Screening and Prevention of GI Cancers

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# GI cancers: Incidence (2014)

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of new cases</th>
<th>% of all Cancer cases</th>
<th>Survival 5 years or more %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>41,265</td>
<td>12</td>
<td>59</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>9,618</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>8,919</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Stomach</td>
<td>6,682</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Liver</td>
<td>5,550</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>All Cancers</td>
<td>356,860</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## GI cancers: Lifestyle risk factors

### WCRF Continuous Update Project

<table>
<thead>
<tr>
<th>Site</th>
<th>Body Fat</th>
<th>Alcohol</th>
<th>Processed meat</th>
<th>Red meat</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal 2011</td>
<td>++</td>
<td>++ (men)</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ (women)</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Stomach 2016</td>
<td>+ (cardia)</td>
<td>+</td>
<td>+ (non-cardia)</td>
<td></td>
<td>Salted foods +</td>
</tr>
<tr>
<td>Oesophageal 2016</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td>Scalding hot drinks ++ (SCC)</td>
</tr>
<tr>
<td>Liver 2015</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td>Aflatoxins ++</td>
</tr>
<tr>
<td>Pancreatic 2012</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

++ convincing increased risk factor  
+ probable increased risk  

http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports
## Diet and lifestyle: Preventability estimates (%)

### WCRF Continuous Update Project

<table>
<thead>
<tr>
<th>Site</th>
<th>Healthy weight &amp; diet &amp; no alcohol</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>47</td>
<td>++ Dietary fibre</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>++ Physical activity</td>
</tr>
<tr>
<td>Stomach</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagusal</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>30</td>
<td>+ Coffee (probable protective effect)</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>19 (healthy weight)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports](http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports)
Cancer Incidence Trends: 1993-2014

Colorectal  + 4%

Pancreatic  + 14%

Oesophageal  + 6%

Stomach  - 48%

Liver  + 142%

European Age-Standardised Incidence Rates per 100,000 Population, by Sex, UK

Pills to prevent bowel cancer

- Aspirin and other NSAIDS eg ibuprofen
- Cox-2 inhibitors eg Vioxx, Celebrex
- Hormone replacement therapy (HRT)

More harm than good for the general population
May have a role for high risk groups

- Vitamins - A, C, E, folic acid, selenium, calcium, curcumin, statins

More research required
Prevention by population screening and surveillance of high-risk groups
Bowel Cancer is the 2nd biggest cancer killer in UK
- 16,000 deaths, 41,000 new diagnoses
- Lifetime risk of diagnosis: 1 in 14 men, 1 in 19 women
- 20% present as emergency*
- Survival 55%

No current feasible strategy for primary prevention

Costs NHS estimated at £1.6 billion / year**
Prevention and early detection of bowel cancer by screening

- Normal mucosa
- Adenoma
- Early asymptomatic treatable cancer
- Late symptomatic untreatable cancer

Chromosome 5 – APC Tumor suppressor gene inactivation
Chromosome 12 – K-ras Proto-oncogene activation
Chromosome 18 – DCC
Chromosome 17 – p53
Other alterations
Methods for Bowel Cancer Screening

**Direct Imaging**
- Colonoscopy or flexible sigmoidoscopy
- CT colonography

**Faecal occult blood testing**
- Guaiac (haem)*
- Immunochemical (globin)

**Molecular markers** in blood or stool
- DNA, RNA, proteins
Bowel Cancer Screening Programme in UK

- Guaiac FOBt, offered every 2 years from age 60-74
- 2 samples collected on 3 consecutive days
- Colonoscopy for test positives
Guaiac gFOBT: Evidence

Cochrane systematic review of 4 RCTs of gFOBT biennially

- CRC mortality reduction
  - 16% in invited population:
  - 27% in persons using ≥ 1 test

- No CRC incidence reduction
- No reduction in all-cause mortality

Hewitson et al., Cochrane Review of CRC screening using FOBT. Am J Gastroenterol 2008;103:1541-9
Problem with gFOBT

Reader positivity (England monthly average 2009)
(Each point represents >500 read kits)

Slide kindly provided by Prof Stephen Halloran MBE, Director NHS BCSP Southern Hub
Advantages of FIT

• Single sample – simple to use
• Only detects human blood
• Fully automated
  - Can deal with 1000s of tests per day
  - Less manpower
  - Better standardisation
  - Strict QA
• Choose cut-off for positivity
FIT Pilot in England 2014

• 6 month pilot using FIT, cut-off 20 μgHb/g faeces
  - using the Eiken OC-Sensor Diana automated machine

• Offered to 40,930 people (1 in 28)
  - Uptake with the guaiac test: 59%
  - Uptake with FIT 66%

## Results of English BCSP FIT Pilot study

<table>
<thead>
<tr>
<th></th>
<th>FIT cut-off concentrations (µg Hb/g faeces)</th>
<th>gFOBt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20µg</td>
<td>40µg</td>
</tr>
<tr>
<td>Positivity (%)</td>
<td>7.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Cancer detection rate (%)</td>
<td>0.27</td>
<td>0.24</td>
</tr>
<tr>
<td>Advanced adenoma detection rate (%)</td>
<td>1.73</td>
<td>1.29</td>
</tr>
<tr>
<td>Cancer PPV (%)</td>
<td>4.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Advanced Adenoma PPV (%)</td>
<td>25.8</td>
<td>29.2</td>
</tr>
</tbody>
</table>

