EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Directorate F – Health and Food (Ispra)
**Disease Prevention**

# European Commission Initiative on Colorectal Cancer (ECICC):

# European guidelines on colorectal cancer primary prevention, screening and diagnosis

## Evidence profile

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**Question:** Screening compared to no screening for colorectal cancer in asymptomatic adults aged 50 - 69 with an average risk of colorectal cancer

**Setting:** European Union

**Bibliography:** JRC Technical Report, Screening age-range recommendations, CCR.F.C943473.X2, available upon request

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | screening | no screening | Relative (95% CI) | Absolute (95% CI) | | |
| **Death from Colorectal Cancer (follow-up: range 5 years to 30 years; assessed with: Intention to treat)** | | | | | | | | | | | | |
| 10[1,2,3,4,5,6,7,8,9,10] | randomised trials[a] | serious[b] | not serious[c] | not serious[d] | not serious[e] | none | | 0.0%[f,g] | **Rate ratio 0.82** (0.75 to 0.89) | **108 fewer per 100000 patient(s) per 20-years** (from 66 fewer to 150 fewer)[g] | ⨁⨁⨁◯ Moderate[b,c] | CRITICAL |
| **Death from Colorectal Cancer (follow-up: range 10 years to 30 years; assessed with: Per-protocol)** | | | | | | | | | | | | |
| 4[3,7,8,9] | randomised trials | serious[h] | not serious[c] | serious[i] | not serious[e] | none | | 0.0%[f,g] | **Rate ratio 0.64** (0.58 to 0.71)[i] | **216 fewer per 100000 patient(s) per 20-years** (from 252 fewer to 174 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **Diagnosis of Colorectal Cancer (follow-up: range 5 years to 30 years; assessed with: Intention to treat)** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | screening | no screening | Relative (95% CI) | Absolute (95% CI) | | |
| 10[1,2,4,5,6,7,8,9,10,11] | randomised trials[a] | serious[k] | not serious[l] | not serious | not serious[m] | none | | 0.1%[f,g] | **Rate ratio 0.88** (0.81 to 0.96) | **240 fewer per 100000 patient(s) per 20-years** (from 80 fewer to 380 fewer)[g] | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Diagnosis of Colorectal Cancer (follow-up: range 10 years to 17 years; assessed with: Per-protocol)** | | | | | | | | | | | | |
| 3[7,8,9] | randomised trials | serious[n] | not serious | serious[i] | not serious[m] | none | | 0.1%[f,g] | **Rate ratio 0.66** (0.61 to 0.71)[i] | **680 fewer per 100000 patient(s) per 20-years** (from 780 fewer to 580 fewer) | ⨁⨁◯◯ Low | CRITICAL |
| **Stage of Colorectal Cancer (follow-up: range 11 years to 19 years; assessed with: stage III/IV or Duke's C/D - Intention to treat)** | | | | | | | | | | | | |
| 7[1,4,6,12,13,14,15] | randomised trials | serious[k] | not serious | not serious | not serious[o] | none | | 0.9%[p] | **RR 0.84** (0.78 to 0.92) | **142 fewer per 100,000** (from 195 fewer to 71 fewer) | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Major Bleeding** | | | | | | | | | | | | |
| 106[16,q] | non-randomised studies | serious[r] | not serious | not serious | not serious | none | The overall incidence of major bleeding after screening was approximately 73 cases (95% CI 45.78 – 117.77) per 100,000 procedures.<br><br>**Colonoscopy:** 104 cases (95% CI 67.79 – 160.81) per 100,000 procedures when colonoscopy<br><br>**Colonoscopy was performed after abnormal results in other screening modalities:** 194 cases (95% CI 112.93 – 333.37) per 100,000 procedures.<br><br>**Flexible sigmoidoscopy alone:** 4 cases (95% CI 0.65 - 22.13) per 100,000 procedures. | | ⨁⨁⨁◯ Moderate | CRITICAL |
| **Colonic Perforation** | | | | | | | | | | | | |

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | screening | no screening | Relative (95% CI) | Absolute (95% CI) | | |
| 106[16,q] | non-randomised studies | serious[r] | not serious | not serious | not serious | none | The overall incidence of perforation after screening was approximately 27 cases (95% CI 18.26 - 41.02) per 100,000 procedures.<br><br>**Colonoscopy:** 34 cases (95% CI 23.13 – 49.38) per 100,000 procedures.<br><br>**Colonoscopy was performed after abnormal results in other screening modalities:** 79 cases (95% CI 55.10 – 112.32) per 100,000 procedures.<br><br>**Flexible sigmoidoscopy alone:** 3 cases (95% CI 1.11 – 9.87) per 100,000 procedures. | | | | ⨁⨁⨁◯ Moderate | CRITICAL |

**Acute Severe Pain**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[17,18] | randomised trials | serious[s] | not serious | serious[t] | not serious | none | After the screening procedure, severe pain ranged from approximately 2001 to 2712 cases per 100,000 procedures. | | | | ⨁⨁◯◯ Low | CRITICAL |

