IARC Handbook Volume 17: Colorectal Cancer Screening

International Agency for Research on Cancer
Lyon, France

Béatrice Lauby-Secretan, PhD
on behalf of the IARC Working Group for Volume 17
IARC Handbooks of Cancer Prevention

An important part of cancer prevention is identify interventions and strategies that can reduce the risk of cancer.

Launch in 1995 to complement the *IARC Monographs’ evaluations of carcinogenic hazards* with evaluations of cancer-preventive agents.

The Handbooks cover primary prevention, including chemopreventive agents and interventions, and secondary prevention (screening).
How are the evaluations conducted?

Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct

Separate criteria for review of human, animal and mechanistic evidence

Decision process for overall evaluations

**IARC Handbooks** meetings: review and evaluations

- Each *Handbook* includes:
  - **Critical review** of the pertinent scientific literature
  - **Evaluation** of the weight of the evidence that the intervention/strategy reduces the risk of cancer

- The *IARC Handbooks* are unique in that the critical reviews and evaluations are developed by the experts who conducted the original research.

- They serve national health agencies to inform their preventive strategies.
Screening techniques evaluated

- **Stool-based blood tests:**
  - Guaiac-based faecal occult blood test (gFOBT) with or without rehydration
  - Faecal immunochemical test (FIT)
- **Endoscopic techniques:**
  - Flexible sigmoidoscopy
  - Full colonoscopy
- **Emerging techniques:**
  - Computed tomographic colonography

Other topics covered

- **Comparison** of effects between stool-based blood tests and endoscopic techniques
- **Other emerging techniques:** capsule endoscopy, mt-sDNA, biomarkers in blood, urine or breath
- **Determinants of participation** in screening and interventions to increase participation
- **Populations at an increased risk** of colorectal cancer: genetic predisposition, family history of CRC, personal history of preneoplastic lesions or CRC
Background (II)

Evidence-based evaluations

- Evaluations are based on a comprehensive review of the published scientific evidence.
- The majority of randomized controlled trials and observational studies have been conducted:
  - in middle- to high-income settings, where colorectal cancer incidence is generally high;
  - in asymptomatic, average-risk populations aged 50–70 years on average;
  - under conditions in which colorectal cancer screening – including subsequent follow-up and treatment – can be delivered with high quality.
- Extrapolation of the conclusions to different settings needs to take into account these and other context-related specificities.
## Evaluations (I): gFOBT

<table>
<thead>
<tr>
<th>Technique</th>
<th>Evidence for reduction in incidence</th>
<th>Evidence for reduction in mortality</th>
<th>Evidence for benefit-harm ratio</th>
</tr>
</thead>
</table>
| Biennial screening with gFOBT of low sensitivity | ✓ 4 large RCTs | ✓ 3 RCTs  
✓ 2 large cohort studies with up to 11 screening rounds  
✓ 1 case–control study of both invitation to and attendance at screening | ± Reduced CRC mortality, gain in quality-adjusted life years  
± Short-term psychological harms of screening per se or of a positive test, medical harms of follow-up colonoscopy after a positive test |
| Annual / biennial screening with gFOBT of increased sensitivity | ✓ One RCT with 11 and 6 rounds of annual and biennial screening, respectively | ✓ 1 RCT of annual or biennial screening with long follow-up  
✓ 1 case–control study of biennial screening | ± Reduced CRC mortality and incidence, gain in quality-adjusted life years  
± Short-term psychological harms of screening per se or of a positive test, medical harms of follow-up colonoscopy after a positive test |
## Evaluations (II): FIT

