochrane Library criteria for systematic reviews of interventions and risk assessment. Observational studies were assessed using the criteria provided by the Newcastle—Ottawa Scale (NOS) [20,21]. In brief, risk of bias was categorised as follows: 'high risk' was assigned to RCTs when at least one of the Cochrane Library criteria was assumed at high risk and to observational studies with an NOS score ≤ 4; 'moderate risk' was assigned to RCTs when at least one of the Cochrane Library criteria was assumed at moderate risk and to observational studies where the NOS score ranged from 5 to 7 and 'low risk' was assumed otherwise. Based on this categorisation, the results were interpreted by both excluding and including studies at high risk of bias to explore the impact of quality assessment on review conclusions. All studies were quality assessed independently by two reviewers. Disagreements between the two investigators were solved by consensus or consulting a third reviewer.

3. Results

A total of 3741 citations were retrieved through the initial searches (Fig. 1). A subsequent updated bibliographic search provided 620 additional references. After removal of duplicates, 3034 potentially relevant citations were identified, and 70 potential articles for detailed evaluation were selected based on the title and abstract review. Fifty-two of these articles were excluded owing to the eligibility criteria (Appendix Tables 3 and 4), and thus, 18 were included in the final analysis.

The included articles varied based on the region (7 from Northern Europe, 5 from Southern and 6 from Western), screening test assessed (11 for gFOBT, 3 for FS, 2 for FIT, 1 for FS in combination with FIT and 1 for colonoscopy) and study design (8 RCTs, 7 cohort studies and 3 case—control studies). No studies were retrieved from Eastern Europe.

Of the 8 RCTs, 4 assessed gFOBT (3 at low risk of bias and one moderate, Appendix Tables 5a and 5b), and 4 trials focused on FS (3 at low and one at high risk of bias caused by a possible bias in the random selection procedure, Appendix Tables 5c and 5d). Considering observational studies, risk of bias varied from 4 to 8 out of 9 on the NOS (Appendix Tables 6 and 7): one study scored 4 (high risk of bias); 6 studies scored 5 or 6 and 3 studies scored 7 or 8 points.
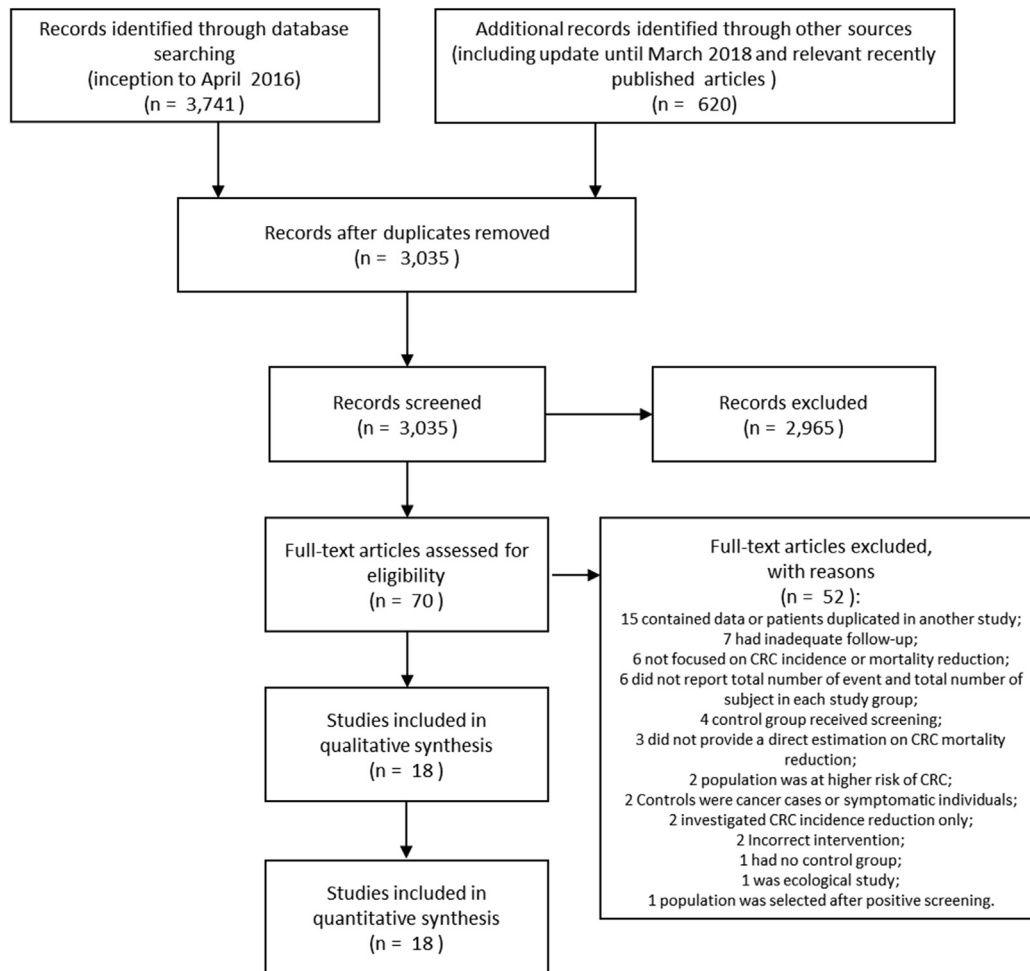
Fig. 1. Flow chart for article search and selection process. CRC, colorectal cancer.

