HEREDITY & CANCER: Breast cancer as a model

Pierre O. Chappuis, MD
Divisions of Oncology and Medical Genetics
University Hospitals of Geneva, Switzerland
Genetics, Cancer and Heredity

- **Cancers are genetic diseases**

- **Predisposition** to some cancers is **hereditary**

  ⇒ “at risk” **individuals**
“Hereditary” cancer: Definition

Cancer resulting from the inheritance, generally as an autosomal dominant trait, of a germline alteration in one gene, conferring a genetic susceptibility to the development of cancer.
“Hereditary” cancer:
RETINOBLASTOMA: a paradigm

- Childhood eye tumor
- Both hereditary and sporadic forms
- Sporadic forms always unilateral
- Hereditary forms usually bilateral
The two-hit hypothesis  [Knudson, 1978]

- Each cell contains 2 copies of each autosomal gene

- In HEREDITARY Rb, one mutation of the RB1 gene is passed to the child  (sometimes de novo)

- Thus there is a single RB1 mutation in all retinoblasts:
  - no advantage to the mutated cell
  - when a second hit occurs (to any retinoblast) there is no functioning Rb protein ⇒ RETINOBLASTOMA
The two-hit hypothesis  [Knudson, 1978]

- Tumors often bilateral because each eye has $10^7$ retinoblasts, so two hits in more than one cell is not so unlikely.

- In **SPORADIC**, non-hereditary Rb, BOTH hits have to occur post-natally in the retinoblasts: this is much less likely to happen, so sporadic Rb is late in onset and unilateral.
Hereditary predispositions to cancer

- 5-10% of all cancers
- Autosomal dominant transmission
  - risk at each conception = 50%
- Low prevalence, high penetrance
<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Genes</th>
<th>Chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast cancer</td>
<td>BRCA1</td>
<td>17q</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>13q</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer (HNPCC; Lynch syndrome)</td>
<td>MSH2</td>
<td>2p</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td>3p</td>
</tr>
<tr>
<td></td>
<td>MSH6, PMS1, PMS2</td>
<td>2p, 2q, 7p</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP)</td>
<td>APC</td>
<td>5q</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
<td>17p</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
<td>13q</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia (MEN) 2</td>
<td>RET</td>
<td>10q</td>
</tr>
<tr>
<td>von Hippel-Lindau</td>
<td>VHL</td>
<td>3p</td>
</tr>
<tr>
<td>Familial melanoma</td>
<td>CDKN2</td>
<td>9p</td>
</tr>
<tr>
<td></td>
<td>CDK4</td>
<td>12q</td>
</tr>
<tr>
<td>Familial gastric cancer</td>
<td>CDH1</td>
<td>16q</td>
</tr>
<tr>
<td>Cowden disease</td>
<td>PTEN</td>
<td>10q</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>19p</td>
</tr>
</tbody>
</table>
Hereditary Cancer Syndromes:
Use of genetic testing

Molecular screening
dHPLC, SSCP, PTT, sequencing

Identification of pathogenic mutations

CARRIERS
Surveillance/prevention

NON CARRIERS
Reassurance
Genetic screening in oncology: Who’s concerned?

Suggestive familial aggregation, if cancer:

• in $\geq 2$ generations
• early age of onset
• identified in gender where usually uncommon
• associated with other types of cancer, congenital malformations or genetic syndromes
• in a defined ethnic background
Genetic screening in oncology: Who’s concerned?

“Individual” susceptibility, if cancer:

- bilateral
- multicentric
- multiple
- at an unusual age, site or gender
- associated with congenital malformations or genetic syndromes
- in a defined ethnic background
Genetic screening in oncology: Why?