<table>
<thead>
<tr>
<th>Technique</th>
<th>Evidence for reduction in incidence</th>
<th>Evidence for reduction in mortality</th>
<th>Evidence for benefit-harm ratio</th>
</tr>
</thead>
</table>
| **Biennial screening with FIT** | ✓ 2 cohort studies with up to 5 rounds of biennial screening  
✓ 1 ecological study with numerous rounds of biennial screening  
✓ Studies with gFOBT:  
  ⇒ ↑ sensitivity and specificity for detection of AA and CRC compared to gFOBT  
  ⇒ Reduction in CRC incidence with gFOBT of higher sensitivity | ✓ Several observational studies of invitation/attendance at biennial screening:  
  o 3 cohort studies, one with incidence-based mortality results after 4 rounds of biennial screening  
  o 2 large ecological studies with numerous rounds of biennial screening  
✓ Increased sensitivity and specificity of FIT compared with gFOBT for the detection of advanced adenomas and CRC | ± Reduced CRC mortality and incidence, gain in quality-adjusted life years  
± Short-term psychological harms of screening per se or of a positive test, medical harms of follow-up colonoscopy after a positive test |
Evaluations (III): sigmoidoscopy

<table>
<thead>
<tr>
<th>Technique</th>
<th>Evidence for reduction in incidence and mortality</th>
<th>Evidence for benefit-harm ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single screening with flexible sigmoidoscopy</td>
<td>✓ 4 RCTs with risk reductions of 20-30%</td>
<td>± Reduced CRC incidence and mortality, gain in quality-adjusted life years</td>
</tr>
<tr>
<td></td>
<td>✓ 2 cohort studies in screening settings</td>
<td>± Short-term psychological harms of screening per se or of a positive test, infrequent procedural harms of sigmoidoscopy, medical harms of follow-up colonoscopy after a positive test</td>
</tr>
<tr>
<td></td>
<td>✓ 9 case–control studies in screening settings</td>
<td></td>
</tr>
</tbody>
</table>

Note: No conclusion can be drawn about the added benefit of subsequent screenings by flexible sigmoidoscopy.
Evaluations (IV): colonoscopy

<table>
<thead>
<tr>
<th>Technique</th>
<th>Evidence for reduction in incidence / mortality</th>
<th>Evidence for benefit-harm ratio</th>
</tr>
</thead>
</table>
| Single screening with colonoscopy | ✓ 5 cohort studies & 5 case-control studies in screening settings  
✓ Meta-analysis with risk reduction of almost 70%  
✓ RCTs with sigmoidoscopy: a full colonoscopy includes a sigmoidoscopy  
⇒ colonoscopy will be at least as good as sigmoidoscopy at detecting advanced adenomas and CRC  
⇒ reduction in CRC incidence and mortality with sigmoido. | ± Reduced CRC incidence and mortality, gain in quality-adjusted life years  
± Harms (bleeding, perforations), psychological harms of screening per se and of a positive test.  
± Variability and related limited accuracy of the effect estimates, harms of colonoscopy, limitations in extrapolating from data of screening by flexible sigmoidoscopy |

*Note: No conclusion can be drawn about the added benefit of subsequent screenings on CRC incidence or mortality.*
### Evaluations (V): CT colonography

<table>
<thead>
<tr>
<th>Technique</th>
<th>Evidence for reduction in incidence / mortality</th>
<th>Evidence for benefit-harm ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single screening with CTC</td>
<td><em>Limited</em>: very high sensitivity and high specificity, high sensitivity for detection of advanced neoplasia; no studies on the effect of CTC on colorectal cancer incidence or mortality in a screening setting</td>
<td>± No direct evidence for a beneficial effect in reducing CRC incidence or mortality</td>
</tr>
<tr>
<td></td>
<td><em>Inadequate</em>: wide extrapolation needed from known detection rates of lesions to reduction in CRC incidence and mortality in a screening setting; lack of studies with incidence and mortality as end-points; lack of studies with repeated CTC screening; only detection rates and test performance (sensitivity and specificity) available</td>
<td>± Harms of ionizing radiation, uncertain harms and benefits of extracolonic findings, uncertainty when quantitative data of beneficial and adverse effects are lacking</td>
</tr>
</tbody>
</table>

*Note*: No conclusion can be drawn about the added benefit of subsequent screenings on CRC incidence or mortality.
## Summary of evaluations