3.1. What is the impact of gFOBT screening across Europe?

Effectiveness of gFOBT was investigated using various study designs and target ages: screening was offered to individuals between the ages 45 and 74 or 75 years in two RCTs [22,23] and a population-based cohort study [24], between the ages 50 and 63−74 years in three cohort studies [9,25,26], between the ages 60 and 64−69 years in two RCTs [7,27] and for anyone older than 40 years in two case−control studies [28,29]. Despite these differences, the estimated impact of gFOBT screening did not vary substantially across studies. Among individuals invited to screening, gFOBT screening (participation rate ranging from 48% to 70%) decreased their CRC mortality by 8−16% compared with that of those not invited (Table 2, not including studies at high risk of bias) [9,22−24,26,27]. When studies at higher risk of bias were included, no effect on CRC mortality was documented in Finland (relative risk [RR] = 1.04, 95% CI: 0.84−1.3, study at moderate risk; standardized mortality ratio (SMR) = 1.2, 95% CI: 0.75−1.7, at high risk of bias; Fig. 2) [7,25].

For individuals participating in screening, the reduction in CRC mortality was up to 40% [29]. However, this effect was estimated only in observational studies (3 case−control and 3 cohort studies) [9,24,28−30] and may be confounded by demographic differences between participants and non-participants in screening. As shown by Libby et al [9], estimates for cancer-specific mortality reduction adjusted for confounding are significantly lower (RR = 0.83, 95% CI: 0.79−0.87) than unadjusted measures (RR = 0.73, 95% CI: 0.65−0.82).

3.2. What is the impact of screening with the FIT in Europe?

Two observational studies assessed the effect of FIT screening on CRC mortality, both from Southern Europe (Italy; Table 1) [31,32]. Among individuals invited to FIT screening, incidence-based CRC mortality (i.e. CRC mortality in those with a confirmed CRC diagnosis in the local cancer registry) was 36% lower than that among those not invited (estimated with a maximum follow-up of 8 years) [31]. The probability of

Table 2
Characteristics of the included studies investigating the effect of stool tests (gFOBT or FIT).

Screening/ region/study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow- up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self- selection bias	RR (95% CI) for colorectal cancer mortality
gFOBT											
Northern Europe											
Lindholm et al [27]	Sweden	RCT	34,144 invited 34,164 not invited[e]	60—64	N/A[e]	9	70	A	Invited vs not invited	—	0.84 (0.71 —0.99)
Kronborg et al [22]	Denmark	RCT	30,762 invited 30,966 not invited[e]	45—75	2	13.9	67	A	Invited vs not invited	—	0.84 (0.73 —0.96)
Bjerrum et al [26]	Denmark	Cohort	166,277 invited 1,240,348 not invited	50—74	Once	8.9	48	6/9	Invited vs not invited *Participants vs not invited*	— *No*	0.92 (0.86 —0.99) *0.77 (0.67 —0.90)*
Pitkaniemi et al [7]	Finland	RCT	180,210 invited 180,282 not invited[e]	60—69	2	4.5	69	B[g]	Invited vs. not invited	—	1.04 (0.84 —1.28)
Malila et al [25]	Finland	Cohort	1785 invited	50—63	N/A	9	69	4/9[h]	Invited vs. control group[i]	—	1.17 (0.75 —1.73)
Southern Europe											
Bertario et al [28]	Italy	Case —control	95 cases (16[b]) 475 controls[c] (109[b])	≥40	2	N/A	N/A	6/9	*Participants vs non-participants*	*No*	*0.64 (0.36 —1.15)*
Zappa et al [29]	Italy	Case —control	206 cases (46[b]) 1030 controls[c] (295[b])	≥41	2.5	N/A	N/A	5/9	*Participants vs non-participants*	*No*	*0.60 (0.40 —0.90)*
Western Europe											
Scholefield et al [23]	UK	RCT	76,056 invited 75,919 not invited[c]	45—74	2	19.5	57	A	Invited vs not invited	—	0.91 (0.84 —0.99)
Libby et al [9]	UK	Cohort	379,655 invited 379,655 not invited	50—69	2	8	61	7/9	Invited vs not invited *Participants vs not invited* *Participants vs not invited*	— *Yes* *No*	0.90 (0.83 —0.99) *0.83 (0.79 —0.87)* *0.73 (0.65 —0.82)*
Faivre et al [30]	France	Case —control	178 cases (92[b]) 712 controls (435[b])	45—80	2	N/A	N/A	7/9	Participants vs non- participants	No	0.67 (0.48 —0.94)
Hamza et al [24]	France	Quasi- experiment	45,642 invited 45,557 not invited	45—74	2	17.3	56	6/9	Invited vs not invited *Participants vs not invited*	— *No*	0.87 (0.80 —0.94) *0.67 (0.59 —0.76)*
FIT											
Southern Europe											
Ventura et al [32]	Italy	Cohort	6961 participants 26,285 non- participants[e]	50—70	2	10.7	N/A	8/9	*Participants vs non- participants<*	*No*	*0.59 (0.37 —0.93)*

Table 2 (*continued*)

Screening/ region/study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow-up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self-selection bias	RR (95% CI) for colorectal cancer mortality
Rossi et al [31]	Italy	Cohort	171,785 invited	50−74	2	8[d]	64	6/9	Invited vs. not invited (incidence-based mortality)[d]	−	0.64[d] (0.52 −0.78)

N/A, not available; gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test; RCT, randomised controlled trial; RR, relative risk; CI, confidence interval; CRC, colorectal cancer; UK, United Kingdom.

