Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial

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Summary

Background Colonoscopy and the faecal immunochemical test are accepted strategies for colorectal cancer screening in the average-risk population (ie, people aged ≥50 years without personal or family history of colorectal cancer). In this trial, we aimed to compare whether invitation to screening with faecal immunochemical test was non-inferior to colonoscopy in a screening programme.

Methods COLONPREV was a pragmatic, randomised, controlled, non-inferiority trial done at 15 tertiary hospitals across eight regions of Spain. Eligible participants were presumptively healthy and aged between 50 years and 69 years without a personal history of colorectal cancer, adenoma or inflammatory bowel disease, family history of hereditary or familial colorectal cancer (ie, two or more first-degree relatives with colorectal cancer or one diagnosed before age 60 years), severe comorbidities, or previous colectomy. Participants were randomly assigned (1:1) to one-time colonoscopy or biennial faecal immunochemical test before invitation to screening. The primary endpoint was colorectal cancer mortality at 10 years, assessed in the intention-to-screen population. An absolute difference of less than 0·16 percentage points was required to show non-inferiority. This trial was registered with ClinicalTrials.gov, NCT00906997.

Findings Between June 1, 2009, and Dec 31, 2021, 57 404 individuals were randomly assigned to receive an invitation for colonoscopy (n=28 708) or the faecal immunochemical test (n=28 696). The intention-to-screen population consisted of 26 332 individuals in the colonoscopy group and 26 719 in the faecal immunochemical test group. In the intention-to-screen population, participation in any form of screening was 31·8% in the colonoscopy group and 39·9% in the faecal immunochemical test group (risk ratio [RR] 0·79 [95% CI 0·77 to 0·82]). Faecal immunochemical testing was non-inferior to colonoscopy with regard to the risk of colorectal cancer mortality at 10 years: the risk was 0·22% (55 deaths) in the colonoscopy group and 0·24% (60 deaths) in the faecal immunochemical test group (risk difference –0·02 [95% CI –0·10 to 0·06; RR 0·92 [95% CI 0·64 to 1·32]; $p_{non\text{-}inferiority}$=0·0005).

Interpretation Participation in screening was higher among individuals invited to faecal immunochemical test screening than colonoscopy screening. On the basis of participation observed in this study, a faecal immunochemical test-based programme was non-inferior to a colonoscopy-based programme for colorectal cancer-related mortality.

Funding Fundación Científica de la Asociación Española contra el Cáncer and Instituto de Salud Carlos III.

Introduction

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related death.[1] Evidence from several studies has shown that colorectal cancer screening is effective and cost-effective in average-risk individuals (ie, people aged ≥50 years without personal or family history of colorectal cancer).[2–5] For these reasons, organised screening programmes, rather than case-finding or opportunistic approaches, should be implemented to maximise impact and ensure high coverage and equity of access.[6]

Recommended colorectal cancer screening strategies can be divided into two broad categories: stool tests (to identify occult blood [guaiac test and faecal immunochemical test] or exfoliated DNA) and structural examinations (flexible sigmoidoscopy, colonoscopy, CT colonography, and endoscopic capsule).[2] Both faecal occult blood tests and colonoscopy have similar performance for detecting cancer, but colonoscopy is

Lancet 2025; 405: 1231–39

Published Online March 27, 2025 https://doi.org/10.1016/S0140-6736(25)00145-X

This online publication has been corrected. The corrected version first appeared at thelancet.com on April 10, 2025

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Research in context

Evidence before this study

We searched PubMed from database inception to June 17, 2024 for randomised controlled trials published in English that assessed the efficacy of colonoscopy and faecal immunochemical test for screening of colorectal cancer in average-risk individuals (ie, people aged ≥50 years without personal or family history of colorectal cancer). We used the following search terms: ("colorectal cancer" OR "colorectal neoplasm" OR "colon cancer") AND ("colonoscopy" OR "faecal immunochemical test" OR "faecal blood testing") AND "screening". Three randomised trials were identified: the TARGET-C study, comparing one-time colonoscopy, annual faecal immunochemical test, and annual risk-adapted screening; the CONFIRM study, comparing one-time colonoscopy and annual faecal immunochemical test; and the SCREESCO trial, comparing one-time colonoscopy, biennial faecal immunochemical testing, and no intervention. None of the studies reported results on colorectal cancer mortality or incidence. Several studies have shown that colorectal cancer screening is effective and cost-effective in individuals with average risk (ie, people aged ≥50 years without personal or family history of colorectal cancer). For this purpose, organised screening programmes are preferred over opportunistic approaches because they ensure coverage and equity of access, thereby maximising the effectiveness of the screening process. The faecal immunochemical test and colonoscopy are accepted strategies for colorectal cancer screening, the faecal immunochemical test being predominantly implemented in Europe and Australia, whereas colonoscopy is the dominant screening modality in the USA. Nevertheless, randomised controlled trials comparing the efficacy of colonoscopy and the faecal immunochemical test in programmatic screening are needed. In an interim analysis done on completion of the first screening round of the COLONPREV study, we demonstrated that individuals in the faecal immunochemical test group were more likely to participate in screening than those in the colonoscopy group. In this baseline examination, the numbers of participants in whom colorectal cancer was identified were similar in the two study groups. However, comparative data on the effectiveness of both screening strategies in reducing colorectal cancer-related mortality, colorectal cancer incidence, and all-cause mortality at 10 years were missing.

