Rational approach to cancer screening

Prof. Jacques De Grève
Medical oncology

With help from dr. Mat Goossens
Cancer prevention
Oncologisch centrum VUB
Overview

• Cancer Statistics
• Prevention is better than screening
• Population based screening
  – Breast, cervix, colon, lung, prostate
  – Identification of high risk groups/individuals
  – Prevention/Screening of high risk groups
• Future developments
Cancer

- Second cause of disease-related mortality
- Second domain in disease burden (DALY)
- Still insufficient therapeutics

How to reduce mortality?
1. Prevention
2. Early diagnosis: screening
3. Improved therapeutics
Oncology Share of Disease Burden in Belgium compared to European benchmark
(Source: WHO and BCG Analysis presented November 2015)
Belgium has very high cancer 5-year relative survival rates (RSR) in comparison to other European countries.
Cancer, a high medical need
Some still with very high mortality

Cancer registry
Prevention vs screening

• Prevention
  – Measures to prevent the pathogenesis of cancer
  – Examples: curbing of smoking, life style changes
    • Smoking rate from > 25 % to 18%
    • Other style changes can have modest impact

• Screening
  – Measures for identification of premalignant lesions or early stages of cancer
Population based screening

• Organized by authorities & Centre for Cancer Detection (CvKO)
  – https://www.bevolkingsonderzoek.be

• Programs
  – Breast cancer
  – Cervical cancer
  – Colon cancer

• Not implemented but should be (in my opinion)
  – Lung cancer screening in heavy smokers

• Controversial
  – Prostate cancer
Breast cancer

International Agency for Research on Cancer

Western Europe
Australia/New Zealand
Northern Europe
Northern America
Southern Europe
More developed regions
- Polynesia
- Micronesia
Central and Eastern Europe
South America
Caribbean
World
- Southern Africa
- Northern Africa
- Western Asia
- Western Africa
- South-Eastern Asia
Less developed regions
- Central America
- Eastern Asia
- South-Central Asia
- Melanesia
- Middle Africa
- Eastern Africa

GLOBOCAN 2008 (IARC)

Incidenc/Mortality
Top incidence in Belgium

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Age-Standardised Rate per 100,000 (World)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Belgium</td>
<td>111.9</td>
</tr>
<tr>
<td>2</td>
<td>Denmark</td>
<td>105.0</td>
</tr>
<tr>
<td>3</td>
<td>France (metropolitan)</td>
<td>104.5</td>
</tr>
<tr>
<td>4</td>
<td>The Netherlands</td>
<td>99.0</td>
</tr>
<tr>
<td>5</td>
<td>Bahamas</td>
<td>98.9</td>
</tr>
<tr>
<td>6</td>
<td>Iceland</td>
<td>96.3</td>
</tr>
<tr>
<td>7</td>
<td>United Kingdom</td>
<td>95.0</td>
</tr>
<tr>
<td>8</td>
<td>Barbados</td>
<td>94.7</td>
</tr>
<tr>
<td>9</td>
<td>United States of America</td>
<td>92.9</td>
</tr>
<tr>
<td>10</td>
<td>Ireland</td>
<td>92.3</td>
</tr>
<tr>
<td>11</td>
<td>French Polynesia</td>
<td>92.2</td>
</tr>
<tr>
<td>12</td>
<td>Germany</td>
<td>91.6</td>
</tr>
<tr>
<td>13</td>
<td>Italy</td>
<td>91.3</td>
</tr>
<tr>
<td>14</td>
<td>Finland</td>
<td>89.4</td>
</tr>
<tr>
<td>15</td>
<td>Luxembourg</td>
<td>89.1</td>
</tr>
<tr>
<td>16</td>
<td>New Caledonia</td>
<td>87.6</td>
</tr>
<tr>
<td>17</td>
<td>Australia</td>
<td>86.0</td>
</tr>
<tr>
<td>18</td>
<td>Malta</td>
<td>85.9</td>
</tr>
<tr>
<td>19</td>
<td>New Zealand</td>
<td>85.0</td>
</tr>
</tbody>
</table>

After adjusting for differences in age distribution between the populations, **Belgian women have the highest risk of breast cancer**, followed by Denmark and France.
Breast cancer mortality: still highest in absolute numbers

Belgium has highest five year survival, followed by Denmark and France
Population-based screening since 2001

- Program Flemish government and CvKO:
  - Screening mammograms
  - 50-69 years
  - Information
  - Accessibility
  - Quality
    - Second reader
    - Radiologist
    - Infrastructure

- Increased awareness

- Not sufficient for women with symptoms or strongly increased risk profile
Breast cancer incidence remains high 70+ age
Decreasing mortality, but not for 70+
Benefits of screening