Target age: ages targeted by the organised screening programme assessed in the study; follow-up: median follow-up time after initiation of the screening programme. RR: standard mortality ratios, hazard ratios and odds ratio are presented as a RR. Screening effects estimated comparing participants and non-participants are shown in italics.

[a] Quality assessment made as per the Newcastle−Ottawa Scale and Cochrane Collaboration criteria for observational studies and RCTs, respectively; risk of bias for RCTs was categorised considering the final judgement of risk of bias as follows: A, low risk; B, moderate risk and C, high risk.

[b] Exposed to screening.

[c] Controls were drawn from the same population as the intervention group.

[d] Maximum follow-up, this short follow-up might have an impact on the incidence-based mortality estimates (longer survival of individuals with screen-detected colorectal cancers).

[e] Study was designed with a not-regular screening interval.

[g] Limited follow-up time to assess CRC mortality reduction.

[h] Lack of information regarding representativeness of the exposed cohort, selection of the non-exposed and ascertainment of the exposure.

[i] General Finnish population was set as the control group.

dying from CRC was 41% lower in those who participated in FIT screening than in those who did not participate. However, this estimate was not adjusted for demographic differences between participants and non-participants [32].

What is the impact of once-in-a-lifetime FS screening across Europe?

The effect of offering FS screening was investigated by 4 RCTs (Table 3, and Fig. 3) [33−36]. Studies differed based on screening participation (58−81%), sample size, age at screening (from 50−55 to 64 years), enrolment and risk of bias. The median follow-up varied from 10.9 to 21.0 years. Long-term outcomes (follow-up up to 21 years) and the effectiveness of FS in combination with FIT screening were investigated only in Northern Europe [33,36]. CRC mortality reductions due to once-only FS screening ranged from 21% to 30% (point estimates; among those invited compared with among those not invited) [33−35]. When FS was offered in combination with the FIT, probability of dying from CRC was 25% lower in the invited group than in the not-invited reference group (RR = 0.75, 95% CI: 0.57−0.99) [33].

Among participants in the FS screening group, CRC mortality was 38−41% lower in the invited participants than in the not-invited control group (estimates adjusted for demographic differences in non-participants; Fig. 3) [34,35].

3.3. What is the impact of colonoscopy in Europe?

The effect of colonoscopy screening on CRC mortality was only evaluated in one Swiss study (Table 3) [37]. In a closed prospective cohort study of 22,686 individuals, the reported risk reduction for CRC death was 88% (95% CI: 7−99%) among those who participated in screening compared with among those who did not participate (not adjusted for demographic differences in non-participants).

3.4. How does the effect of CRC screening differ across Europe?

Effectiveness of FIT and colonoscopy screening was only investigated in a few countries, and therefore, a direct comparison across different European regions was not possible. For gFOBT, the effectiveness of screening in terms of CRC reduction mortality varied from 9% to 13% in Western Europe [9,23,24] to 16% in Northern Europe [22,27]. For FS screening, effects on CRC mortality varied from a 21%30% reduction across European regions, when studies at high risk of bias were excluded [33−35].
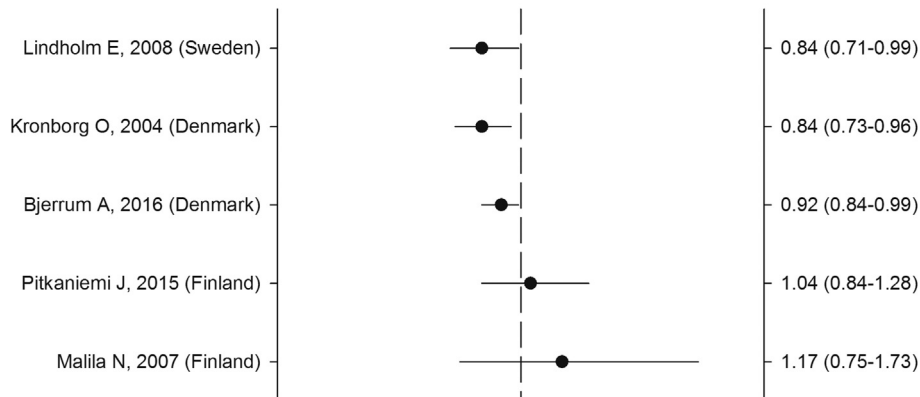
For individuals participating in screening (especially with gFOBT), demographic differences between participants and non-participants were not considered in the effect estimations, limiting the comparison between studies.
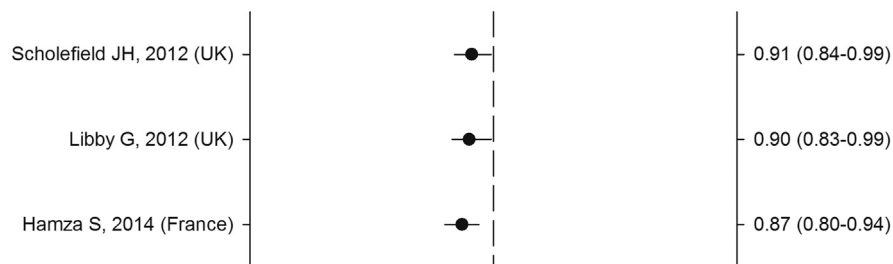
4. Discussion

