What is the Screening Target?

Uri Ladabaum, M.D., M.S.
Professor of Medicine; Director, GI Cancer Prevention Program
Stanford University School of Medicine
Questions

- Beyond early-stage CRC? i.e. preinvasive lesions?
- Which preinvasive lesions?
- How to assess benefit on CRC incidence / mortality?
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Reflex: **OF COURSE!**

Advanced adenomas and SSLs

Modeling
Questions

- Beyond early-stage CRC? i.e. preinvasive lesions?
- Which preinvasive lesions?
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Questions

- Beyond early-stage CRC? i.e. preinvasive lesions?
- Which preinvasive lesions?
- How to assess benefit on CRC incidence / mortality?

Philosophical?

“Progressive ones”

Modeling based on progression rates; AND observation
Questions

- Beyond early-stage CRC? i.e. preinvasive lesions?
- Which preinvasive lesions?
- How to assess benefit on CRC incidence / mortality?
Questions

- Beyond early-stage CRC? i.e. preinvasive lesions?  
  ...Q1
- Which preinvasive lesions?  
  ...Q2
- How to assess benefit on CRC incidence / mortality?  
  ...Q3
Q1: Preinvasive?

Early-stage CRC detection

CRC prevention
Q1: Preinvasive?

Early-stage CRC detection

CRC prevention
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Atkin *et al*, Lancet 2010;375:1624
Segnan *et al*, JNCI 2011;103:1310

Schoen *et al*, NEJM 2012;366:2345
Holme *et al*, JAMA 2014;312:606
We CAN reduce incidence

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Cumulative cases

- Colorectal cancer incidence - Control
- Colorectal cancer incidence - Screening
- Colorectal cancer mortality - Control
- Colorectal cancer mortality - Screening

Years after screening

CRC deaths averted (PLCO, estimated):

- Early detection 29-35%
- CRC prevention 65-71%

Cumulative cases

Years after screening

We CAN reduce incidence...
We CAN reduce incidence…

…and we should (if resources permit)
Q2: Which lesions?

- We know some things about size, histology
- Knowledge gaps (e.g. natural history)

To a first approximation, CRC risk attributable to:

- ...WITHOUT lesion removal \(\rightarrow\) the lesion
- ...AFTER lesion removal? \(\rightarrow\) the patient \(\textit{(colon)}\)
Q2: Which lesions?

- We know some things about size, histology
- Knowledge gaps (e.g. natural history)
- *To a first approximation*, CRC risk attributable to:
  - …WITHOUT lesion removal $\rightarrow$ the lesion
  - …AFTER lesion removal? $\rightarrow$ the patient (colon)
Q2: Which lesions? **Larger ones**

<table>
<thead>
<tr>
<th>Size of tumor</th>
<th>Total number</th>
<th>Number with malignancy</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 1 cm</td>
<td>1479</td>
<td>19</td>
<td>1.3</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>580</td>
<td>55</td>
<td>9.5</td>
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<tr>
<td>Over 2 cm</td>
<td>430</td>
<td>198</td>
<td>46.0</td>
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</tbody>
</table>

Muto *et al.*, Cancer 1975; 36: 2251-2270
CRC risk in $\geq 1$ cm polyps not removed

Stryker et al., Gastro 1987;93:1009
Natural Hx: Small / Diminutive Adenomas

- 9 studies, n= 721, 2-3 y
- 1,034 adenomas 1-9 mm:
  - 6% → AA
  - ?1 → CRC
  - NO LONG TERM DATA ON CRC RISK

Vleugels et al., GIE 2017;85:1169
Sekiguchi et al., AJG 2019;114:964
Q2: Which lesions? Villous

Table 7. Adenomatous Polyps and Villous Adenomas: Relationship of Histological Type to Percent of Carcinoma

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Total number</th>
<th>Number with malignancy</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular adenoma</td>
<td>1880</td>
<td>90</td>
<td>4.8</td>
</tr>
<tr>
<td>Intermediate type</td>
<td>383</td>
<td>86</td>
<td>22.5</td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>243</td>
<td>99</td>
<td>40.7</td>
</tr>
</tbody>
</table>

Muto et al., Cancer 1975; 36: 2251-2270
Q2: Which lesions?

- We know some things about size, histology
- Knowledge gaps (e.g. natural history)
- To a first approximation, CRC risk attributable to:
  - ...WITHOUT lesion removal $\rightarrow$ the lesion
  - ...AFTER lesion removal? $\rightarrow$ the patient \((\text{colon})\)
Q2: Which lesions?