• **Mortality reduction** after 13 years (meta-analyses of clinical trials)
  – UK Independent Panel: RR = 0.80 [95% CI, 0.73-0.89]
  – Canadian Task Force: RR = 0.82 [95% CI, 0.74-0.94]
  – Cochrane: RR = 0.81 [95% CI, 0.74-0.87])

• **Uncertainty about the magnitude of mortality reduction**
  – women 40 to 49 years
  – annual screening compared with biennial screening

• **Clinical breast examination (CBE)** adds false positive biopsy rates (55 per extra breast cancer detected), but no effect on mortality

• At the moment, communication uses **relative risk**
• **This says nothing about absolute benefit**
• Harms and benefits of screening are poorly understood
• Strive to communicate in **absolute** numbers
• New communication tools being developed
Morbidity of screening

- **Overdiagnosis** rates in randomized trials: 11% to 22%
  - Consequences: anxiety, distress, and breast cancer-specific worry which are in fact needless
  - Needless morbidity
  - Uncertainty about the magnitude of overdiagnosis; contribution of DCIS

- **Pain** during mammography (1% to 77%)
  - Best approach: women can express fear of pain and mark when she wants to stop. This leads to higher tolerance, less pain and more successful exams

- **Models** estimate 2 to 11 screening-related deaths from radiation-induced cancer per 100,000 women using digital mammography, depending on age and screening interval

Factors from previous screening that influence drop-out from breast screening:

- False positive result (OR=5.0, 95% CI 3.6–6.8)
- Excessive waiting times at radiologist (OR=2.1, 95% CI 1.2–3.7)
- Difficulties in reaching radiologist (OR=2.5, 95% CI 1.4–4.4)

Pain was not found to be correlated to drop-out
False-positive recall → women subsequently at increased risk of breast cancer

**BUT**, 22% of these excess cancers are in fact cancers that were missed at the diagnostic assessment that followed the baseline screening (seen at screen)

The Hazard Rates dropped to 1.69 (95% CI 1.52 - 1.87) when these cancers were excluded.
Avoiding false-positives:

1) EU limits for recall rates

2) Teaching files
   Link made with cancer registry → provide feedback **for each screening**
   - interval cancer
   - false-positive
Controversy mammographic screening

• Negative
  – Benefits are emphasized & overdiagnosis minimized
  – Iatrogenic morbidities associated with false positives and overdiagnosis

• Positive
  – Earlier diagnosis
    • Less morbid treatments sometimes possible
  – Impact on breast cancer mortality
Cervical cancer

Carcinoma is situ

Etiology: HPV infection
Cervical cancer

• Prevention: **HPV vaccination** will reduce incidence by half

• **PAP-smear q 3 years 25-64 years**
  – Alternative methods low-income areas

• **High impact:** Decreases cervical cancer mortality by > 90%

High impact of cervical cancer screening on mortality


<table>
<thead>
<tr>
<th>Age group at diagnosis (years)</th>
<th>In the absence of screening</th>
<th>For regular screening</th>
<th>Age group at death (years)</th>
<th>Observed deaths (average 2011–2014)</th>
<th>Estimated deaths in the absence of screening</th>
<th>Estimated deaths with regular screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–34</td>
<td>1.96 (1.66–2.31)</td>
<td>0.68 (0.61–0.76)</td>
<td>25–39</td>
<td>103</td>
<td>202</td>
<td>70</td>
</tr>
<tr>
<td>35–49</td>
<td>4.13 (3.59–4.75)</td>
<td>0.42 (0.38–0.47)</td>
<td>40–54</td>
<td>175</td>
<td>721</td>
<td>73</td>
</tr>
<tr>
<td>50–64</td>
<td>5.30 (4.36–6.44)</td>
<td>0.35 (0.33–0.37)</td>
<td>55–69</td>
<td>199</td>
<td>1054</td>
<td>70</td>
</tr>
<tr>
<td>65–79</td>
<td>2.51 (2.18–2.90)</td>
<td>0.61 (0.58–0.65)</td>
<td>70–84</td>
<td>216</td>
<td>542</td>
<td>132</td>
</tr>
<tr>
<td>25–79</td>
<td>3.64 (3.29–4.03)</td>
<td>0.50 (0.48–0.52)</td>
<td>25–84</td>
<td>692</td>
<td>2519</td>
<td>345</td>
</tr>
<tr>
<td>All ages</td>
<td>3.30 (2.92–3.72)</td>
<td>0.56 (0.55–0.58)</td>
<td>All ages</td>
<td>796</td>
<td>2623</td>
<td>449</td>
</tr>
</tbody>
</table>
Cervical cancer: a disease of the developing world

http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp
Cervical cancer screening in low-income areas