In this systematic review, we evaluated the variation in the effectiveness of different CRC screening strategies across European regions. To our knowledge, no previous studies have investigated the variation in screening effectiveness across countries, especially countries that

Intention to treat analysis

Northern Europe, gFOBT

Study	Relative Risk (95% CI)
Lindholm E, 2008 (Sweden)	0.84 (0.71-0.99)
Kronborg O, 2004 (Denmark)	0.84 (0.73-0.96)
Bjerrum A, 2016 (Denmark)	0.92 (0.84-0.99)
Pitkaniemi J, 2015 (Finland)	1.04 (0.84-1.28)
Malila N, 2007 (Finland)	1.17 (0.75-1.73)

Western Europe, gFOBT

Study	Relative Risk (95% CI)
Scholefield JH, 2012 (UK)	0.91 (0.84-0.99)
Libby G, 2012 (UK)	0.90 (0.83-0.99)
Hamza S, 2014 (France)	0.87 (0.80-0.94)

Southern Europe, FIT

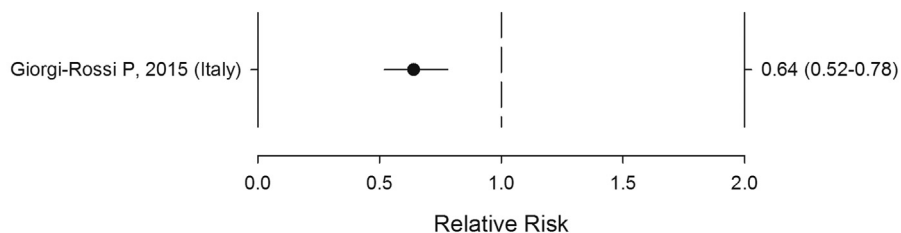| Study	Relative Risk (95% CI)
Giorgi-Rossi P, 2015 (Italy)	0.64 (0.52-0.78)

Relative Risk

Fig. 2. Impact of gFOBT and FIT screening per European region (intention-to-treat analysis). gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test.

share similar health goals such as EU member states. We found that citizens invited to CRC screening in some European countries were at lower risk of dying from CRC than those not invited: up to 30% for FS and up to 16% for gFOBT (excluding studies with a high risk of bias). The effect of gFOBT and sigmoidoscopy screening varied only moderately between and within European regions, with variations ranging from 8% to 13% in Western to 16% in Northern Europe for the effect of gFOBT; and from 21% in Northern to 30% in Western Europe for the effect of FS. Moreover, evidence from RCTs showed consistent results across Europe, especially when the duration of follow-up was adequate (>10 years).

Screening with gFOBT was mainly conducted in Northern and Western Europe, varying in screening target ages and reporting different screening participation rates. Participation geographically varied across Europe, indicating a higher willingness to accept gFOBT screening among individuals included in studies conducted in Northern (67−70%) than in Western Europe (56−61%). Nevertheless, an 8−16% reduction in CRC mortality was found across Europe in those invited to gFOBT screening [9,22−24,26,27], and recent population-based cohort analyses, performed in Scotland and France, indicated a 10−13% lower risk of dying from CRC [9,24]. Although two studies from Finland showed no impact on CRC mortality in that

Table 3
Characteristics of the included studies investigating the effect of endoscopy tests (FS or colonoscopy).

| Screening/region/study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow-up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self-selection bias	RR (95% CI) for colorectal cancer mortality
FS											
Northern Europe											
Holme et al [33]	Norway	RCT	10,283 invited to FS 10,289 invited to FS + FIT 78,220 not invited[d]	50−64	Once	15	61−65	A	Invited vs not invited Invited vs not invited	− −	0.79 (0.65−0.96) FS + FIT group: 0.75 (0.57−0.99)
Thiis-Evensen et al [36]	Norway	RCT	400 invited 399 not invited[d]	50−59	Once (colonoscopy after 13 years[c])	21.7	81	C	Invited vs not invited	−	0.16 (0.02−1.28)
Southern Europe											
Segnan et al [35]	Italy	RCT	17,136 invited 17,136 not invited[d]	55−64	Once	11.4	58	A	Invited vs not invited *Participants vs not invited (per-protocol analysis)*	− *Yes*	0.78 (0.56−1.08) *0.62 (0.40−0.96)*
Western Europe											
Atkin et al [34]	UK	RCT	57,099 invited 112,939 not invited[d]	55−64	Once	17.1	71	A	Invited vs not invited *Participants vs not invited (per-protocol analysis)*	− *Yes*	0.70 (0.62−0.79) *0.59 (0.49−0.70)*
Colonoscopy											
Western Europe											
Manser et al [37]	Switzerland	Cohort	1912 participants 20,774 non-participants[d]	50−80	Once	6	N/A	6/9	*Participants vs non-participants*	*No*	*0.12 (0.01−0.93)*