Added value of this study

This pragmatic, randomised, controlled, non-inferiority trial demonstrated that 31·8% of participants in the colonoscopy group and 39·9% of participants in the faecal immunochemical test group participated in screening (risk ratio [RR] 0·79 [95% CI 0·77 to 0·82]). Additionally, invitation to faecal immunochemical test screening was non-inferior to invitation to colonoscopy screening with regard to risk of colorectal cancer mortality at 10 years (0·22% [55 deaths] in the colonoscopy group; 0·24% [60 deaths] in the faecal immunochemical test group; risk difference −0·02 [95% CI −0·10 to 0·06]; RR 0·92 [0·64 to 1·32]; $p_{non\text{-}inferiority}$=0·0005). For colorectal cancer incidence (RR 0·92 [0·79 to 1·08]) and for all-cause mortality (RR 0·99 [0·94 to 1·06]) both strategies appeared to be also similar. Additionally, secondary analyses suggested that both strategies reduced the risk of colorectal cancer mortality with respect to those individuals who did not participate in screening, and reductions in colorectal cancer incidence and death seemed larger with colonoscopy than faecal immunochemical test.

Implications of all the available evidence

The COLONPREV study demonstrates that participation in colorectal cancer screening was higher among participants invited to faecal immunochemical test than to colonoscopy. Invitation to a faecal immunochemical test-based programme was non-inferior to a colonoscopy-based programme in terms of colorectal cancer-related mortality. Accordingly, a less invasive approach, such as faecal immunochemical test, has been validated as an effective strategy for population-based, organised colorectal cancer screening, with potentially significant implications for global health-care policies.

superior for detecting premalignant lesions.[2] Whereas faecal occult blood testing is predominantly implemented in Europe and Australia, colonoscopy is the dominant screening modality in the USA.[7] However, comparisons of the efficacy of colonoscopy and the faecal immunochemical test in programmatic screening are needed.

Efficacy of faecal occult blood testing is supported by randomised controlled trials that have demonstrated that annual or biennial stool guaiac testing reduces colorectal cancer-related mortality and colorectal cancer incidence when compared with no screening.[8–10] Comparative studies have shown that the faecal immunochemical test is more accurate than the guaiac test for the detection of colorectal cancer and advanced adenoma,[11] and is now the recommended option for faecal occult blood testing. In the past decade, organised screening programmes that use faecal immunochemical testing have been associated with reductions in colorectal cancer mortality in a population scenario.[12,13]

Colonoscopy is considered the most accurate method for early detection and prevention of colorectal cancer, and it is also recommended as a first-line screening test. Case–control studies suggested that colonoscopy markedly reduces colorectal cancer incidence[14] and colorectal cancer-related mortality.[15] Additionally, a systematic review and meta-analysis of six observational studies found that screening colonoscopy was associated with a 40–60% reduced risk of colorectal cancer incidence and colorectal cancer-related mortality when compared

with screening sigmoidoscopy.[16] In 2022, the first randomised controlled trial evaluating the efficacy of colonoscopy demonstrated that the risk of colorectal cancer at 10 years was lower among individuals invited to colonoscopy than among those who were assigned to no screening; however, no benefit was observed with regard to colorectal cancer-related mortality at 10 years.[17]

The COLONPREV study is a pragmatic, randomised, controlled, trial designed to assess whether invitation to faecal immunochemical test is non-inferior to invitation to colonoscopy in programmatic colorectal cancer screening. In an interim analysis at completion of the first screening round,[18] we demonstrated that individuals in the faecal immunochemical test group were more likely to participate in screening than those in the colonoscopy group. On the baseline examination, the number of participants in whom colorectal cancer was detected was similar in the two study groups.[18] In the present analysis, we aimed to compare whether invitation to screening with the faecal immunochemical test was inferior to colonoscopy with regard to colorectal cancer-related mortality, colorectal cancer incidence, and all-cause mortality at 10 years, and we also compared the diagnostic yield and detection rate of screen-detected premalignant neoplastic lesions of both screening programmes.

Methods

Study design and participants

COLONPREV was a pragmatic, randomised, controlled non-inferiority trial done at 15 tertiary hospitals across eight regions of Spain, designed to assess whether invitation to screening with biennial faecal immunochemical test was non-inferior to invitation to one-time colonoscopy for reducing colorectal cancer-related mortality at 10 years. The study was preceded by an informative nationwide campaign in November, 2008. The recruitment period was initiated on June 1, 2009, the first screening round finished on June 30, 2011,[18] and the 10-year follow-up was completed on Dec 31, 2021.

The study protocol (appendix p 34) was approved by the ethics committee of the Hospital Clinic of Barcelona (approval number 2006/3379), and all participants provided written informed consent.

Eligible participants were presumptively healthy and aged between 50 years and 69 years. Exclusion criteria were ascertained after randomisation by means of a questionnaire at the local screening office, and included personal history of colorectal cancer, adenoma or inflammatory bowel disease, family history of hereditary or familial colorectal cancer (ie, two or more first-degree relatives with colorectal cancer or one diagnosed before age 60 years), severe comorbidity, and previous colectomy. Patients were also temporarily excluded if they had already received faecal occult blood testing in the previous 2 years, or sigmoidoscopy or colonoscopy within the previous 5 years, or if they had symptoms requiring additional investigations; these patients were eligible for the trial once previous screening tests had expired or if the results of clinical investigations were negative.