<table>
<thead>
<tr>
<th>Screening technique</th>
<th>Strength of evidence ¹</th>
<th>Reduction in CRC incidence</th>
<th>Reduction in CRC mortality</th>
<th>Benefit–harm ratio ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biennial screening with gFOBT without rehydration</td>
<td><strong>ESLE</strong></td>
<td></td>
<td></td>
<td><strong>Sufficient</strong></td>
</tr>
<tr>
<td>Annual or biennial screening with gFOBT of higher sensitivity</td>
<td><strong>Limited</strong></td>
<td><strong>Sufficient</strong></td>
<td></td>
<td><strong>Sufficient</strong></td>
</tr>
<tr>
<td>Biennial screening with FIT</td>
<td><strong>Limited</strong></td>
<td><strong>Sufficient</strong></td>
<td></td>
<td><strong>Sufficient</strong>²</td>
</tr>
<tr>
<td>Single screening with sigmoidoscopy</td>
<td><strong>Sufficient</strong></td>
<td><strong>Sufficient</strong></td>
<td></td>
<td><strong>Sufficient</strong></td>
</tr>
<tr>
<td>Single screening with colonoscopy</td>
<td><strong>Sufficient</strong></td>
<td><strong>Sufficient</strong></td>
<td></td>
<td><strong>Sufficient</strong>³</td>
</tr>
<tr>
<td>Single screening with CTC</td>
<td><strong>Limited</strong> ³,⁴</td>
<td></td>
<td></td>
<td><strong>Inadequate</strong></td>
</tr>
</tbody>
</table>

ESLE, evidence suggesting a lack of effect.

¹ *Sufficient evidence* applies only with the assumption that screening can be delivered with high quality and follow-up ensured.

² A variety of qualitative and quantitative FIT tests are available, with wide ranges of sensitivity and specificity. The net balance of benefits and harms will depend on the cut-off level for positivity.

³ A minority of the Working Group favored a different evaluation.

⁴ The evaluation of *limited evidence* applies to the reduction in incidence and/or mortality (one single evaluation).
Other topics covered

• Comparison of effects between stool-based blood tests and endoscopic techniques
• Other emerging techniques: capsule endoscopy, mt-sDNA, biomarkers in blood, urine or breath
• Determinants of participation in screening and interventions to increase participation
• Populations at an increased risk of colorectal cancer: genetic predisposition, family history of CRC, personal history of preneoplastic lesions or CRC
HB17 Working Group

**Working Group members**
- Samar Alhomoud, Saudi Arabia
- Johannes Blom, Sweden
- Michael Bretthauer, Norway
- Jean-Luc Bulliard, Switzerland
- Douglas Corley, USA
- Montserrat Garcia Martinez, Spain
- Michael Hoffmeister, Germany
- Rolf Hultcrantz, Sweden
- Iris Lansdorp-Vogelaar, The Netherlands
- Iris Nagtegaal, The Netherlands
- Paul Pinsky, USA (Overall Chair)
- Linda Rabeneck, Canada
- Suleeporn Sangrajrang, Thailand
- Peter Sasieni, United Kingdom
- Robert Smith, USA
- Robert Steele, United Kingdom
- Joseph Sung, Hong Kong SAR, People’s Republic of China

**Invited Specialists**
- Josep M. Augé Fradera, Spain
- Douglas Robertson, USA
- Carlo Senore, Italy

**IARC Secretariat**
- David Forman

**IARC Secretariat**
- David Forman
The IARC Handbooks (IHB) Group

Financial support
Financial support for HB17 was received from:
- American Cancer Society, USA
- Centers for Disease Control and Prevention, USA

ACKNOWLEDGEMENTS
We acknowledge the participation as rapporteur during the meeting of HB17 of:
- Franca Bianchini (DKFZ, Germany)
- Neela Guha (ESC/IMO).
Thank you

- Visit our website at
  http://handbooks.iarc.fr/

- Evaluation tables

- Overview poster of the all Group 1 agents and cancer-preventive strategies, by cancer site
  http://handbooks.iarc.fr/docs/OrganSitePoster.pdf

The IARC Handbooks programme is seeking funding for future projects