N/A, not available; RR, relative risk; FIT, fecal immunochemical test; RCT, randomised controlled trial; RR, relative risk; CI, confidence interval; UK, United Kingdom; FS, flexible sigmoidoscopy. Target age: ages targeted by the organised screening programme assessed in the study; follow-up: median follow-up time after initiation of the screening programme. RR: standard mortality ratios, hazard ratios and odds ratio are presented as a RR. Screening effects estimated comparing participants and non-participants are shown in italics.

[a] Quality assessment made as per the Newcastle−Ottawa Scale and Cochrane Collaboration criteria for observational study and RCT, respectively; risk of bias for RCTs was categorised considering the final judgement of risk of bias as follows: A, low risk; B, moderate risk; and C, high risk.

[c] Different screening period in the study design. (Both the control and intervention group were invited to participate in a colonoscopy investigation.)

[d] Controls were drawn from the same population as the intervention group.

Intention to treat analysis
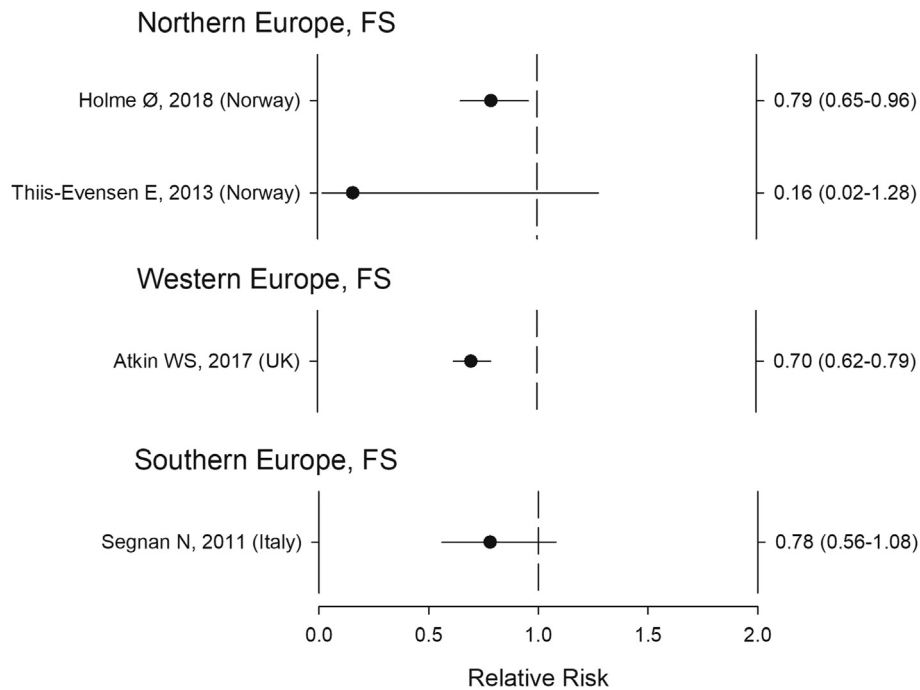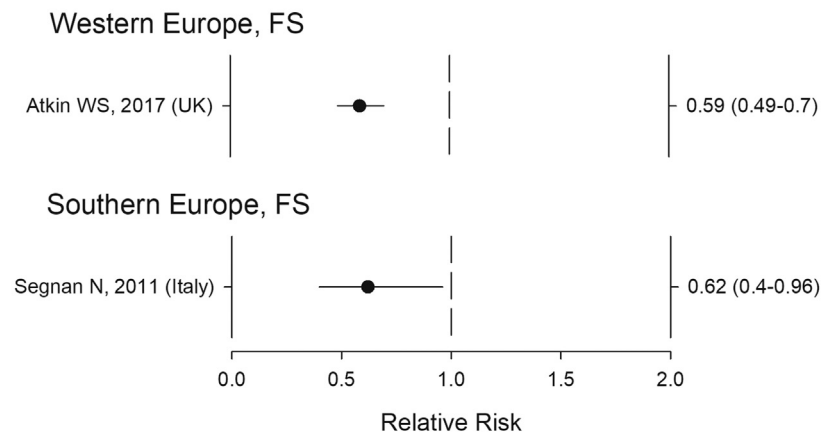

Per-protocol analysis

Fig. 3. Impact of flexible sigmoidoscopy screening per European region and the type of assessment (intention-to-treat or per-protocol analysis). FS, flexible sigmoidoscopy.

country, the small sample size (the study at high risk, which was conducted by Malila *et al.* [25]) or limited follow-up (the study at moderate risk of bias, which was conducted by Pitkaniemi *et al.* [7]) may explain those results.A recent modeling modelling study (conducted by Chiu *et al.* [38]) supported the latter explanation, predicting a 9% CRC mortality reduction after 10 years of follow-up for the Finnish study of Pitkaniemi *et al.* For those persistently participating in gFOBT screening, effectiveness was higher (up to 40% lower CRC mortality), but this effect was mainly observed in

case–control studies that did not take into consideration the demographic differences between participants and non-participants [24,28–30]. Therefore, these results may be biased and driven by other factors, such as different underlying CRC risks or the healthy screenee effect.