This trial was registered with ClinicalTrials.gov, NCT00906997.

Randomisation and masking

Participants were randomly assigned (1:1) to one-time colonoscopy or biennial faecal immunochemical test before invitation to screening. Individuals were sent a pre-invitation presentation letter containing information on colorectal cancer screening and the rationale for this study. After 2 weeks, an invitation letter was sent indicating the specific group in which the participant was allocated. Two additional reminder letters were sent to non-responders 3 months and 6 months after initial invitation. Individuals who agreed to participate in the study received an appointment at the local screening office where they completed the questionnaire. The study design allowed for crossover between both screening strategies based on participant preference. Masking was not possible due to the nature of the trial.

Eligible individuals who did not participate in the baseline screening round were able to participate in the study at any time, provided that they met the inclusion criteria, and were assigned to the initial randomisation group. Individuals who did not participate in the COLONPREV study could be invited to participate in institutional faecal immunochemical test-based screening programmes as they were gradually introduced in each Spanish region.

Procedures

In individuals invited for colonoscopy, bowel cleansing and sedation were performed as previously described.[18] All colonoscopies were performed by experienced endoscopists (>200 colonoscopies per year). For faecal immunochemical testing, one single sample was tested using the automated semiquantitative OC-senso (Eiken Chemical, Tokyo, Japan), without specific dietary or medication restrictions. Samples were processed at each regional reference hospital. The cutoff threshold for indicating the work-up colonoscopy was 15 µg (first round) or 20 µg (subsequent screening rounds) of haemoglobin per gram of faeces.

Further details on study population, randomisation, study interventions, and the quality assurance programme have been reported previously[18] and are in the appendix (pp 6–7).

Outcomes

The primary endpoint was colorectal cancer mortality at 10 years. The key secondary endpoints were the incidence of colorectal cancer at 10 years, rate of major complications, and the diagnostic yield and detection rate of screen-detected premalignant neoplastic lesions at 10 years. Additional secondary endpoints were cost-effectiveness,

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factors influencing participation (demographics, personal and familial characteristics, and socioeconomic status), and colorectal cancer incidence at 15 years, which will be reported elsewhere. Survival data were confirmed by cross-checking the National Mortality Index (Índice Nacional de Defunciones).[19] Colorectal cancer-related deaths were defined as those that were listed as such in the corresponding hospital or regional registry; for ambiguous cases, a consensus was reached within the study quality committee. Identification of incident cases was done by cross-checking the regional cancer registries and other sources of information (ie, primary care electronic medical records and hospital databases). Diagnosis of colorectal cancer was defined according to the International Classification of Diseases, 10th revision. Among participants in the study, tumour staging was established according to the American Joint Committee on Cancer TNM staging system.[20] Invasive cancer was considered when malignant cells were observed beyond the muscularis mucosa; accordingly, intramucosal carcinoma (in-situ carcinoma) was not counted as an event. Additionally, tumours with a histopathological diagnosis other than adenocarcinoma were not counted as events. Finally, the diagnostic yield of screen-detected premalignant neoplastic lesions was the number of participants with true positive results divided by the number of eligible participants in the intention-to-screen population, whereas the detection rate was calculated as the number of participants with true positive results divided by the number of participants who actually underwent screening in the as-screened analysis (appendix pp 8–9).

Screening participation was defined as the number of participants who underwent screening divided by the number of eligible participants per group. Individuals randomly assigned to the faecal immunochemical test were considered participants if they completed at least one faecal immunochemical test and the work-up colonoscopy if a positive test occurred.

Among participants in the study, any colorectal examination for screening, surveillance, and diagnostic purposes was registered in an online electronic case report form and stored in a central database. This information was confirmed by consultation of both regional screening programmes and hospital databases. Among people who were randomly assigned but chose not to participate in screening (referred to hereafter as non-participants), information was limited to survival data, development of colorectal cancer, and participation in institutional faecal immunochemical test-based screening programmes. Faecal immunochemical tests performed within institutional programmes were regarded as screening tests for participants in the study, while for non-participants, these tests were counted but not included in the evaluation of study outcomes; in non-participants, this measure served as an estimate of study contamination. Duration of follow-up was calculated from the date of randomisation to the date when any permanent exclusion criterion, absent at the baseline evaluation, was identified, diagnosis of colorectal cancer (for analyses of colorectal cancer incidence), death from colorectal cancer (for analyses of colorectal cancer-related mortality), death from causes other than colorectal cancer, or to the end of follow-up (ie, Dec 31, 2021), whichever came first. In analyses of colorectal cancer mortality, non-colorectal cancer-related deaths were treated as censoring events. In individuals who were temporarily excluded, all of their follow-up time was included but they were ineligible for trial screening during the exclusion period.