VIA: visual inspection with acetic acid


Cervical cancer screening in low-income areas

VIA: visual inspection with acetic acid

| Table 7 | Sensitivity, specificity, positive predictive value, negative predictive value of Pap test, VIA and colposcopy. |
|-----------------|-------------------------------------------------|-------------------------------------------------|
| Result           | Pap test (%) | VIA (%) | Colposcopy (%) |
| Sensitivity      | 50.1         | 90      | 77               |
| Specificity      | 93.1         | 37      | 70               |
| + Ve predictive value | 89.3     | 52      | 68               |
| − Ve predictive value | 65.6     | 81      | 75               |

H.S. Saleh, Can visual inspection with acetic acid be used as an alternative to Pap smear in screening cervical cancer?
Middle East Fertility Society Journal 19 (2014) 187-191
Colon cancer
9400 new cases each year (BE), mortality 35%

Globocan, IARC
Colon cancer screening

A long route from premalignant lesions towards invasive malignancy

100% prevention

Early diagnosis

> 95% cure rate

Better prognosis, less morbidity
Colon cancer: age-related

Totaal in 2012: man 3048, Vrouw 2390
Screening test: fecal (occult) blood

- Immunohistochemical Hb test
- More specific than guac (vegetables, meat, vitamin C)
- More specific for lower digestive blood
Colon cancer screening

• Premalignant lesions removal or earlier diagnosis of cancer

• Most recently implemented (2013) in Flanders
  – 56-74 years; q 2 years invitation
  – Envelop contains iFOBT + return instruction
  – Analyzed in central lab, results sent by post (subject & GP)
  – CRC patients + recent colonoscopy are excluded from mailing list through link with cancer registry

• Screening could prevent > 750 colon cancer deaths each year and even more with continued repetitive efforts

• Not fit for familial risk or symptomatic individuals
<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>EU-norm</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total target group</strong></td>
<td>1.412.122</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respons rate</strong></td>
<td>51,4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>49,5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>53,3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total coverage</strong></td>
<td>63,4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive iFOBT</strong></td>
<td>7,5%</td>
<td>4,4% - 11,1%</td>
<td>20.478</td>
</tr>
<tr>
<td>Men</td>
<td>9,3%</td>
<td></td>
<td>12.210</td>
</tr>
<tr>
<td>Women</td>
<td>5,8%</td>
<td></td>
<td>8.268</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>EU-norm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-situ Cancer DR</strong> (per 1000 screens)</td>
<td>5,1‰</td>
<td>1,8 – 9,5‰</td>
<td>1.430</td>
</tr>
<tr>
<td><strong>Invasive Cancer DR</strong> (per 1000 screens)</td>
<td>5,2‰</td>
<td>1,8 – 9,5‰</td>
<td>1.450</td>
</tr>
<tr>
<td><strong>Adenoma DR</strong> (per 1000 screens)</td>
<td>32,6‰</td>
<td>13,3 – 22,3‰</td>
<td>9.151</td>
</tr>
<tr>
<td>Diagnostic assessment after positive iFOBT</td>
<td>2014</td>
<td>EU-norm</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>None within 12 months</td>
<td>12,5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complete</strong> diagnostic assessment (includes colonoscopy)</td>
<td>82%</td>
<td>[60% - 93,1%]</td>
<td></td>
</tr>
<tr>
<td><strong>Incomplete</strong> Diagnostic assessment</td>
<td>5,5%</td>
<td>(2° iFOBT: 4,1%)</td>
<td></td>
</tr>
<tr>
<td>- repeat iFOBT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- imaging only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ...</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time between positive iFOBT &amp; colonoscopy</th>
<th>2014</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 33 days</td>
<td>25%</td>
<td>95% (!)</td>
</tr>
<tr>
<td>&lt; 48 days</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>&lt; 96 days</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>
Geographical difference in coverage
2015

Total coverage | 63.4%
Difference in response: gender & province

Bron: Centrum voor Kankeropsporing vzw, Stichting Kankerregister

<table>
<thead>
<tr>
<th>Wijzig</th>
<th>Responsgraad 2015 - Provincies</th>
<th>DDK</th>
<th>DDK mannen</th>
<th>DDK vrouwen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antwerpen</td>
<td>Orange</td>
<td>52,7</td>
<td>50,3</td>
<td>55,0</td>
</tr>
<tr>
<td>Limburg</td>
<td>Red</td>
<td>57,7</td>
<td>55,7</td>
<td>59,7</td>
</tr>
<tr>
<td>Oost-Vlaanderen</td>
<td>Blue</td>
<td>51,7</td>
<td>49,8</td>
<td>53,5</td>
</tr>
<tr>
<td>Vlaams-Brabant</td>
<td>Orange</td>
<td>45,1</td>
<td>43,3</td>
<td>46,9</td>
</tr>
<tr>
<td>West-Vlaanderen</td>
<td>Blue</td>
<td>50,2</td>
<td>48,6</td>
<td>51,8</td>
</tr>
</tbody>
</table>
High risk groups