- Clarify risk evaluation
- Target screening/prevention efforts to the identified carriers of genetic predisposition to cancer
- Exclude the non-carriers of specific programs of screening/prevention
- No risk for the children of proven non-carriers
- Knowledge of the genetic status: “need to know”
Oncogenetic counseling process

1st Consultation
- Motivation, expectation
- Genetics, heredity and cancer
- Detailed personal and family history

Consensus consultation
- Risk evaluation
- Probability of genetic predisposition
- Screening and prevention measures
- Availability of genetic analysis

2nd consultation
- Limit and consequence of genetic analysis
- Types of result

Genetic testing
- Affected family member available?

3rd consultation
- Transmission of results
- Follow-up

• Validation of diagnosis
1. Genetic alteration identified
   - pathogenic mutation
   - variant (unknown biological significance)
   - polymorphism

2. No genetic alteration ("no mutation detected")
   - does not exclude a genetic predisposition!
   - technical limits, other gene, phenocopy

3. Genetic alteration excluded
   - only when previously identified in the family
GENETIC PREDISPOSITION to BREAST CANCER

[Clin Breast Ca 2000]
BRCA1/BRCA2 germline mutations and breast cancer

- Major genetic predisposition to breast/ovarian cancer
- Autosomal dominant transmission
- BRCA1/2-related breast cancers: histo-pathological characteristics usually associated with worse outcome
- Clinical outcomes incompletely defined
- Clinical management questions unanswered
## Hereditary breast cancer:

### Other predisposing genes

- **TP53**  
  Li-Fraumeni syndrome
- **ATM**  
  Ataxia telangiectasia
- **STK11/LKB1**  
  Peutz-Jeghers syndrome
- **PTEN**  
  Cowden syndrome
- **BRCA3 (?)**  
  locus on chromosome 13q21
**BRCA1 gene**

- 17q21
- > 100 kb
- 24 exons
- > 500 different genetic alterations
- Nuclear phosphoprotein: 1863 aa / 220kDa
- Responsible for ~30% of site-specific hereditary breast cancer and ~50% of hereditary breast/ovarian cancer

![BRCA1 gene diagram](image)
BRCA2 gene

- 13q12
- > 70 kb
- 27 exons
- > 200 different genetic alterations
- Nuclear protein: 3418 aa / 384kDa
- Responsible for ~40% of site-specific hereditary breast cancer and ~15% of hereditary breast and ovarian cancer

Transcriptional activation  BRC Repeats  NLS
P/CAF  RAD51
BRCA1 & BRCA2: Multifunctional proteins

- Transcriptional regulation
- Cell cycle regulation (checkpoint control)
- Growth suppression
- **Response to DNA damage**
  - double strand-break repair
  - base excision repair (BRCA1)
- **Maintenance genome stability**
- Apoptosis induction
BRCA1/2 mutations: Risk of breast/ovarian cancer

[Eeles & Powles, J Clin Oncol 2000]
### BRCA1/BRCA2 germline mutations: Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General population</strong></td>
<td>1/830</td>
<td>?</td>
</tr>
<tr>
<td><strong>Ashkenazi Jews</strong></td>
<td>1/86</td>
<td>1/74</td>
</tr>
<tr>
<td></td>
<td>(185delAG, 5382insC)</td>
<td>(6174delT)</td>
</tr>
</tbody>
</table>

### BREAST CANCER

<table>
<thead>
<tr>
<th></th>
<th>BRCA1 + BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General population</strong></td>
<td>2 - 5%</td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>6 - 16%</td>
</tr>
<tr>
<td><strong>Ashkenazi Jews</strong></td>
<td>~12%</td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>~40%</td>
</tr>
</tbody>
</table>
**BRCA1-related breast cancer: Clinicopathological features**

- Younger age of onset
- Invasive ductal; $P = 0.05$
- Medullary/atypical med.; $P < 0.0001$
- Histological grade 3; $P < 0.0001$
- ER/PR negativity; $P < 0.0001$
- *TP53* mutation; $P = 0.0003$
- HER2 positivity (less); $P < 0.0001$

[Sem Surg Oncol 2000; 18:287-95]
BRCA2-related breast cancer: Clinicopathological features

- Invasive ductal $P = 0.06$
- Less tubule formation $P < 0.0001$
- TP53 mutations $P = 0.03$