Offering FS once in a lifetime was associated with a reduction in CRC mortality ranging from 21% to 30% when studies at high risk of bias were excluded [33–35]. Variations in the screening participation rate and intervention group sample size may explain the slight

difference in the effect range: compared with the UK RCT, the Italian and Norwegian trials had fewer individuals invited and participating in FS screening (sample size of the intervention group: 17,136−10,283 versus 57,099 individuals, respectively; participation rate: 58−65% versus 71%, respectively) [33−35].

It is important to note that evidence of the effectiveness of FS was reported only in RCTs based on predefined populations willing to accept this screening modality [34,35]. At this time, few population-based organised screening programmes were implemented using this test (Italy [Piedmont], Norway and England) [5,39], and based on their monitoring data, FS screening uptake was found to be lower in the unselected population than that observed in the RCTs (i.e. ≥ 58%): response rates varied from 29% (Italy [Turin and Verona]) to 43% (England) [40]. Nevertheless, FS has the possibility to better detect and remove adenomatous polyps (by participating in screening once in a life-time) and could be superior in reducing CRC mortality compared to at least gFOBT (if we restrict and compare only the RCT results).

There was much less evidence for the effectiveness of FIT and colonoscopy screening. The FIT was implemented mainly in Southern and Eastern Europe (Italy, Spain, Malta, Slovenia and Hungary) and in a few countries in Western Europe (the Netherlands and Ireland) [5]. However, almost all of these population-based screening programmes were implemented relatively recently, making it impossible at this point to observe a mortality effect. Until now, the impact of the FIT in reducing CRC mortality was only reported in Italian studies [31,32]. Opportunistic or pilot colonoscopy screening programmes have been implemented in more countries [5,39] although evidence of their impact on CRC mortality is lacking, with only one European observational study providing information on the beneficial effect of participating in colonoscopy screening [37]. Three RCTs comparing FIT and colonoscopy screening are underway, but their results may not be available for another 10 years [41−43].

Since 2003, the EU has recommended CRC screening for men and women, suggesting starting and ending gFOBT screening within the ages 50−74 years (the effectiveness of other CRC screening modalities was not yet assessed by RCTs at the time of the recommendation) [4]. However, in 2012, new multidisciplinary, evidence-based European guidelines for quality assurance in CRC screening were proposed, reporting that the FIT, FS and total colonoscopy might be commonly considered as reasonable alternatives to gFOBT screening [44]. Our study suggests that the effect of FS and gFOBT on CRC mortality may be consistent across several European settings, indicating that FS screening is more effective than gFOBT. Several studies have highlighted the impact of FS in reducing CRC incidence

(another critical outcome of CRC screening) [33−35], whereas gFOBT seems not to have had a statistically significant effect on this outcome [23]. Although it may be reasonable to assume a higher efficacy from endoscopy screening than from gFOBT, the current recommended stool test across Europe is the FIT, which can achieve at least the same CRC mortality reduction as that observed with gFOBT (or potentially similar to that observed with FS) [31,32] but with the additional effect on reducing CRC incidence [31,32]. Thus, policymakers should consider test-specific effectiveness and population preferences (such as expected participation in screening) as the essential determinants in deciding which CRC screening program to implement. Results from a RCT in the Netherlands showed a far higher initial uptake with stool tests (FIT: 61.5% and gFOBT: 49.5%) than with endoscopy investigations (FS: 32.4%) [45]. Similarly, annual screening participation rates were higher in Italian FIT screening programmes than in FS (compliance in 2011: FIT, 47.1%; FS, 24.5%) [13]. Nevertheless, FS is offered once in a lifetime, whereas screening with stool tests needs recurrent participation over several screening rounds to achieve their expected effects on CRC mortality. Considering initial uptake or annual participation rates instead of cumulative uptake over time may therefore not be appropriate [40], especially in light of the recent data showing that there were significantly fewer regular participants than the participants in the first screening round [46−48]. In addition, potential constraints in endoscopy resources and harms of screening need to be considered by decision makers. Depending on the type of screening, the demand for endoscopy may increase substantially. Shortage of colonoscopy capacity may reduce the potential benefit of the CRC screening (especially among those with lower social economic status). Increasing colonoscopy efficiency, training and regulations may curb this demand, but at least 10−15 years are needed to completely overcome the shortage [49]. Furthermore, screening might lead to the overtreatment of some precancerous lesions that would never develop into CRC, increasing risks of screening. In some rare cases, colonoscopy examinations could even cause severe complications or death (especially when polypectomy is performed).