Statistical analysis

This study was based on the assumption that invitation to biennial faecal immunochemical test would not be inferior to invitation to one-time colonoscopy with regard to the risk of colorectal cancer mortality at 10 years. The sample size was calculated on the basis of an overall compliance rate of 30% and a crude 10-year rate of colorectal cancer death of 0·696%. Therefore, assuming a crude 10-year rate of colorectal cancer death of 0·174% among participants undergoing colonoscopy (a 75% reduction) and of 0·341% among participants screened by faecal immunochemical test (a 51% reduction), an absolute difference of less than 0·16 percentage points was required to show non-inferiority. Thus, using a one-sided test of proportions with an α risk of 0·025 and a β risk of 0·10, we determined that 27749 participants were required in each trial group.

Primary and secondary endpoints were assessed according to the intention-to-screen population (main analysis) and the as-screened and per-protocol populations (secondary analyses). Individuals were excluded from these analyses if they attended the screening office and met one or more exclusion criteria. Patients who did not attend the screening office and, consequently, did not provide information about exclusion criteria, were classified as eligible and included in the analyses. Any colorectal cancer identified in either attenders or non-attenders was verified, and those individuals in whom this tumour was diagnosed before study entry were excluded.

The primary endpoint, secondary endpoint of colorectal cancer incidence, and post-hoc endpoint of all-cause mortality were assessed in the intention-to-screen, as-screened, and per-protocol populations, with the Kaplan–Meier estimator for all causal contrasts. The secondary endpoint of diagnostic yield of screen-detected premalignant neoplastic lesions was assessed in the intention-to-screen population, the detection rate of screen-detected premalignant neoplastic lesions was assessed in the as-screened population, and major complications were assessed in the intention-to-screen and per-protocol populations. The intention-to-screen population was defined as all individuals who were randomly assigned to the respective study group and was the main analysis reported in this Article. The as-screened population was

defined as all individuals who participated in screening classified according to the screening procedure actually done. The per-protocol population was defined as all individuals who completed the procedure originally allocated. Risks were compared using risk ratios (RRs) and differences with 95% CIs for all analyses, with the exception of diagnostic yield and detection of premalignant neoplastic lesions, for which odds ratios (ORs) were used. Additionally, for the as-screened and per-protocol analyses, adjustment for age, gender, and centre was performed using inverse probability weighting.

There was no prespecified plan to adjust for multiple testing. The widths of the 95% CI were not adjusted for multiple testing and cannot be used in place of hypothesis tests.

All-cause mortality was assessed as a post-hoc outcome. We also did a post-hoc sensitivity analysis to address potential biases that might affect the data from the Canary Islands (ie, imbalance between study groups in the number of individuals who could not be contacted and an overall lower colorectal cancer-related mortality rate).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 1, 2009, and Dec 31, 2021, 57 404 individuals were randomly assigned to receive an invitation for colonoscopy (n=28 708) or the faecal immunochemical test (n=28 696), of whom 3215 could not be contacted or had died before invitation (1782 [6·2%] individuals in the colonoscopy group and 1433 [5·0%] individuals in the faecal immunochemical test group), and 1138 were excluded (594 [2·2%] individuals in the colonoscopy group and 544 [2·0%] individuals in the faecal immunochemical test group; figure 1).

The intention-to-screen population included 26 332 individuals in the colonoscopy group and 26 719 individuals in the faecal immunochemical test group. Both groups were almost identical regarding demographic characteristics (appendix p 23) and representative of the condition under research (appendix p 24). The follow-up duration was 304 669 person-years in the colonoscopy group and 310 521 person-years in the faecal immunochemical test screening group.

Among 26 332 participants who were eligible to undergo colonoscopy, 5293 individuals accepted the proposed strategy, whereas 3074 were screened by faecal immunochemical test (figure 1), resulting in a participation rate of 31·8%, according to the intention-to-screen analysis. Among 26 719 participants eligible to undergo faecal immunochemical test, 10 525 individuals accepted the proposed strategy, whereas 126 were screened by colonoscopy (figure 1), resulting in a participation rate of 39·9%. Therefore, differences were identified between study groups with regard to the rate of participation (RR 0·79 [95% CI 0·77–0·82]). According to the screening procedure performed, 5419 participants had colonoscopy and 13 599 had faecal immunochemical testing.

Of the 13 599 individuals screened by faecal immunochemical test, 7203 (53·0%) participated in more than 80% of offered screening tests, and 1932 participants (14·2%) participated in 60–80% of offered screening tests.

