Genetic tests detecting cancer predisposition

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Prof. Dr. Bernard Weber
Laboratoires Réunis
Luxembourg

What is cancer?

• Cancer is a disease of cells
• Cancer arises from normal cells that have been altered in some way
All cancer is genetic

➢ Hereditary
  • 5% to 10% of all cancers
  • Born with a known gene mutation altered in some way
➢ Family history
  • Gene mutation(s) unknown
  • Acquired (sporadic)
  • Age

Who is at risk?

• Growing older (most cancers at age >60)
• Tobacco
• Sunlight
• Ionizing radiation
• Certain chemicals and other substances
• Some viruses (HPV, HBV, HCV, HTLV-1, HIV) and bacteria (H.pylori)
• Certain hormones (estrogen, progesterin, DES)
• Family history of cancer (genetic background)
• Alcohol
• Poor diet, lack of physical activity, or being overweight

Susceptibility factors (e.g. genetic variation)

• Consequences for counseling:
  • Most individuals with a «high» risk never develop the disease
  • Few individuals with a «low» risk will develop the disease
  • True for genetic variation, ethnic and clinical risk factors
But also true for fast driving and car accidents
(Many people who had a fatal car accident drove too fast; but many more drive too fast and survive)

Nutrition and cancer

• From a nutrigenomics point of view, nutrients are dietary signals that are detected by cellular sensor systems that can regulate gene and protein expressions and affect metabolite productions

Food
• Is connected to 50% to 60% of cancer deaths
• Is causally linked to cancers of the lung, upper respiratory tract, oesophagus, bladder, pancreas
• Is probably a cause of cancers of the stomach, liver, kidneys, colon, and rectum

But also: e.g. cruciferous vegetables lower cancer risk

Burger Heat

Nonmutagenic metabolites

Risk of Colon cancer

Heterocyclic aromatic amines

Mutagens

Kynurenic metabolizing enzymes

Activator

Glucosinolates

Broccoli

Absorbed in Digestive Tract

Metabolized by Liver Enzymes
Genetic tests detecting cancer predisposition

- Colorectal cancer (CRC)
- Breast cancer (BC)

Colorectal Cancer

- Colorectal cancer (CRC) is the second cause of cancer-related deaths in the Western world.
- **BUT** if detected at early stages, CRC is curable.
- Incidence (Luxembourg): 17.5 per 100,000
  - Cases in Luxembourg (2007): 292
  - Deaths (2010): 97

**Major forms:**
1. Sporadic CRC (sCRC)
2. Familial CRC
3. HNPCC (Hereditary non-polyposis colorectal cancer)
4. FAP (Familial adenomatous polyposis)

Pathogenesis of colorectal cancer

- APC, MSH2, MLH1
- Methylation abnormalities
- K-ras mutations
- DCC deletion

Further accumulation of genetic abnormalities

Note: Colorectal cancer does not appear de novo, meaning that the previous (benign and malignant) developmental stages are always appearing before the final carcinoma stage

Hereditary Colon Cancer

Heritability of CRC

<table>
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<tr>
<th>Environment</th>
<th>Genes</th>
</tr>
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<tbody>
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<td>42%</td>
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Causes of Hereditary Susceptibility to CRC

- Sporadic (65%–85%)
- Rare CRC syndromes (>0.1%)
- Familial adenomatous polyposis (FAP) (1%)
- Hereditary non-polyposis colorectal cancer (HNPCC) (5%)
Colorectal cancer:
Life-time risk and impact of genes and environment

FAP (benefits of genetic testing)
Once the family mutation is identified, at-risk individuals can pursue testing to clarify whether they do or do not have FAP.