[Sem Surg Oncol 2000; 18:287-95]
“Hereditary” breast cancer: Clinical presentation

• Early age of onset (< 45 years)

• Several family members affected (≥ 3)

• More than one generation involved (autosomal dominant)

• Bilateral breast cancer

• Associated cancers:
  - #1: ovarian cancer, peritoneal and fallopian tube cancer
  - others: male breast, prostate, pancreas cancer (BRCA2)
High risk women for breast cancer: OPTIONS

• SCREENING

• CHEMOPREVENTION

• PROPHYLACTIC SURGERY

• Lifestyle modification?
## High risk women for breast cancer: Screening recommendations

<table>
<thead>
<tr>
<th>Technique</th>
<th>Start</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self examination</td>
<td>20 years</td>
<td>1x / month</td>
</tr>
<tr>
<td>Clinical breast examination</td>
<td>25 years</td>
<td>2-3x / year</td>
</tr>
<tr>
<td>Mammography ± US</td>
<td>25-30 years</td>
<td>1x / year</td>
</tr>
<tr>
<td>MRI (investigational)</td>
<td>25-30 years</td>
<td>1x / year</td>
</tr>
</tbody>
</table>
## Surveillance in BRCA1/2 mutation carriers: Prospective studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1/2 carriers</strong></td>
<td>128</td>
<td>63</td>
<td>165</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>BSE 1x/m, CBE 2x/y, mammo ± US 1x/y</td>
<td>BSE 1x/m, CBE 2x/y, mammo ± US 1x/y; MRI 1x/y (since 1995)</td>
<td>BSE 1x/m, CBE 2-4x/y, mammo ± US 1x/y</td>
</tr>
<tr>
<td><strong>Mean follow-up</strong></td>
<td>3 years</td>
<td>3 years</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>In situ carcinoma</strong></td>
<td>0</td>
<td>n/s</td>
<td>3</td>
</tr>
<tr>
<td><strong>Invasive carcinoma</strong></td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>N+</strong></td>
<td>5/9</td>
<td>4/8</td>
<td>3/9</td>
</tr>
<tr>
<td><strong>Interval cancers</strong></td>
<td>4/9</td>
<td>4/8</td>
<td>6/12</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>56%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Mammography and MRI

- 5 studies in high risk women
- No randomization
- No data on mortality rates
## High risk women for breast cancer: Mammography & MRI 1x/year

<table>
<thead>
<tr>
<th>Study</th>
<th>Population studied</th>
<th>Type of study</th>
<th>Mean follow-up</th>
<th>In situ/invasive BC</th>
<th>Mammography</th>
<th>MRI</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuhl et al.</td>
<td>192 “high risk”</td>
<td>prospective</td>
<td>2.5 years</td>
<td>2/7</td>
<td>3/9 (2/9: “fibroadenomas”)</td>
<td>9/9</td>
<td>Mammo: 30% MRI: 64%</td>
</tr>
<tr>
<td>([Radiology 2000])</td>
<td>35 BRCA1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tilanius-Linthorst et al.</td>
<td>109 &gt; 25% risk + &gt; 50% dense tissue 12 BRCA1/2</td>
<td>retrospective</td>
<td>n/s</td>
<td>0/3</td>
<td>0/3</td>
<td>3/3</td>
<td>Mammo: 0% MRI: 33%</td>
</tr>
<tr>
<td>([Breast Ca Res Treat 2000])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meijers-Heijboer et al.</td>
<td>63 BRCA1/2</td>
<td>prospective</td>
<td>3 years</td>
<td>0/8</td>
<td>2/8</td>
<td>6/6</td>
<td>n/s</td>
</tr>
<tr>
<td>([N Engl J Med 2001])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stoutjesdijk et al.</td>
<td>179 “high risk”</td>
<td>historical cohort</td>
<td>n/s</td>
<td>3/10</td>
<td>6/12</td>
<td>13/13</td>
<td>Mammo: 33% MRI: 43%</td>
</tr>
<tr>
<td>([J Natl Cancer Inst 2001])</td>
<td>47 BRCA1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warner et al.</td>
<td>196 high risk</td>
<td>prospective</td>
<td>1.5 years</td>
<td>1/6</td>
<td>3/6</td>
<td>6/7</td>
<td>(in situ not detected)</td>
</tr>
<tr>
<td>([J Clin Oncol 2001])</td>
<td>96 BRCA1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
High risk women for breast cancer:

