Genetic risk factors contributing to young-onset colorectal cancer (YOCRC)

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Disclosures

I have no relevant financial disclosures.
Complex factors contributing to the rise in YOCRC

- Genetic and hereditary risk factors in YOCRC

Outline

1) Genetic changes during colorectal cancer development
2) Hereditary versus non-hereditary (somatic) genetic factors: what's the difference?
3) What we know about YOCRC and hereditary cancer syndromes
4) Conclusions
Colorectal cancer represents a physical and molecular transformation of healthy cells
Normal colorectal tissue → Early adenoma (polyp) → Advanced adenoma → Colorectal cancer
Colorectal cancer represents a physical and molecular transformation of healthy cells

**Normal colorectal tissue/cells**

- Each cell carries two copies of every genes in the human genome
- We **inherit** one copy of a gene from each parent
  - Copy inherited from egg
  - Copy inherited from sperm
- Some copies of a gene may contain a "variant" (mutation) that affects the normal function of that gene

**Colorectal cancer**

- Each cancer cell contains an altered genome
- An individual gene may be mutated in a way that greatly affects its function (e.g., stimulate cancer growth and metastases)
Differences between hereditary (germline) and non-hereditary (tumor/somatic) testing

**Somatic DNA changes**
- Acquired over a persons lifetime in single cells
- Can lead to cancer
- Can NOT be inherited

**Germline DNA changes**
- Present in every cell of the body including egg and sperm
- Can increase cancer susceptibility
- Can be inherited

http://www.bcgsc.ca
Known hereditary cancer syndromes

Colorectal Cancer

- Adenomatous polyposis
  - APC
  - MUTYH
  - POLE
  - POLD1

- Non-polyposis CRC
  - MLH1
  - MSH2
  - MSH6
  - PMS2
  - EPCAM

- Lynch syndrome
  - PTEN
  - SMAD4
  - BMPR1A
  - STK11

Breast/Ovarian Cancer

- BRCA1
- BRCA2
- PALB2

- ATM
- CHEK2
- NBN

- CDH1
- TP53
- CDKN2A

Various

- Stomach
- Pancreas
- Sarcoma
- Melanoma

*Darker shading represents higher penetrance
†Size approximates population prevalence

Stoffel EM, et al. Gastroenterology. 2018
Testing for known hereditary cancer syndromes

• Must be ordered by a clinician

• A sample of DNA is extracted from healthy tissue (such as blood or saliva) using a test kit. This represents the DNA a person inherits.

• DNA undergoes genetic sequencing ("spell checking") to detect mutations/variations present within a panel of genes that are linked to hereditary colon cancer

• A mutation is categorized based on its impact on gene function and predisposition to cancer

• Results are reported back to patients and their clinicians

• Examples of testing kits/companies:
Hereditary colon cancer syndromes are found more often in people with YOCRC
<table>
<thead>
<tr>
<th>Cohort characteristics</th>
<th>Genes tested</th>
<th>Pathogenic or likely pathogenic variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mork et al&lt;sup&gt;1&lt;/sup&gt; 193 patients aged &lt;35 years; mean age at diagnosis 29 years</td>
<td>Phenotype driven; all patients had been referred for genetic counselling</td>
<td>44/193 (23%)</td>
</tr>
<tr>
<td>Yurgelun et al&lt;sup&gt;2&lt;/sup&gt; 336 patients aged &lt;50 years selected from 1058 consecutive patients with colorectal cancer of all ages with mean age at diagnosis 56 years</td>
<td>25-gene panel</td>
<td>52/336 (14%)</td>
</tr>
<tr>
<td>Pearlman et al&lt;sup&gt;3&lt;/sup&gt; 450 patients aged &lt;50 years; mean age at diagnosis 43 years</td>
<td>25-gene panel</td>
<td>75/450 (16%)</td>
</tr>
<tr>
<td>Stoffel et al&lt;sup&gt;4&lt;/sup&gt; 430 patients aged &lt;50 retrospectively selected from genetic counseling service; mean age at diagnosis 40 years</td>
<td>124-gene or 67-gene panel</td>
<td>79/315 (25%)</td>
</tr>
<tr>
<td>Uson et al&lt;sup&gt;5&lt;/sup&gt; 124 patients aged &lt;50 years; mean age at diagnosis 43 years</td>
<td>83-gene or 84-gene panel</td>
<td>33/124 (22%)</td>
</tr>
<tr>
<td>Toh et al&lt;sup&gt;6&lt;/sup&gt; 88 patients aged &lt;50 years; mean age at diagnosis 41 years</td>
<td>64-gene panel, excluding MMR genes</td>
<td>12/88 (14%)</td>
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</tbody>
</table>

Patel, SW, et al., Lancet Gastroenterology and Hepatology, 2022
How often are people with YOCRC found to have a hereditary cancer syndrome? 14-25%

What is the most common hereditary cancer syndrome among people with YOCRC? Lynch syndrome

I don’t have a family history of colorectal cancer. Could I still have a hereditary cancer syndrome? Yes!

My tumor was already tested for biomarkers/genes that can determine treatment options. Could I still benefit from hereditary genetic testing? Yes!

Patel, SW, et al., Lancet Gastroenterology and Hepatology, 2022
Under-utilization of hereditary genetic testing in YOCRC

Figure 2. Proportion of patients referred to genetic counseling by race/ethnicity and age (n = 225).

Dharwadkar, P., et al., Clinical Gastroenterology and Hepatology, 2022
Conclusions

- People with YOCRC have an estimated ~14-25% risk of carrying a hereditary colon cancer syndrome
- Genetic testing should be offered and strongly considered for all individuals with YOCRC
Next frontier: how to hereditary factors interact with environmental factors?
Thank you
Questions?