**CI:** confidence interval; **RR:** risk ratio

## Explanations

a. The RCTs informing this outcome assessed colonoscopy, flexible sigmoidoscopy, and guaiac fecal occult blood test as screening tests.

b. Most of the studies had concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about measuring the outcome, as the definition of mortality was based on the specific cause reported; however, we do not consider this to be a differential bias between the arms. Additionally, six studies have some concerns about the potential impact of missing outcome data, particularly regarding adherence to the intervention, considering that the estimations are based on the intention-to-treat analysis.

c. The inspection of the forest plot identified heterogeneity (I2=64%), but it was not considered relevant.

d. The ECICC WG defined the threshold for goinf from trivial to small effect as 35 CRC deaths per 100,000 participants on screening.

e. The ECICC WG defined the threshold for going from trivial to small effect as 35 CRC deaths per 100,000 participants on screening.

f. The baseline risk was obtained from the rates of colorectal cancer in the 50-69 age group reported by the European Cancer Information System for European Union countries (EU-27) and converted for 20 years time frame

g. The absolute risk was obtained as follows, considering a standardization for 20 years: 1) We converted the annual basal risk into a rate (r) per unit time (20 years) r= basal risk*20; 2) We estimated the probability (RB) of an event occurring at a given time (20-years) using the formula: RB= 1 – exp(-r); 3) Finally, we calculated the absolute risk (AR) using the formula: AR= (RB*IRR) – RB, where IRR is the incidence risk.

h. Most of the studies had some concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about measuring the outcome, as the definition of mortality was based on the specific cause reported; however, we do not consider this to be a differential bias between the arms.

i. Given the method of analysis (adjusted by non-compliance), the estimates only applied to participants who would be adherent to screening and whose characteristics can not be clearly distinguished.

j. Per-protocol analysis was based on the method developed by Cuzick and colleagues which adjusted for non-compliance by subtracting the rate of events of non-adherents from both arms (assumed comparable groups exist in the control arm) and estimating the effect only between adherent participants,

k. Most of the studies had some concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about the measurement of the outcome, as they relied on public databases, which may not have captured all the cases; however, we do not consider this to introduce a significant differential bias, and its impact is expected to be minimal. Three studies were considered at a high risk of bias because of the impact of missing outcome data, particularly regarding adherence to the intervention, considering that the estimations are based on the intention-to-treat analysis. However, their impact on the overall findings is minimal due to their weight being less than 30%.

l. The inspection of the forest plot identified heterogeneity (I2=87%), but it was not considered relevant.

m. The ECICC WG defined the threshold for going from trivial to small effect as 75 CRC incident cases per 100,000 participants on screening.

n. Most of the studies had some concerns regarding the reporting of the randomization process and concealment of the allocation sequence until participants' enrollment, which probably affected the balance of the arms and, consequently, the estimates. All of the studies included in the analysis had some concerns about the measurement of the outcome, as they relied on public databases, which may not have captured all the cases; however, we do not consider this to introduce a significant differential bias, and its impact is expected to be minimal.

o. The ECICC WG defined the threshold for going from trivial to small effect as 58 CRC incident cases at a late stage per 100,000 participants on screening.

p. Median basal risk reported in the included studies

q. We identified one systematic review including 106 observational studies assessing flexible sigmoidoscopy and colonoscopy.

r. Most of the studies did not disclose their follow-up duration and there are some concerns about the possibility of reporting bias regarding the outcome.

s. There are some concerns regarding the reporting of outcomes, primarily stemming from a lack of explicit clarification regarding the measurement methods and criteria employed to define severity

t. All of the included studies evaluated the incidence of events in endoscopy tests, with a particular emphasis on colonoscopy; thus these estimates cannot be extrapolated to any screening strategy directly.

## References

1.Miller, E.A.,et al.. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: long-term follow-up of the randomised US PLCO cancer screening trial. Lancet Gastroenterol Hepatol; 2019.

2.Pitkäniemi, J.,et al.. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterology; 2015.

3.Shaukat, A.,et al.. Long-Term Mortality after Screening for Colorectal Cancer. New England Journal of Medicine; 2013.

4.Lindholm, E.,H. Brevinge,and E. Haglind. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg; 2008.

5.Kronborg, O.,et al.. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol; 2004.

6.Scholefield, J.H.,et al.. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut; 2012.

7.Bretthauer, M.,et al.. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. New England Journal of Medicine; 2022.

8.Atkin, W.,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.

9.Senore, C.,et al.. Long-Term Follow-up of the Italian Flexible Sigmoidoscopy Screening Trial. Ann Intern Med; 2022.

10.Holme, Ø.,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.

11.Mandel, J.S.,et al.. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med; 2000.

12.Kronborg, O.,et al.. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet; 1996.

13.Mandel, J.S.,et al.. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst; 1999.

14.Segnan, N.,et al.. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst; 2011.

15.Holme, Ø.,et al.. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA; 2014.

16.Lin JS, Perdue LA,Henrikson NB,Bean SI,Blasi PR. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA; 2021.

17.Atkin, W.S.,et al.. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet; 2002.

18.Segnan, N.,et al.. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"--SCORE. J Natl Cancer Inst; 2002.