THE RISK OF MISSING UPPER GASTROINTESTINAL CANCER IN FIT-POSITIVES IN A COLORECTAL CANCER SCREENING PROGRAM

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Disclosures

• No conflicts of interest
Introduction

• CRC screening programs use FOBT on assumption that AN have a tendency to bleed.

• gFOBT detects haem, whereas FIT detects intact human Hb

• However, > ½ of FIT positives do not have AN at colonoscopy

1. van Turenhout et al. Gastrointest Endosc. 2012
Introduction

- Systematic review concluded that there is not enough evidence to recommend for/against routine EGD in FOBT positives\(^4\)

- Some recent studies argue for EGD in FIT positives\(^5,6\)

- Overall, varying definitions and quality of studies

4. Allard et al, Can J Gastroenterol. 2010
6. Ng et al. Int J Colorectal Dis 2017
Aim

• Assessing the number of proximal cancers diagnosed within two years after a FIT test in FIT-positive and FIT-negative participants in a FIT-based screening program
Methods

• Randomly selected asymptomatic persons aged 50-74 years
• Municipal population register
• Exclusion criteria:
  History of IBD or CRC
  Symptoms of CRC
  Colonoscopy ≤ 2 years
  ASA IV or life-expectancy < 5 years
Dynamic FIT screening program

Cut-off FIT ≥10 μg Hb/g feces
Linkage until 31 March 2015

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## Basic characteristics cohort

<table>
<thead>
<tr>
<th></th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitees</td>
<td>14,651</td>
<td>18,383</td>
<td>19,618</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>59 (54-65)</td>
<td>60 (55-66)</td>
<td>60 (55-66)</td>
</tr>
<tr>
<td>Sex (male;%)</td>
<td>50</td>
<td>49</td>
<td>49</td>
</tr>
</tbody>
</table>
Methods

• Proximal cancers identified through linkage with the Netherlands Cancer Registry

• Definition proximal cancer: oral cavity, throat, esophageal, gastric and small bowel cancer

• All types of histopathological diagnosis

• Data: tumor type, site, follow up time since cancer diagnosis
Definitions

FIT-positives with a positive colonoscopy (AN*)
FIT-positives with a negative colonoscopy (no AN)
FIT-negatives

Potentially detectable cancers: tumors diagnosed < 2 years after the last performed FIT

*CRC or adenoma with a diameter ≥10 mm, and/or with a ≥25% villous component, and/or high-grade dysplasia.
Linkage to FIT screening program

Cut-off FIT ≥10 μg Hb/g feces
Linkage until 31 March 2015

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Results

Cumulative incidence prox cancers FIT pos vs FIT neg: 0.33% vs 0.24%; $P = 0.43$

Cumulative incidence prox cancers between three groups; $P = 0.65$
## Histopathology and location

<table>
<thead>
<tr>
<th></th>
<th>Positive FIT, negative colonoscopy</th>
<th>Positive FIT, positive colonoscopy</th>
<th>Negative FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of persons at risk</strong></td>
<td>1367</td>
<td>729</td>
<td>14,027</td>
</tr>
<tr>
<td><strong>Oral/Throat</strong>*</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>-carcinoma unspecified</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>-squamous cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-squamous cancer</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>-adenocarcinoma</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td><strong>Gastric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-adenocarcinoma</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>-linitis plastica</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>-GIST</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Small bowel</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-carcinoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-GIST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total number of cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No difference when comparing FIT positives (n=2) and FIT negatives (n=22) for only esophagus/gastric \( P = 0.48 \)
### Patient characteristics with proximal cancers < 2 years after FIT

<table>
<thead>
<tr>
<th></th>
<th>Positive FIT, negative colonoscopy</th>
<th>Positive FIT, positive colonoscopy</th>
<th>Negative FIT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of cancers</strong></td>
<td>5</td>
<td>2</td>
<td>33</td>
<td>.645</td>
</tr>
<tr>
<td><strong>Age at diagnosis, median (IQR)</strong></td>
<td>68 (59-73)</td>
<td>61</td>
<td>65 (58-73)</td>
<td>.864</td>
</tr>
<tr>
<td><strong>Sex (male, n (%))</strong></td>
<td>4 (80%)</td>
<td>1 (50%)</td>
<td>22 (67%)</td>
<td>.918</td>
</tr>
<tr>
<td><strong>Type of cancer (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral/Throat</td>
<td>2 (40%)</td>
<td>1 (50%)</td>
<td>11 (33%)</td>
<td></td>
</tr>
<tr>
<td>- Esophagus/gastric</td>
<td>1 (20%)</td>
<td>1 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Small bowel</td>
<td>2 (40%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Time between test and diagnosis cancer (mean, ±SD, yr)</strong></td>
<td>1.11 (0.51)</td>
<td>0.6 (0.01)</td>
<td>1.2 (0.6)</td>
<td>.237</td>
</tr>
</tbody>
</table>

But very small numbers!!
Number needed to scope (NNSc)

- The NNSc to detect 1 gastric/esophageal cancer in FIT + with negative colonoscopy = 1,367
Conclusion

• Similar & very low risk for prox cancers between FIT positives and FIT negatives < 2 years after FIT testing

• Hypothecial NNSc in FIT + with – colo = 1367

• So…. EGD is not recommended in (asymptomatic) persons participating FIT screening
Acknowledgements

- Foundation of Population Screening Mid-West Netherlands, Amsterdam, The Netherlands (BoMW)
- Foundation of Population Screening South-West Netherlands, Rotterdam, The Netherlands (BoZW)
- Netherlands Comprehensive Cancer Organisation (IKNL)
- Netherlands Organization for Health Research and Development of the Dutch Ministry of Health (ZonMW)
All identified proximal cancers

N = 93
Proximal cancers delivered by Cancer Registry

n = 3 proximal cancers in gFOBT screenees only

n = 90
Proximal cancers FIT cohort

n = 22
Proximal cancers among FIT positives

n = 10
Diagnosis before participation (5)
Refused colonoscopy (5)

n = 68
Proximal cancers among FIT negatives

n = 5
Proximal cancers in positive colonoscopy

n = 2
Proximal cancers < 2 years after FIT

n = 7
Proximal cancers in negative colonoscopy

n = 5
Proximal cancers < 2 years after FIT

n = 54
Proximal cancers in FIT negatives

n = 14 diagnosis before participation

n = 3 proximal cancers in gFOBT screenees only
Hemoglobin

- Hb contact 4 types of subunits of which \textbf{haem} is one (green image)

- gFOBT: hydrogen peroxide oxidizes alpha guaiaconic acid to blue colored quinone and \textbf{haem} catalyzes this reaction

- FIT uses antibodies directed against \textbf{intact human Hemoglobin}