CHEMOPREVENTION

• TAMOXIFEN

• LHRH agonists
aromatase inhibitors
retinoids, …
High risk women for breast cancer:
PREVENTION by SURGICAL MEASURES

• MASTECTOMY
• OOPHORECTOMY
### BRCA1/2 mutation carriers: Breast cancer risk after prophylactic mastectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up (years)</th>
<th># breast cancer</th>
<th>Type of mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartmann et al. [J Natl Cancer Inst 2001]</td>
<td>BRCA1/2: 26</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Meijers-Heijboer et al. [N Engl J Med 2001]</td>
<td>BRCA1/2: 76</td>
<td>2.9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Scheuer et al. [J Clin Oncol 2002]</td>
<td>BRCA1/2: 29</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
### BRCA1/2 mutation carriers: Breast cancer risk after prophylactic mastectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-up (years)</th>
<th># breast cancer</th>
<th>Type of mastectomy</th>
<th>Surveillance group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartmann et al. [J Natl Cancer Inst 2001]</td>
<td>BRCA1/2: 26</td>
<td>16</td>
<td>0</td>
<td>total</td>
<td>-</td>
</tr>
<tr>
<td>Meijers-Heijboer et al. [N Engl J Med 2001]</td>
<td>BRCA1/2: 76</td>
<td>2.9</td>
<td>0</td>
<td>total</td>
<td>8 breast cancers in 63 carriers ($P = 0.003$)</td>
</tr>
<tr>
<td>Scheuer et al. [J Clin Oncol 2002]</td>
<td>BRCA1/2: 29</td>
<td>2</td>
<td>0</td>
<td>n/s</td>
<td>12 breast cancers in 165 carriers ($P = 0.13$)</td>
</tr>
</tbody>
</table>
## Prophylactic oophorectomy and breast cancer risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Gene</th>
<th>n</th>
<th>Follow-up</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebbeck et al.,</td>
<td>BRCA1</td>
<td>43</td>
<td>9.6 years</td>
<td>0.53 (0.33-0.84)</td>
</tr>
<tr>
<td>[J Natl Cancer Insr 1999]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Eisen et al.,       | BRCA1/2  | n/s | n/s       | BRCA1: 0.39 (0.2-0.75)  
| [J Clin Oncol 2000] |          |     |           | BRCA2: 0.56 (0.16-1.95)  |

- Lower risk with > 10 year follow-up
- Reduction risk not lost by HRT
- **Risk reduction greatest when oophorectomy ≤ 40 years**
Prophylactic surgery and breast cancer risk: Remaining issues

- Early data look encouraging
- No evidence of long-term effectiveness mastectomy in BRCA1/2 mutation carriers ascertained prospectively
- Psychological impact
- Prolongation of survival?
Genetic testing in oncology: **Conclusions**

- Highly specific, but low sensitivity
- Population concerned is limited
- Predictive oncology = probabilistic medicine
- Standard of care
- Multidisciplinary approach
- Psycho-social and ethical implications
Genetic testing in oncology: Unresolved issues

- Validation of tests
- Pathogenicity of rare variants
- Geno/phenotypic correlations
- Modifier genes/environmental factors
- Psycho-social issues
- Surveillance and prevention
Genetic testing in oncology: Perspectives

- Multigenic disorders

- Sporadic cancers: *population screening*

- Changes in social/medical behaviors:
  
  "medicine for well-being individuals"

- Innovative preventive strategies