Red meat and CRC-risk

CRC pilot study: genetic markers
- Transforming growth factor β type 1 receptor (TGFBR1)
  - Key receptor
  - Most important inhibitor of cell growth
- Reduction of allele-specific expression (ASE) is associated with CCR:
  - Frequency 10–20 % in CCR vs. 1–3 % in healthy controls
  - Odds ratio estimate: 8.7 (95 % CI: 2.6–29.1 %)
  - Estimated life-time risk: 50 % vs. 6 % in the general population

SNP-markers of pathways related to CRC
- p53=antagonist of NF-κB transcription factor (role in inflammation)
  - Rs1042522 > reduced p53 activity
- MDM2 = negative regulator of p53
  - Rs229744 > Increased inactivation of p53 protein
- TGFβ1, TGFβ4 = heteromeric complex with type II TGFβ receptors when bound to TGFβ (signal transduction)
  - Rs334348, rs334349, rs1590, rs7871490 > Impaired signal transduction
- SMAD7 = antagonist of TGFβ signaling pathway
  - Rs12953717, rs4939827, rs4464148
- PROC3 = protein of unknown function
  - Rs1042522 > Clearly associated with increased risk for sCRC
- CHR8 & CHR9 = proteins of unknown function
  - Rs7014346, rs719725 > Clearly associated with increased risk for sCRC
- FLJ = uncharacterized proteins LOC120376 of unknown function
  - Rs3802842 > Clearly associated with increased risk for sCRC

Bernard Weber, Alain Menzel, Marc Pauly, Natacha van der Taelem, Mario Dicato
1 Laboratoires Réunis, Luxembourg; 2 Laboratoire de Recherche sur le Cancer et les Maladies du Sang, Luxembourg.

Genetic analysis of different SNPs as potential prognostic biomarkers in CRC – a pilot study

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Conclusions

1.) The following SNPs seem to be promising markers for sCRC risk assessment:
- p53 rs1042522
- MDM2 rs229744
- TGFBR1 e.g. rs334348
- CHR8 rs7014346
- SMAD7 rs12953717

2.) More SNPs of the TGF signaling pathway as well as SNPs related to apoptosis seem to be good candidates for genetic sCRC predisposition markers

3.) Possibility to assess a patient’s risk for sCRC by combining the risk associated to his genetic background (identified sCRC markers) with general risk factors (age, gender, environmental risk factors e.g. diet, lifestyle…) allowing to give risk reducing recommendations

Clinical validity and utility of TGFBR1 genetic testing:
- TGFBR1: Major contribution to CCR
- Data are only from a Caucasian population
- Candidate for predictive genetic testing
- Predictive value can be increased by combination with other genetic markers: p53, MDM2,…
- Potential clinical utility:
  - Molecular mechanism may be a target for preventive strategies
  - Recommendations for carriers of TGFBR1 variants: strong risk assessment and risk reduction strategies

Example of COLOgen profile: general risk assessment

Non-invasive test to evaluate the genetic predisposition for CRC

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**Example of COLOgen profile: global risk**

- **GENETIC RISK**
  - Colonoscopy every 5 years beginning at age 40
  - Regular intake of aspirin, NSAR
  - Vitamin D (haplotypes 765GG)
  - Reduction of IL6 (23R, 6)
  - 2V (381RR), IL6
  - SOD2 (16VV)
  - MTHFR (677TT)
  - GSTM1/GSTT1 (0/0)

- **HIGH RISK**
  - Increased relative risk for colorectal cancer:
    - Avoid exposure to endotoxins
    - Inhibition of CYP1A2: umbiliferous vegetables
    - Induction of GSTM1: lycopenes, vitamin E, selenium
    - Inhibition of NAT2 (RA = rapid acetylator): low dose NSAID

- **LOW RISK**
  - Moderate red meat consumption
  - Avoid food rich in saturated fatty acids
  - Avoid / quit smoking
  - Avoid alcohol consumption

- **MODERATE RISK**
  - Consume dietary soluble fibres
  - Consume fruits and vegetables
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**Nutrigenetics: Reduction of the risk for CRC by nutrition**

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Ca supplementation & decrease CRC (7 cohort studies)

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<th>Study</th>
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<tr>
<td>Black, 1993 Women</td>
<td>0.66 (0.43 - 1.00)</td>
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<td>Komulainen, 1996</td>
<td>0.89 (0.56 - 1.41)</td>
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<td>Wu, 2002 Men</td>
<td>0.70 (0.43 - 1.17)</td>
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<td>McCullough, 1993 Men</td>
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<td>Fendon, 2009 Wayne Women</td>
<td>0.87 (0.59 - 1.31)</td>
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<td>Lee, 2009 Women</td>
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Summary Effect Estimate L/U

CRC / Diet-Gene interactions

VDR (Fok1-Polymorphism)