- We know some things about size, histology
- Knowledge gaps (e.g. natural history)

To a first approximation, CRC risk attributable to:
- ...WITHOUT lesion removal $\rightarrow$ the lesion
- ...AFTER lesion removal? $\rightarrow$ the patient (colon) *

* Incomplete resection?
CRC incidence (mortality) AFTER removal

- ≥10 mm adenomas
- Villous / HGD
- ≥3 adenomas

Odds ratio
HRA : No adenoma

2.92 [2.31-3.69]

Heterogeneity: \( \tau^2 = 0.04 \); \( \chi^2 = 11.71, \) df = 7 (\( P = 0.11 \)); \( I^2 = 40\% \)

Test for overall effect: \( Z = 9.00, (P < 0.00001) \)

Duvvuri et al., Gastroenterology 2021; In press
**CRC incidence (mortality) AFTER removal**

- **1-2 adenomas <10 mm**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LRA Events</th>
<th>Total Events</th>
<th>No adenoma Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
<th>Year</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Chung 2011</td>
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<td>Chiu 2015</td>
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<td>Click 2018</td>
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<td>He 2020</td>
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<td>Lee 2020</td>
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<td>Liberman 2020</td>
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<td>Wieszczy 2020</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<td></td>
<td></td>
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<td></td>
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Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.60, df = 6 (P = 0.47); I^2 = 0%
Test for overall effect: Z = 2.54 (P = 0.01)

**Odds ratio**

LRA : No adenoma

1.26 [1.06-1.51]

Duvvuri et al., Gastroenterology 2021; In press
CRC incidence (mortality) AFTER removal

Sessile Serrated Lesions (SSLs)

Song et al., Lancet GastroHep 2020;5:537
Q2: Which lesions?

CRC incidence reduction =
- Non-advanced adenoma removal
  + Advanced adenoma removal
  + Low-risk SSL removal
  + Advanced SSL removal
Q2: Which lesions?

CRC incidence reduction =

Minor? → Non-advanced adenoma removal
+ Advanced adenoma removal
+ Low-risk SSL removal
+ Advanced SSL removal

Minor →
Q2: Which lesions?

CRC incidence reduction =

Minor? \rightarrow Non-advanced adenoma removal +

MAJOR \rightarrow Advanced adenoma removal +

Minor \rightarrow Low-risk SSL removal +

Important? \rightarrow Advanced SSL removal
A better answer than “AA and Adv SSL”?

The adenoma hunt in colorectal cancer screening: defining the target

Anke H Sillars-Hardebol, Beatriz Carvalho, Manon van Engeland, Remond JA Fijneman and Gerrit A Meijer

1 Department of Pathology, VU University Medical Centre, Amsterdam, The Netherlands
2 Department of Pathology, GROW—School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands
A better answer than “AA and Adv SSL”? ...

...for most of the >1,000,000 new CRCs..., it is simply not known whether these cancers have progressed from small or large adenomas, tubular or villous adenomas, nor from flat or polypoid adenomas.

...the adenoma–carcinoma sequence model has started to live a life of its own, and the perception...has overtaken real-life observations.

Sillars-Hardebol et al., J Pathol 2012;226:1
CRC development and progression model

Activation Wnt pathway → adenoma formation
Additional mutations → adenoma outgrowth

Normal mucosa
- Proliferation
- Differentiation
- Apoptosis
- Hypoxia
- Glycolysis

Adenoma
- Senescence
- Proliferation
- Differentiation
- Chromosomal instability
- Angiogenesis
- Invasion
- Stroma activation
- Fatty acid metabolism

Carcinoma

No progression (95%)
Progression (5%)

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Stroma activation
Fatty acid metabolism

Carcinoma

No progression (95%)
Progression (5%)

Molecular targets?

Sillars-Hardebol et al., J Pathol 2012;226:1
Molecular targets?

Molecular tests!

(vs. “morphology” tests)

Sillars-Hardebol et al., J Pathol 2012;226:1
Q3: How assess benefit?
Q3: How assess benefit? **Large N, long t**

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Q3: Assessing benefit, short of RCTs

- Test performance characteristics / extrapolation
- Modeling
Models can help, but CAVEAT…

Table 2  Dwell Time Summary Measures from 3 Microsimulation Models of Colorectal Cancer

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<th>MISCAN</th>
<th>CRC-SPIN</th>
<th>SimCRC</th>
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<td>Time from adenoma incidence to adenoma progression to preclinical cancer (i.e., adenoma dwell time), y</td>
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<td>16–31</td>
<td>12–29</td>
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<td>1.6</td>
<td>4.0</td>
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Kuntz et al., Med Decis Making 2011;31:530
# Models can help, but CAVEAT…

## Serrated Pathway
- ASCCA model
- 15% serrated

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Greuter et al., Ann Int Med 2017;167:544

Kuntz et al., Med Decis Making 2011;31:530
Modeling and reality

Prediction

Model

Observation (RCT, cohort)

Re-calibration
Questions

- Beyond early-stage CRC? i.e. preinvasive lesions?
- Which preinvasive lesions?
- How to assess benefit on CRC incidence / mortality?
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Yes (where feasible)

“Advanced”— ok for now (Molecular targets?)

Model & observation, and iterate