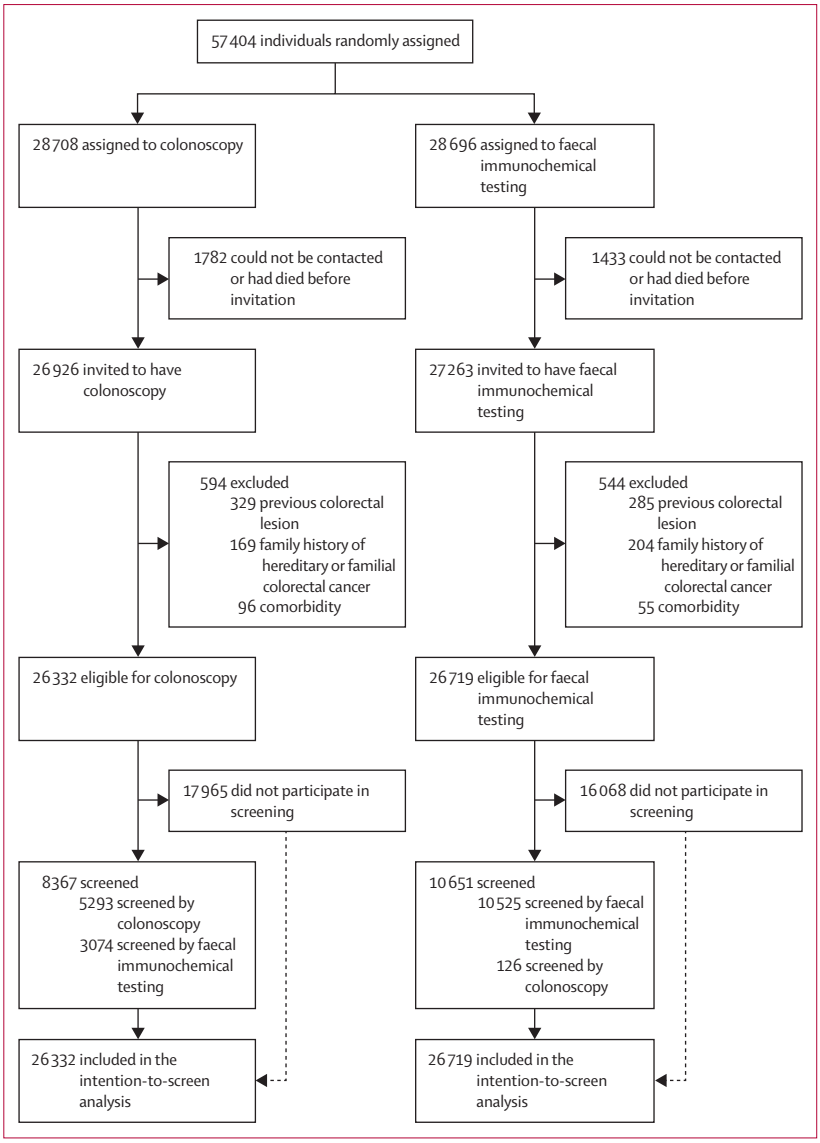

Figure 1: **Trial profile**
The number of participants included in each of the analysis populations (intention-to-screen, as-screened, and per-protocol populations) are shown in the appendix (p 11). The number of eligible individuals shown in this figure differs from that in the previously published preliminary results of the COLONPREV study[18] because 1245 additional participants could not be contacted after being randomly assigned because they had died before randomisation or had an inaccurate mailing address, and due to permanent exclusions among participants recruited in subsequent rounds of the study after the publication of the preliminary results.

	Colonoscopy (n=26 332)		Faecal immunochemical test (n= 26 719)		Colonoscopy versus faecal immunochemical test	
	Individuals with event, n	10-year risk % (95% CI)	Individuals with event, n	10-year risk % (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Colorectal cancer-related mortality	55	0·22% (0·16 to 0·28)	60	0·24% (0·18 to 0·30)	−0·02 (-0·1 to 0·06)	0·92 (0·64 to 1·32)
Colorectal cancer incidence	286	1·13% (1·00 to 1·26)	314	1·22% (1·09 to 1·36)	−0·09 (-0·28 to 0·10)	0·92 (0·79 to 1·08)
All-cause mortality*	1989	7·64% (7·32 to 8·01)	2034	7·68% (7·36 to 7·96)	−0·04 (-0·50 to 0·42)	0·99 (0·94 to 1·06)

*All-cause mortality was a post-hoc endpoint.

Table 1: **Primary and key selected secondary endpoints in the intention-to-screen analyses**

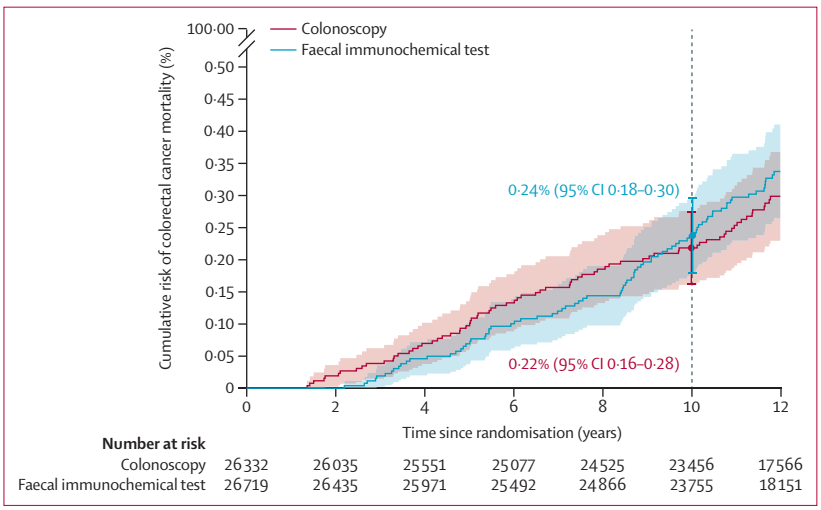

Figure 2: **Cumulative risk of colorectal cancer mortality at 10 years in the intention-to-screen analysis population**
Shaded areas indicate 95% CIs.

The number of participants in each screening round, including those who requested to crossover to the alternative group, is shown in the appendix (p 25).

