Can we predict cancer risk? – monogenic versus complex traits

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Overview

• introduction
• clinical utility managing hereditary cancer syndromes
• tasks in counselling cancer families
• summary
The hallmarks of cancer

self-sufficiency in growth signals

evading apoptosis

insensitivity to anti-growth signals

sustained angiogenesis

tissue invasion & metastasis

limitless replication potential

adapted from Douglas Hanahan and Robert A. Weinberg, Cell 100 (2000)
"While we believe that virtually all cancers must acquire the same six hallmark capabilities, their means of doing so will vary significantly, both mechanistically and chronologically."

adapted from Douglas Hanahan and Robert A. Weinberg, Cell 100 (2000)
Genetic aberrations in cancer cells

- **gains**
- **losses**
- **translocations**
- **point mutation**

Wild type, heterozygous mutation, and homozygous mutation are shown in the graph.
Acquired or constitutional aberration?

- Tumor suppressor gene
- 2 acquired mutations
- Constitutional first hit
- Acquired second hit
Familial predisposition to cancer

"a short trip to cancer"

family history

- many cancer patients
- early onset of cancer
- multiple diseases in one individual
Can we predict cancer risk?
Why do we need to predict cancer risk?

Can we predict cancer risk?
Cancer risk prediction & our common future

- Clinical criteria
- Risk assessment
- Genetic testing
- Surveillance
- Risk-reducing surgery
- Reduced cancer-associated morbidity and mortality
• well established monogenetic traits
e.g. hereditary non-polyposis colorectal cancer (HNPCC)

• novel monogenetic traits
e.g. familial platelet disorder with propensity to myeloid malignancy (FPDMM)

• complex traits
e.g. common low penetrance SNPs associated with familial breast cancer
• **well established monogenetic traits**
  
  e.g. hereditary non-polyposis colorectal cancer (HNPCC)

• **novel monogenetic traits**
  
  e.g. familial platel disorder with propensitiy to myeloid malignancy (FPDMM)

• **complex traits**
  
  e.g. common low penetrance SNPs associated with familial breast cancer
Hereditary non-polyposis colorectal cancer

- 3-5% of colorectal cancer
- heterozygous germline mutation in mismatch repair genes
- increased life-time risk for

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer (men)</td>
<td>28–75%</td>
</tr>
<tr>
<td>Colorectal cancer (women)</td>
<td>24–52%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>27–71%</td>
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<tr>
<td>Ovarian cancer</td>
<td>3–13%</td>
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<tr>
<td>Gastric cancer</td>
<td>2–13%</td>
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<tr>
<td>Urinary tract cancer</td>
<td>1–12%</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>1–4%</td>
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<tr>
<td>Bile duct/gallbladder cancer</td>
<td>2%</td>
</tr>
<tr>
<td>Small-bowel cancer</td>
<td>4–7%</td>
</tr>
</tbody>
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HNPCC – criteria & surveillance

- clinical criteria (Amsterdam/Bethesda guidelines)
- genetic screening
- defined surveillance programs:
  - e.g. periodic examination by colonoscopy
    - detection of early stage tumors
    - reduces colorectal cancer morbidity, and
    - significant reduction of colorectal cancer associated mortality

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Novel monogenic traits, e.g. FPDMM

familial plateled disorders with propensity to myeloid malignancies

• heterozygous RUNX1 germline mutations,

• incomplete penetrance, variable expressivity,

• bleeding history due to low platelets or platelet dysfunction

• MDS/ AML in 1-3 of 5 affected individuals
Novel monogenic traits, e.g. FPDMM

**familial plateled disorders with propensity to myeloid malignancies**

Ripperger et al. Leukemia 2009
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Familial breast cancer

BRCA1/2

20-40% of affected families
10-fold increased relative risk

Monogenic vs. complex traits

BRCA1 / 2

risk prediction

whole set of SNP

models?
Can we predict cancer risk?

- Clinical criteria
- Risk Assessment
- Genetic testing
- Surveillance
- Reduced cancer-associated morbidity and mortality
Can we predict cancer risk?

- Clinical criteria
  - ✓ HNPCC

- Risk Assessment

- Genetic testing
  - ✓ HNPCC

- Surveillance
  - ✓ HNPCC

- Reduced cancer-associated morbidity and mortality

- ✓ HNPCC
Can we predict cancer risk?

- **Clinical criteria**: HNPCC

- **RISK ASSESSMENT**

- **Genetic testing**: HNPCC, FPDMM, complex traits

- **Surveillance**: HNPCC

- **Reduced cancer-associated morbidity and mortality**
Can we predict cancer risk?

- **Clinical criteria**
  - ✓ HNPCC
  - ✗ FPDMM
  - ✗ Complex traits

- **RISK ASSESSMENT**

- **Genetic testing**
  - ✓ HNPCC
  - ✓ FPDMM
  - ✓ Complex traits

- **Surveillance**
  - ✓ HNPCC
  - ✗ FPDMM
  - ✗ Complex traits

- **Reduced cancer-associated morbidity and mortality**
More and more gene tests

Predicting cancer risk

GENETIC TESTING

MIND THE GAP

CLINICAL VALIDITY

CLINICAL UTILITY

Number of diseases for which testing is available

Acknowledgement

Brigitte Schlegelberger
Doris Steinemann
Dorothea Gadzicki
Marcel Tauscher

HBRS, PhD Program Molecular Medicine

Volkswagenstiftung