FIT – faecal immunochemical test  
gFOBt – guaiac-based faecal occult blood test  
Hb – haemoglobin  
PPV – positive predictive value

Bowelscope (flexible sigmoidoscopy) screening
Evidence for efficacy of FS screening

60–80% reduction in development of distal CRC in observational studies

Long duration of protection…

- St Mark’s series: Atkin et al. NEJM 1992;326:658-62
  » Risk of rectal cancer reduced for remainder of life

- Selby et al., NEJM, 1992;326:653-7
  » Risk of fatal distal cancer reduced for ≥ 10 years

- Newcomb et al., JNCI, 2003;95:622-5
  » Protection lasts ≥ 15 years
Rationale for once-only flexisig at around age 60

Atkin et al, Lancet 1993;341:736-40
<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>Participants</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>PLCO</td>
<td>154 000</td>
<td>3-5 yearly</td>
</tr>
<tr>
<td>UK</td>
<td>Flexi-Scope trial</td>
<td>170 000</td>
<td>Once-only</td>
</tr>
<tr>
<td>Italy</td>
<td>SCORE</td>
<td>35 000</td>
<td>Once-only</td>
</tr>
<tr>
<td>Norway</td>
<td>NORCAPP</td>
<td>56 000</td>
<td>Once-only</td>
</tr>
</tbody>
</table>

Shoen et al., NEJM 2012;366:2345-57  
Atkin et al., Lancet 2010, 375:1624-33  
Segnan et al., JNCI 2011;103:1-13  
Hoff et al., BMJ 2009;338:1846
UK Flexible Sigmoidoscopy Screening Trial regimen

- **Once-only** flexible sigmoidoscopy screen between ages 55 and 64 years

- Remove small polyps (< 10 mm) during screening

- Colonoscopy only for high-risk adenomas (5%): \(\geq 3, \geq 10 \text{ mm}, \geq 25\% \text{ villous, high grade dysplasia}\)

*Atkin et al., Lancet 2010, 375:1624-33*
Aimed to examine…

- Safety and acceptability
- Effectiveness in preventing bowel cancer
- Duration of protection
- Optimum age for a single FS screen
Trial recruitment

368,142
Sent questionnaire:
Would you have the screening if invited?

194,726 (53%)
Responded ‘yes interested’

24,294 Excluded

170,432
Randomised 2:1

113,195
Control
No contact

57,237
Invited for screening

40,000
Had the Flexi-scope test

UK FS Screening Trial: findings after 11 years

<table>
<thead>
<tr>
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<th>Incidence reduction in attenders for the test %</th>
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<tbody>
<tr>
<td>Colorectal cancer (all sites)</td>
<td>33</td>
</tr>
<tr>
<td>Rectum and sigmoid colon</td>
<td>50</td>
</tr>
<tr>
<td>Colorectal cancer deaths</td>
<td>43</td>
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Atkin et al. Lancet. 2010;375: 1624-33
Cumulative incidence distal cancer in UK FS trial (%)

Control
Screened
Not Screened

Atkin et al. Lancet. 2010;375: 1624-33
UKFSST: findings after 11 and 17 years

<table>
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<th>Incidence reduction after 11 years %</th>
<th>Incidence reduction after 17 years %</th>
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<tbody>
<tr>
<td>Colorectal cancer (all sites)</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Rectum and sigmoid colon</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>Colorectal cancer deaths</td>
<td>43</td>
<td>41</td>
</tr>
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Atkin et al. Lancet. Published online February 21, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30396-3
Curves are truncated at 10 years of follow-up because of incomplete ascertainment of cancers in the final calendar year of the study.
Annual incidence rate ratio for distal CRC (95% CI)

Figure 2

Atkin et al. Lancet. Published online February 21, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30396-3
Cancers in the lower bowel can be prevented by removing polyps using the Flexi-Scope

Flexi-Scope is a one-off, five minute screening exam the benefit of which may last a lifetime

A once-only Flexi-Scope test
  - Prevented one third of bowel cancers
  - Prevented 43% of bowel cancer deaths

11 years after the test, no waning of protection
FS in the NHS Bowel Cancer Screening Programme

October 2010
• PM David Cameron announced £60 million to introduce FS screening at age 55
• Renamed the test bowel scope

April 2011
• UK National Screening Committee granted approval
• Department of Health announced that FS screening will be available for people aged 55-59 and then FOBT from age 60-74

National roll-out started 2012, with complete coverage of the English population expected by 2018


Flexible sigmoidoscopy (FS) is the only modality shown to reduce CRC incidence in randomised trials
- The duration of protection is very long-lasting, at least 17 years

Colonoscopy screening is also effective
- BUT the incremental benefit over FS is not known and is not feasible in the UK

Guaiac FOBT is not effective in preventing CRC

FIT detects more advanced adenomas so should reduce incidence
- BUT the magnitude of incidence reduction is not known
- Cumulative colonoscopy requirements with a low threshold over multiple rounds could be high.