In the intention-to-treat population (26 332 participants in the colonoscopy group; 26 719 participants in the faecal immunochemical test group; figure 1), the risk of colorectal cancer mortality at 10 years was 0·22% (55 deaths) among participants in the colonoscopy group and 0·24% (60 deaths) among those in the faecal immunochemical test group (RR 0·92 [95% CI 0·64–1·32]; $p_{non\text{-}inferiority}$=0·0005; table 1, figure 2). The risk of colorectal cancer at 10 years was 1·13% (286 cases) in the colonoscopy group and 1·22% (314 cases) in the faecal immunochemical test group (RR 0·92 [95% CI 0·79–1·08]; table 1, figure 3).

Colorectal polyposis was detected in 46 (0·2%) of 26 332 participants in the colonoscopy group and 19 (0·1%) of 26 719 participants in the faecal immunochemical test group (odds ratio 2·50 [95% CI 1·46–4·27]; table 2). Advanced colorectal lesions were identified in 853 (3·2%) of 26 332 participants in the colonoscopy group and in 630 (2·4%) of 26 719 participants in the faecal immunochemical test group (1·39 [1·25–1·54]). Non-advanced colorectal lesions were identified in 1176 (4·5%) of 26 332 participants in the colonoscopy group and in 391 (1·5%) of 26 719 participants in the faecal immunochemical test group (3·17 [2·82–3·56]).

Study outcomes assessed in the as-screened and per-protocol populations, including the timing of colorectal cancer diagnosis and detection rate of both screening strategies, are in the appendix (pp 13–19, 26–31).

Major complications occurred in 82 (0·3%) of 26 332 participants in the colonoscopy group (including 26 individuals with bleeding and four individuals with perforation) and in 80 (0·3%) of 26 719 participants in the faecal immunochemical test group (including 24 individuals with bleeding and five individuals with perforation, all of whom required colonoscopy because of a positive result on the faecal immunochemical test). No differences in the rate of major complications were identified between study groups (RR 1·04 [95% CI 0·76–1·41]).

In post-hoc analysis, the risk of all-cause mortality at 10 years was 7·64% (1989 deaths) among participants in the colonoscopy group and 7·68% (2034 deaths) among those in the faecal immunochemical test group (RR 0·99 [95% CI 0·94–1·06]; table 1; appendix p 12).

We did a post-hoc sensitivity analysis to address potential biases that might affect the data from the Canary Islands (ie, difference of 358 individuals who could not be contacted between study groups, thus resulting in a difference in the corresponding eligible population [ie, 3445 people for colonoscopy and 3803 people for faecal immunochemical test] and an overall lower colorectal cancer-related mortality rate). After excluding individuals recruited in the Canary Islands, the results were almost identical with respect to colorectal cancer-related mortality (RR 0·95 [95% CI 0·66–1·38]), colorectal cancer incidence (0·92 [0·72–1·08]), and all-cause mortality (0·99 [0·93–1·06]; appendix pp 20–22, 32).

Discussion

This pragmatic, randomised, controlled trial demonstrated that invitation to faecal immunochemical test screening was non-inferior to invitation to colonoscopy screening

for colorectal cancer-related mortality (RR 0·92 [95% CI 0·64–1·32]; $p_{non\text{-}inferiority}$=0·0005). Both strategies seemed similar with regard to colorectal cancer incidence (0·92 [0·79–1·08]) and for all-cause mortality (0·99 [0·94–1·06]). Additionally, secondary analyses might suggest that both strategies reduce the risk of death from colorectal cancer with respect to those individuals who did not participate in screening, and reductions in colorectal cancer incidence and death seemed greater with colonoscopy than faecal immunochemical test.

Rather than evaluating the efficacy of colonoscopy and faecal immunochemical test techniques, the present study investigated how they performed in programmatic colorectal cancer screening where people were randommy assigned receive an invitation to screening by either colonoscopy or faecal immunochemical test. This difference is crucial to adequately interpret these results. In that sense, it is important to emphasise that organised screening programmes are highly recommended to maximise the impact of intervention and ensure high coverage and equity of access at population level, as opposed to case-finding or opportunistic approaches.[3,4] In such a context, as anticipated on the basis of the analyses of results on the baseline screening examination,[18] we demonstrated that a less intrusive strategy based on biennial faecal immunochemical test is comparable with colonoscopy in reducing the risk of death from colorectal cancer and the risk of developing colorectal cancer, at least at the participation rates observed in our study. Ongoing cost-effectiveness analysis as part of ths trial will scrutinise this hypothesis, with a particular focus on the impact of participation in such a balance and the balance between survival benefit and the risk of harm.