Important limitations are evident and noteworthy. First, in assessing the effect of participating in screening, few studies corrected their estimates to take into account demographic differences among participants and non-participants, therefore affecting external comparability of their findings. Thus, any review of the effect of participating in screening between and within European regions may be affected by selection bias. Moreover, the evidence of effectiveness for various screening strategies was limited: evidence for FIT and colonoscopy screening was available only for a few countries, and it was impossible to compare their effectiveness across

different European regions. The impact of these screening modalities was assessed mainly in observational studies distinguished by a selected group of individuals actively participating in screening (especially for colonoscopy). With such designs, the results are particularly prone to selection bias. In our review, we included some evidence based on data collected in periods and populations with less favourable CRC survival (i.e. evidence for gFOBT screening in England and Denmark) [50]. CRC survival has substantially increased in the last decades owing to improvements in surgical and medical oncology (especially in managing rectal carcinoma) [51,52]. Thus, the effect of gFOBT on CRC mortality may be overestimated in those studies. Finally, this study is limited by the absence of studies conducted in Eastern European countries. Considering the recent GLOBOCAN estimates, CRC mortality was higher in Central and Eastern Europe than in the European average in both men and women [1]. Hence, CRC screening could be more effective in that region [53].

To conclude, this review highlights the beneficial effect of CRC screening across Europe. The impact on CRC mortality of inviting individuals with screening strategies adopting gFOBT or FS seems to be consistent across several European settings. As a consequence, to improve or implement CRC screening programmes, European policymakers should carefully consider national endoscopy resources and population preferences in conjunction with efficacy of screening modalities.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.12.014.

References

[1] Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356−87.

[2] Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer 2015;51:1164−87.

[3] Elmunzer BJ, Singal AG, Sussman JB, Deshpande AR, Sussman DA, Conte ML, et al. Comparing the effectiveness of competing tests for reducing colorectal cancer mortality: a network meta-analysis. Gastrointest Endosc 2015;81:700−709 e3.

[4] Council of the European Union. Council recommendation of 2 december 2003 on cancer screening (2003/878/EC). Off J Eur Union 2003;L 327:34−8.

[5] Altobelli E, Lattanzi A, Paduano R, Varassi G, di Orio F. Colorectal cancer prevention in Europe: burden of disease and status of screening programs. Prev Med 2014;62:132−41.

[6] Malila N, Anttila A, Hakama M. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. J Med Screen 2005;12:28−32.

[7] Pitkaniemi J, Seppa K, Hakama M, Malminiemi O, Palva T, Vuoristo MS, et al. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterol 2015;2:e000034.

[8] Leuraud KJ-SD, Saline E. Evaluation épidémiologique du programme de dépistage organisé du cancer colorectal en France. Première évaluation depuis la généralisation du programme pour 46 départements sur la période 2008-2009. Saint-Maurice: Institut de veille sanitaire; 2012. p. 29.

[9] Libby G, Brewster DH, McClements PL, Carey FA, Black RJ, Birrell J, et al. The impact of population-based faecal occult blood test screening on colorectal cancer mortality: a matched cohort study. Br J Canc 2012;107:255−9.

[10] van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343−50.

[11] Rácz I, Szabó A, Goda M, Oláh A. Preliminary colorectal cancer screening program model in Hungary. Gastrointest Oncol 2002; 4(2−3):119−21.

[12] Tepes B, Bracko M, Novak Mlakar D, Stefanovic M, Stabuc B, Frkovic Grazio S, et al. Results of the FIT-based national colorectal cancer screening program in Slovenia. J Clin Gastroenterol 2017;51:e52−9.

[13] Zorzi M, Da Re F, Mantellini P, Naldoni C, Sassoli De'Bianchi P, Senore C, et al. Screening for colorectal cancer in Italy: 2011-2012 survey. Epidemiol Prev 2015;39:93−107.

[14] Cancer Screening in the European Union. Report on the implementation of the Council recommendation on cancer screening. 09 february 2017. 2017. Available at: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf.

[15] European Colorectal Cancer Screening Guidelines Working G, von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy 2013;45:51−9.

[16] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

[17] Zielonke N, Gini A, Jansen EEL, Bramer W. Evidence for cancer specific and all-cause mortality reduction due to screening for breast, cervical and colorectal cancer: a systematic review. PROSPERO 2016. CRD42016042433.

[18] Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997; 16:1017−29.

[19] Multilingual Thesaurus of the European union (EUROVOC). Available at: http://eurovoc.europa.eu/drupal/? q=request&uri=http://eurovoc.europa.eu/100277.

[20] van der Meulen MP, Lansdorp-Vogelaar I, van Heijningen EM, Kuipers EJ, van Ballegooijen M. Nonbleeding adenomas: evidence of systematic false-negative fecal immunochemical test results and their implications for screening effectiveness-A modeling study. Cancer 2016;122:1680−8.

[21] Higgins JPGS. Cochrane handbook for systematic review of interventions v5.1.0. Available at: http://training.cochrane.org/ handbook. [Accessed April 2016].

[22] Kronborg O, Jørgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 2004;39:846−51.

[23] Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036−40.

