Is colonoscopy less effective in the right colon?

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Is colonoscopy less effective in the right colon?

In the following:
Focus on relative effectiveness
(not absolute effectiveness)
There is consistent evidence from observational studies suggesting that colonoscopy is less effective in preventing right- vs. left-sided CRC (death).

**Case-control studies:**
- E.g. Baxter et al.:*
  - CRC mortality reduction
  - Left-sided CRC: 67%
  - Right-sided CRC: None
- E.g. Brenner et al.*:
  - CRC incidence reduction
  - Left-sided CRC: 84%
  - Right-sided CRC: 56%

**Cohort studies:**
- E.g. Guo et al.*:
  - CRC incidence reduction
  - Left-sided CRC: 64%
  - Right-sided CRC: 31%

Agenda

Is colonoscopy less effective in the right colon?

1. Unrecognized (self-inflicted) biases in existing observational studies on this question, example of cohort study

2. First results of a study avoiding these types of biases (target trial approach)
Unrecognized (self-inflicted) biases in existing studies

Imagine the following RCT:

Colonoscopy

No colonoscopy
Unrecognized (self-inflicted) biases in existing studies

Imagine the following RCT:

Colonscopy

Cumulative CRC incidence

No colonoscopy

Cumulative CRC incidence
Imagine the following RCT:

Exclusion of persons with screen-detected CRC

Colonoscopy

No colonoscopy

Cumulative CRC incidence

Flawed study design, effect of colonoscopy over-estimated

Cumulative CRC incidence
Unrecognized (self-inflicted) biases in existing studies

Example of cohort study (observational):

1) Colonoscopy in the past? Yes / No
Unrecognized (self-inflicted) biases in existing studies

Example of cohort study (observational):

1) Colonoscopy in the past? Yes / No

Colonoscopy

No colonoscopy
Unrecognized (self-inflicted) biases in existing studies

Example of cohort study (observational):

1) Colonoscopy in the past? Yes / No
   
   Colonoscopy  
   ![Emoji Faces]

2) Ever CRC? If yes, exclusion
   
   No colonoscopy  
   ![Emoji Faces]
Unrecognized (self-inflicted) biases in existing studies

Example of cohort study (observational):

1) Colonoscopy in the past? Yes / No
2) Ever CRC? If yes, exclusion

Exclusion of persons with prior CRC

Colonoscopy

No colonoscopy
Unrecognized (self-inflicted) biases in existing studies

Example of cohort study (observational):

- Exclusion of persons with prior CRC

Colonscopy


cumulative CRC incidence

No colonoscopy

Cumulative CRC incidence

- Flawed study design, effect of colonoscopy over-estimated *

*Garcia-Albeniz et al. Eur J Epidemiol 2017
Unrecognized (self-inflicted) biases in existing studies

➢ Vast majority of CRCs detected at the typical starting age of screening are in the left-sided colon

➢ CRCs newly growing at older age more often in the right colon

➢ Self-inflicted biases in existing observational studies mainly affect left-sided CRC, i.e. they overestimate the effectiveness of colonoscopy for left-sided CRC

➢ This leads to a seemingly high difference in the effectiveness of colonoscopy for right- vs. left-sided CRC
Agenda

Is colonoscopy less effective in the right colon?

1. Unrecognized (self-inflicted) biases in existing observational studies on this question, example of cohort study

2. First results of a study avoiding these types of biases (target trial approach)
Target trial to avoid self-inflicted biases

Methods:

➢ German claims database (GePaRD) covering 20% of the German population
➢ Methodology as described by Garcia-Albeniz et al.*
➢ Inclusion of persons aged 50-69 years, exclusion criteria similar to RCTs
➢ Sequential emulated trials starting each quarter from 2007 – 2011

Target trial to avoid self-inflicted biases

Methods:

➢ Effect of screening colonoscopy on 11-year risk of overall, proximal, and distal CRC (observational analogue of the intention-to-screen effect)

➢ Adjustment for baseline confounders using inverse probability treatment weighting
Target trial to avoid self-inflicted biases

Results:

<table>
<thead>
<tr>
<th></th>
<th>Screening group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=198,389</td>
<td></td>
<td>N=349,092</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61.1</td>
<td>61.8</td>
</tr>
<tr>
<td>Proportion women</td>
<td>50%</td>
<td>54%</td>
</tr>
<tr>
<td>Number of CRCs</td>
<td>1,564</td>
<td>2,541</td>
</tr>
<tr>
<td>Left-sided</td>
<td>1,046</td>
<td>1,710</td>
</tr>
<tr>
<td>Right-sided</td>
<td>385</td>
<td>496</td>
</tr>
</tbody>
</table>
Target trial to avoid self-inflicted biases

Results:

Adjusted cumulative incidence curve

Left-sided CRC  
RR = 0.64  
(0.54; 0.73)

Right-sided CRC  
RR = 0.73  
(0.59; 0.95)

7.5 years (later in men than in women)

6 years
Discussion

- Emulated target trial suggests that there is only a minor difference in relative effectiveness of colonoscopy in preventing left- vs. right-sided CRC

- Measuring the preventive effect in the right-colon requires longer follow-up (particularly in men)

- Confounder information suboptimal in claims data, but unlikely that this played a major role here
Discussion

➢ It seems plausible that the big difference observed in existing observational studies regarding effectiveness of colonoscopy for right vs. left-sided CRC was due to self-inflicted biases (as they overestimated effectiveness for left-sided CRC)

➢ Critical appraisal of further studies (case-control, etc.) regarding self-inflicted and other types of biases ongoing

➢ An individual level re-analysis of tandem colonoscopy studies found no higher miss rate for left-sided vs. right-sided adenomas*

* Zimmermann-Fraedrich et al. 2019
Thank you for your attention!
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SAVE THE DATE!
Adjusted cumulative incidence curve

<table>
<thead>
<tr>
<th></th>
<th>male</th>
<th>female</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>distal</td>
<td>RR=0.66 (0.55;0.84)</td>
<td>RR=0.61 (0.47;0.79)</td>
<td>RR=0.64 (0.54;0.73)</td>
</tr>
<tr>
<td>proximal</td>
<td>RR=0.70 (0.49;1.02)</td>
<td>RR=0.78 (0.58;1.20)</td>
<td>RR=0.73 (0.59;0.95)</td>
</tr>
</tbody>
</table>
3. Results

b) Cumulative Incidence, Overall

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.66 (0.56;0.79)</td>
<td>0.68 (0.57;0.81)</td>
<td>0.67 (0.59;0.76)</td>
</tr>
</tbody>
</table>

Adjusted cumulative incidence curve

Follow-up time [years]
3. Results

b) Cumulative Incidence, by Sex & Site