Clotting factor Gene Polymorphisms and colorectal Cancer Risk

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<td>Factor V Leiden (G-&gt;A)</td>
<td>rs5060</td>
<td>Activated protein C resistance</td>
<td>GG 1* AG 0.70 AA 6.34</td>
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<td>Prothrombin (G20210A)</td>
<td>rs1799963</td>
<td>Thrombin generation</td>
<td>GG 1* GA 0.71 AA nd</td>
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<td>PAI-1 (4G/5G)</td>
<td>rs1799889</td>
<td>Plasminogen activator inhibitor</td>
<td>5G/5G 1* 4G/5G 0.87 4G/4G 1.06</td>
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<td>MTHFR (C677T)</td>
<td>rs1801133</td>
<td>Regulation of folate metabolism</td>
<td>CC 1* CT 1.08 TT 1.01</td>
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<td>FGG (10034 C&gt;T)</td>
<td>rs2066865</td>
<td>Fibrin precursor polymerization</td>
<td>CC 1* CT 1.07 TT 0.84</td>
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<tr>
<td>Factor XIII (Val34 Leu)</td>
<td>rs5985</td>
<td>Stabilization of fibrin</td>
<td>Val/Val 1* Val/Leu 0.85 Leu/Leu 1.13</td>
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* Reference category / Nd: Not determined because numbers of this genotype are too low to produce a valid OR

Vossen and al.: J Clin Oncol 2011;29:1722-1727

Breast cancer

Hereditary Breast Cancer

Heritability of BCA

- Heritability BCA - 27-40%
- Environmental factors contribute more to risk than genetics

How much Breast and Ovarian Cancer is Heredity?

Breast cancer: 15%-20%
Ovarian cancer: ~10%
Sporadic
Family clusters
Hereditary

Source: ASCO
**RISK FACTORS FOR BREAST CANCER**

- **Inherited gene mutations or family history**
  - BRCA1 or BRCA2
  - First-degree relatives with breast cancer

- **Environmental**
  - Estrogen

- **Personal**
  - Female gender
  - Age over 65
  - Prior breast cancer

**Established risk factors for breast cancer**

- Starting periods early
- Late onset on the menopause
- Not having children or having them later in life
- Not breastfeeding or breast feeding for only a short time
- Use of oral contraceptives
- Use of HRT
- Obesity
- Regular intake of alcohol

**BRCA1 & BRCA 2**

- Breast cancer & Ovarian cancer susceptibility genes
- Tumor suppressor genes
- Regulate cell cycle, cells are kept away from growing and dividing too rapidly or in an uncontrolled way
- Involved in many other functions including control of DNA replication and damage repair

- Germline mutations within BRCA1 predispose heterozygous carriers to early onset of BCA
- Heterozygous carriers of BRCA1 mutations have an 80%
- Increase risk of ovarian cancer

- Later age of onset compared to BRCA1 and lead to other tumors: gastric, colon, pancreatic, prostate and melanoma
- BRCA2 mutations confer higher risk of male breast cancer

**BRCA1 & BRCA2 CHEK2**

- Regulates the function of BRCA1
- Recent meta-analysis suggests that heterozygotes for CHEK2*1100delC have 37% risk of breast cancer by 70
- Clinical testing not routinely recommended by thought leaders at this time based on technical issues with the study JCO 26:542-548, 2008

**Estrogen metabolism**

- CYP1A1/2 Transformation of estradiol (E2) to 2-OH E2
- CYP1B1 Transformation of E2 to 4-OH E2
- CYP3A4 Transformation of E2 to 2-OH E2 and 16-OH E2
- COMT Transformation of 2-OH E2, 4-OH E2 to 6-OH E2
- GST oxidative stress
- SOD2 oxidative stress
- SULT1A1 Sulfonation: enhanced elimination
- UGT1A1 Glucuronidation: enhanced elimination
COMT (Catechol-O-Methyltransferase)

**Function:**
Protection of estrogen target cells against an excessive response

- No estrogenic activity = not toxic

- **Estrogen**

  2-OH-estrogen → **COMT** → 2-**Methoxy-estradiol**

  - Anti-proliferative
  - Anti-angiogenic
  - Apoptogenic

**COMT V158M polymorphism**

- Decreased enzymatic activity
- Reduced synthesis of 4-Methoxy-estradiol
- Reduced synthesis of methoxyestradiol – 3 - ester