Participation is, therefore, one of the most important parameters in population-based screening,[7,21–23] along with sensitivity of screening examinations and accessibility to them. Indeed, a 2022 seminal study evaluating the usefulness of colonoscopy in colorectal cancer screening did not demonstrate that this strategy reduces the risk of death from colorectal cancer at 10 years when colonoscopy was accepted by 42% of invitees; however, the adjusted per-protocol analysis, estimating the screening effect if all participants had undergone the procedure, suggested that colonoscopy might reduce colorectal cancer-related mortality by half.[17] In that sense, although participation in both groups of the present study is lower than that observed in current screening programmes[7,24] and similar clinical trials,[17,25] our results reinforce that a less invasive approach might be better accepted in accordance with previously reported observations,[26,27] and that, at least in some populations, this fact might counterbalance the benefit from a potentially more effective strategy. In such a context, it should be kept in mind that the selected threshold of faecal immunochemical test might have had an impact on the study results and, accordingly, it is a crucial factor to consider when planning an organised screening programme. Finally, it is important to mention

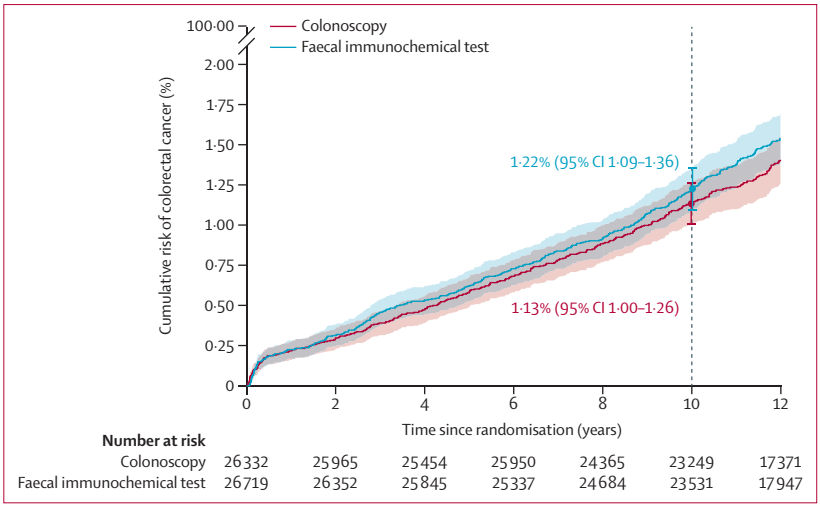

Figure 3: **Cumulative risk of colorectal cancer at 10 years in the intention-to-screen population**
Shaded areas indicate 95% CIs.

	Colonoscopy (n=26 332)	Faecal immunochemical test (n=26 719)	OR (95% CI)†	p value
Colorectal polyposis	46 (0·2%)	19 (0·1%)	2·50 (1·46–4·27)	<0·0001
Advanced colorectal lesion‡	853 (3·2%)	630 (2·4%)	1·39 (1·25–1·54)	<0·0001
Non-advanced colorectal lesion§	1176 (4·5%)	391 (1·5%)	3·17 (2·82–3·56)	<0·0001
Most advanced lesion¶				
Colorectal polyposis	46 (0·2%)	19 (0·1%)	NA	NA
Advanced colorectal lesion	839 (3·2%)	616 (2·3%)	NA	NA
Non-advanced colorectal lesion	1167 (4·4%)	372 (1·4%)	NA	NA

Data are n (%), unless otherwise specified. OR=odds ratio. NA=not applicable. *The diagnostic yield was calculated as the number of individuals with true positive results divided by the number of individuals who were eligible to undergo screening (intention-to-treat analysis) and limited to screen-detected lesions. †Adjusted for age, sex, and participating centre. ‡Defined as an adenoma measuring ≥10 mm in diameter, with villous architecture (>25%), high-grade dysplasia or intramucosal carcinoma, or a serrated lesion measuring ≥10 mm in diameter or with dysplasia. §Defined as a tubular adenoma measuring <10 mm in diameter with low-grade dysplasia, or a serrated lesion measuring <10 mm in diameter without dysplasia. ¶Individuals were classified according to the most advanced colorectal lesion.

Table 2: **Diagnostic yield of colonoscopy and faecal immunochemical test with respect to premalignant neoplastic lesions***

that approximately a third of colorectal cancer cases diagnosed in both the colonoscopy and faecal immunochemical test groups were detected by examinations performed for non-screening purposes (appendix p 28). This is an interesting finding that was made possible by the pragmatic nature of this study, which helps to clarify the true impact of screening programmes.

Our study had several strengths. It was a large randomised controlled trial comparing colonoscopy with faecal immunochemical test for programmatic colorectal cancer screening at the population level. The pragmatic design included randomisation before invitation and allowed crossover between groups to specifically evaluate acceptance and participation in each strategy. Sample size and duration of the study allow us to evaluate the

main endpoint of cancer screening—ie, colorectal cancer-related mortality. Centralised supervision of prospectively collected data combined with information obtained from the national mortality registry and regional screening and hospital databases enabled a complete dataset to be built of all examinations performed for screening, diagnosis, and surveillance purposes.