[24] Hamza S, Cottet V, Touillon N, Dancourt V, Bonithon-Kopp C, Lepage C, et al. Long-term effect of faecal occult blood screening on incidence and mortality from colorectal cancer. Dig Liver Dis 2014;46:1121−5.

[25] Malila N, Hakama M, Pukkala E. A 25-year follow-up of a population screened with faecal occult blood test in Finland. Acta Oncol 2007;46:1103−6.

[26] Bjerrum A, Andersen O, Fischer A, Lindebjerg J, Lynge E. Colorectal cancer mortality 10 years after a single round of guaiac faecal occult blood test (gFOBT) screening: experiences from a Danish screening cohort. BMJ Open Gastroenterol 2016;3.

[27] Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg 2008;95:1029−36.

[28] Bertario L, Russo A, Crosignani P, Sala P, Spinelli P, Pizzetti P, et al. Reducing colorectal cancer mortality by repeated faecal occult blood test: a nested case-control study. Eur J Cancer 1999; 35:973−7.

[29] Zappa M, Castiglione G, Grazzini G, Alini PF, Giorgi D, Paci E, et al. Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. Int J Cancer 1997;73:208−10.

[30] Faivre J, Tazi MA, El Mrini T, Lejeune C, Benhamiche AM, Dassonville F. Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study. Br J Canc 1999; 79:680−3.

[31] Rossi PG, Vicentini M, Sacchettini C, Di Felice E, Caroli S, Ferrari F, et al. Impact of screening program on incidence of colorectal cancer: a cohort study in Italy. Am J Gastroenterol 2015;110:1359−66.

[32] Ventura L, Mantellini P, Grazzini G, Castiglione G, Buzzoni C, Rubeca T, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig Liver Dis 2014; 46:82−6.

[33] Holme O, Loberg M, Kalager M, Bretthauer M, Hernan MA, Aas E, et al. Long-term effectiveness of sigmoidoscopy screening on colorectal cancer incidence and mortality in women and men: a randomized trial. Ann Intern Med 2018; 168:775−82.

[34] Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017;389:1299−311.

[35] Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian randomized controlled trial - SCORE. J Natl Cancer Inst 2011;103:1310−22.

[36] Thiis-Evensen E, Kalager M, Bretthauer M, Hoff G. Long-term effectiveness of endoscopic screening on incidence and mortality of colorectal cancer: a randomized trial. United Eur Gastroenterol J 2013;1:162−8.

[37] Manser CN, Bachmann LM, Brunner J, Hunold F, Bauerfeind P, Marbet UA. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. Gastrointest Endosc 2012;76:110−7.

[38] Chiu SY, Malila N, Yen AM, Chen SL, Fann JC, Hakama M. Predicting the effectiveness of the Finnish population-based colorectal cancer screening programme. J Med Screen 2017. 969141316684524.

[39] Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637−49.

[40] Senore C, Ederle A, Benazzato L, Arrigoni A, Silvani M, Fantin A, et al. Offering people a choice for colorectal cancer screening. Gut 2013;62:735−40.

[41] Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM). NCT01239082, available at: https://clinicaltrials.gov/ct2/show/NCT01239082, last access: November 22, 2019.

[42] Kaminski MF, Bretthauer M, Zauber AG, Kuipers EJ, Adami HO, van Ballegooijen M, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. Endoscopy 2012;44:695−702.

[43] Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697−706.

[44] Malila N, Senore C, Armaroli P, International Agency for Research on C. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Organisation. Endoscopy 2012;44(Suppl 3):SE31−48.

[45] Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JC, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Canc 2009;100:1103−10.

[46] van der Vlugt M, Grobbee EJ, Bossuyt PM, Bongers E, Spijker W, Kuipers EJ, et al. Adherence to colorectal cancer screening: four rounds of faecal immunochemical test-based screening. Br J Canc 2017;116:44−9.

[47] Crotta S, Segnan N, Paganin S, Dagnes B, Rosset R, Senore C. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. Clin Gastroenterol Hepatol 2012;10:633−8.

[48] Liang PS, Wheat CL, Abhat A, Brenner AT, Fagerlin A, Hayward RA, et al. Adherence to competing strategies for colorectal cancer screening over 3 years. Am J Gastroenterol 2016;111:105−14.

[49] Coebergh JW. Colorectal cancer screening in Europe: first things first. Eur J Cancer 2004;40:638−42.

[50] Holleczek B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - results from the EUROCARE-5 study. Eur J Cancer 2015;51:2158−68.

[51] Lemmens V, van Steenbergen L, Janssen-Heijnen M, Martijn H, Rutten H, Coebergh JW. Trends in colorectal cancer in the south of The Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. Acta Oncol 2010;49:784−96.

[52] Angell-Andersen E, Tretli S, Coleman MP, Langmark F, Grotmol T. Colorectal cancer survival trends in Norway 1958-1997. Eur J Cancer 2004;40:734−42.

[53] Minicozzi P, Walsh PM, Sanchez MJ, Trama A, Innos K, Marcos-Gragera R, et al. Is low survival for cancer in Eastern Europe due principally to late stage at diagnosis? Eur J Cancer 2018;93: 127−37.