**Consequences:**
- High levels of estrogen and metabolites
- Increased RR for sporadic breast cancer

**SNP-SNP interactions in breast cancer susceptibility**

<table>
<thead>
<tr>
<th>SNP-SNP</th>
<th>COMT CCND1</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT V158M</td>
<td>CCND1 Pro241Pro</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>COMT V158M</td>
<td>CCND1 Met108Val</td>
<td>2.4</td>
<td>[1.0 - 4.9]</td>
</tr>
<tr>
<td>COMT V158M</td>
<td>CCND1 Val108Met</td>
<td>1.6</td>
<td>[1.0 - 3.2]</td>
</tr>
<tr>
<td>COMT V158M</td>
<td>CCND1 Ala108Val</td>
<td>1.4</td>
<td>[0.7 - 3.4]</td>
</tr>
</tbody>
</table>

**Non-invasive test to evaluate the genetic predisposition for sporadic breast cancer in relation with HRT**

- **Assessment of the relative risk (RR) for sporadic breast cancer**
  1. **Questionnaire:**
     - General risk factors
     - Family history of breast cancer
     - HRT, contraception, lifestyle
  2. **Genetic risk factors**
    - CYP1A1, CYP1B1, CYP17A1, GSTM1, GSTT1, SULT1A1, COMT, ER
  3. **Determination of the cumulative relative risk**

**Conclusion and recommendations according to predisposition for sporadic breast cancer in relation with HRT**

- **Adaptation of:**
  - Food and lifestyle habits
  - Intervals of medical check-ups

**Example of FEMgen profile: General risk assessment**

<table>
<thead>
<tr>
<th>Gene / Allele</th>
<th>Genotype</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT</td>
<td>Pro158Met</td>
<td>6</td>
</tr>
<tr>
<td>CCND1</td>
<td>Pro241Pro</td>
<td>2</td>
</tr>
<tr>
<td>GSTM1</td>
<td>X</td>
<td>1</td>
</tr>
<tr>
<td>GSTT1</td>
<td>X</td>
<td>2</td>
</tr>
</tbody>
</table>

**Example of FEMgen profile: genetic risk assessment**

- **General impact of genetic risk factors:**

  - OR: Odds Ratio
  - CI: Confidence Interval

**Conclusion:**

- Identification of the relative risk of sporadic breast cancer on the basis of the impact of different genetic polymorphisms involved in steroidal hormone metabolism.
Example of FEMgen profile: Cumulative risk for BC

Interpretation and recommendations

- Increased activity of CYP1B1, decreased activity of GSTM1, GSTT1, SULT1A1, COMT
- RR of patient for BC further increased due to age, late menopause, HRT
- RR is reduced because patient <30 years at 1st childbirth, breastfeeding, physical active, regular consumption of fruit & vegetables

RR for sporadic breast cancer can be reduced by lifestyle and nutritional interventions

- Reduce exposure to estrogens and xenoestrogens
- Stimulate COMT activity
- Reduce CYP1B1 activity
- Compensate functional loss of GST

Recommendations associated to this profile

Compensation of GSTM1 / SULT
- Selenium, folic acid, omega-3
- Watercress, broccoli, Brussels sprouts

Stimulation of COMT
- Ensures sufficient intake of folate acid
- Black & green tea
- Sprouted wheat
- Spinach
- Baas

Inhibition of CYP1B1
- Avoid the regular consumption of alcohol, tobacco and weight excess

Nutrition & Lifestyle

- Avoid the regular consumption of alcohol, tobacco and weight excess
- Ensure sufficient intake of folate acid
- Black & green tea
- Sprouted wheat
- Spinach
- Baas
- Orange juice
- Magnesium supplementation
- Antioxidants (blueberries, pomegranate, grapes, red cabbage, Brussels sprouts, celery, etc.)
- Omega-3 (tuna, salmon, sardines, flaxseeds, nuts, olive oil)
- Isoflavonoids
- Soy, red clover
- Resveratrol
- Indoles (broccoli, Brussels sprouts, kale, cauliflower, pomegranate, blueberries, blackberries)
- Avoid smoking
- Reduce consumption of grilled and smoked products
- Avoid prolonged exposure to xenobiotics

Thank you