We are also aware of some limitations of the study. First, our clinical trial was conducted during the deployment period of colorectal cancer screening in Spain. This circumstance might have influenced participant preferences, as reflected by the higher participation and acceptance rates for faecal immunochemical test than for colonoscopy, since the nationwide screening programme is based on this approach. To overcome this limitation, we also report the results of the per-protocol analyses, since they estimate the effect of screening on the compliers. Second, data derived from both as-screened and per-protocol secondary analyses should be interpreted with caution because the non-screening group assessed in the as-screened population consists of individuals who were randomly assigned but did not undergo screening, rather than those assigned to a putative third no screening group and, more importantly, the estimates could be affected by a bias introduced through participant self-selection. Indeed, the pragmatic nature of the study, a valuable approach to clarify whether an intervention works under real-life conditions, makes it more susceptible to potential biases. We tried to minimise this limitation by reporting results adjusted by inverse probability weighting with variables such as age, gender, and participating centre.[28,29] However, even after this adjustment, bias persisted as reflected by the fact that differences in all-cause mortality were observed from the beginning of the evaluated period and that the size of these differences were bigger than those achieved in colorectal cancer-related mortality (appendix pp 13, 15, 17, 19). These observations suggest that, besides a beneficial effect of screening through both early detection of colorectal cancer and prevention of colorectal cancer by polypectomy of precursor lesions, a healthy screenee bias[30] related to unmeasured sociodemographic, lifestyle, or alimentary factors might be more influential in an individuals' prognosis than screening strategies by themselves,[31] as shown by the marked differences observed in all-cause mortality between participants and non-participants in the study. Information about these conditions was not available in our study, and no other adjustment method could be applied. Although individual preferences introduce a notable bias, the results of these analyses suggest that both screening approaches were effective compared with no screening, underscoring the relevance of colorectal cancer screening. Third, the observed rate of colorectal cancer mortality was lower than expected and the prespecified non-inferiority margin tended to be relatively large when compared with the results obtained in the study; consequently, the calculated sample size might have been insufficient to detect smaller differences between groups. Fourth, data from the Canary Islands might have had some biases, since there was a difference between study groups in the number of individuals who could not be contacted, and an overall lower colorectal cancer-related mortality rate was observed in this subpopulation compared with other Spanish regions. An error in the invitation process, such as an issue with the mailing list, seems to be the most likely explanation for the differences in the number of individuals who could not be contacted; differences in the criteria used by the Canarian health information system to classify causes of death might provide an explanation as to why an overall lower colorectal cancer-related mortality rate was observed in this subpopulation, since there is no known epidemiological evidence suggesting that colorectal cancer incidence or mortality rates differ significantly in this region. A post-hoc sensitivity analysis conducted during the peer-review process, which excluded individuals recruited from the Canary Islands, did not alter the study findings. Fifth, the study duration might be insufficient to demonstrate a reduction in colorectal cancer incidence for both screening strategies in the as-screened analysis. In that sense, colonoscopy did confirm reduction in the risk of developing colorectal cancer as observed in previous studies,[17] thus reflecting its preventive nature in detecting and removing precancerous lesions, whereas demonstration of a similar effect with faecal immunochemical test might require analysis of data at 15 years of randomisation, which is already planned (December, 2026).

In conclusion, a faecal immunochemical test-based colorectal cancer screening programme was better accepted by participants than a screening strategy based on direct colonoscopy. With the participation observed in this study, invitation for faecal immunochemical test was non-inferior to invitation for colonoscopy with regard to colorectal cancer mortality. Ongoing randomised controlled trials[25,32] might confirm our results and contribute to the generalisation of these conclusions globally.

Contributors

AC and EQ designed the study. EF-A and CH gathered the data. AC, EQ, and MS-B analysed the data. AC, EQ, LB, SC-C, JC, JD-T, ÁL, AO, RJ, MA, FC, JDM, DS, RA, IA-A, JMB, VH, IP, MV-E, and MdlV vouch for the data and the analysis, and decided to publish the paper. AC and EQ wrote the first draft of the manuscript. Data reported in the Article were verified by AC, EQ, MS-B, EF-A, and CH.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data (including data dictionaries) underlying the results reported in this Article will be available after de-identification. The study protocol, statistical analysis plan, and informed consent forms will also be available immediately following publication, with no end date. Investigators who provide a methodologically sound proposal approved by an independent review committee identified for this purpose can request this information to achieve the aims of the

approved proposal. Proposals should be directed to castells@clinic.cat; to gain access, data requestors will need to sign a data access agreement.

Acknowledgments

This work was supported by grants from the Fundación Científica de la Asociación Española contra el Cáncer (AECC07185 and GCB13131592CAST) and the Instituto de Salud Carlos III (PI08/90717). CIBERehd is funded by the Instituto de Salud Carlos III. In Catalonia, the study received additional support with grants from Agència de Gestió d'Ajuts Universitaris i de Recerca (2009SGR849, 2014SGR135, 2017SGR653 and 2021SGR716). In the Basque Country, the study received additional support with grants from Obra Social de Kutxa, Diputación Foral de Gipuzkoa (DFG 07/5), and Departamento de Sanidad del Gobierno Vasco, EITB-Maratoia (BIO 07/CA/19). In Galicia, the study received additional support from Conselleria de Sanidade, Xunta de Galicia (PS09/74, direct support from Dirección Xeral de Saude Pública), Axencia Galega de Innovación (IN607B-2023/09, IN606A-2023/021), Instituto de Salud Carlos III (INT22/00009, FI22/00203, and CD22/00087), and Fundación Científica de la Asociación Española contra el Cáncer (CLJUN235180GARC). Eiken Chemical and its Spanish representatives—Palex Medical and Biogen Diagnóstica—donated supplies and technology used for faecal immunochemical tests during the first screening round and provided support for the online database maintenance, and Persei Vivarium provided technical support for database maintenance and data extraction; none of them were involved in the design of the study or in the analysis and interpretation of results.

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