First degree relatives of individuals with CRC or polyps > should have colonoscopy
Individuals with genetic risks

• In all cancer types 5-10% genetic

• Highly selectable population with potentially high impact prevention/screening

• Most frequent: colon and breast cancer

• Applicable to other cancer types
Familial breast cancer

- Genetic risk in ~25%

- 5%-10% : 4 or more breast/ovarian cancer
  - = high risk
    - Half germline mutation in BRCA1/2

- 15-20% weaker familial context
  - = low to moderate risk
Genes routinely tested

- BRCA1/2
- CHEK2
- PALB2
- BARD1*

*Only in UZ Brussels
High risk, high mortality
High cancer risks

Breast

Ovarian

BRCA2: Prostata, pancreas, colon,...
Multiplicom: breast and colon cancer genes

BRCA1/2
CDH1
PTEN
STK11
TP53
MLH1
MSH2
MSH6
PMS2
EPCAM
MUTYH
ATM
BLM
CHEK2
NBN
BRIP1
FAM175A
MEN1
MRE11A
PALB2
RAD50
RAD51C
RAD51D
XRCC2
BARD1*

Since april 2016

Identification of cancer predisposing germline mutations is highly actionable
Preventive options for high risk

1. Preventive surgery
   *100 % effective*
   
   **DIEP flap: 3% residual risk**

2. Screening
   *Efficient, but less effective*
   
   *MRI is most important*

3. Reproductive options

4. Avoidance of DNA damage
   
   **Mammography**

DIEP flap method leads to satisfactory cosmetic results
Diep flap method
Therapeutic implications

• New breast cancer diagnosis and mutation diagnosis
  – Concommitant oncological and immediate reconstructive surgery possible

• Medical treatment
  – Platinum sensitivity
  – PARP inhibitors
No family history, no test
Young proband, 19 years old
Current testing model is not very preventive
Universal access to BRCA1/2 testing and (and other high risk genes)

Because of high actionability

Cost: 7,5 M €
Savings > 30 M € and avoidance of a lot of suffering

Yearly preventive effect:
• 500 breast cancers could be prevented
• 250 ovarian cancers could be prevented
Arguments for universal access to predictive genetic testing in the first place BRCA1/2 testing

1. Often lethal if no early diagnosis
2. Even if mutation found in family: defective dissemination to relevant family members
3. Grand majority (90%) of BRCA1/2 diagnosis made after already diagnosis breast/ovarian cancer in individual/family > test fails in prevention
4. Familial anamnesis is highly defective
5. Paternity issues (3%)
6. Important preventive measures including procreation
   – Waves a lot of cost and suffering
7. Therapeutic implications
8. Right to self-determination
Genetic risk colorectal cancer

- Sporadic Cases: 99.8%
- Cases with Familial Risk: 10-30%
- Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer): 5%
- Hamartomatous Polyposis Syndromes: <0.1%
- Familial Adenomatous Polyposis: 0.2%
### Hereditary colon cancer syndromes

<table>
<thead>
<tr>
<th>Syndroom</th>
<th>Genen</th>
<th>Kenmerken</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPCC= Lynch</td>
<td>MSH2, MLH1, MSH6, PMS2</td>
<td>Meest: CRC, meestal rechtszijdig en endometriumcarcinoom</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minder vaak: maag, overium, blaas, urinewegen, nier, galblaas en hersenen</td>
</tr>
<tr>
<td>Familiale adenomateuze polypose (FAP)</td>
<td>APC</td>
<td>Talrijke poliepen (&gt; 100) over hele colon vanaf tienerjaren; mogelijk ook hoog-digestief en duodenaal; extracolon verschijnselen mogelijk</td>
</tr>
<tr>
<td>Geattenueerde FAP</td>
<td>APC</td>
<td>Minder poliepen (&lt; 100, vaak rechtszijdig); Ook hoog digestief mogelijk</td>
</tr>
<tr>
<td>MYH polyposes</td>
<td>MYH recessief</td>
<td>Zoals FAP of geattenueerde APC; &gt; 10 poliepen, vaak rechtszijdig, ook hoog digestief</td>
</tr>
</tbody>
</table>
Hereditary colon cancer syndromes: risks
HNPCC: cause

- Mutations in DNA mismatch repair genes (MMR)
- Rare mutations in other genes: axin2, tgfbr2, pold/e

Mensenkamp AR et al. Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch-repair deficiency in Lynch syndrome-like tumors. Gastroenterology 2014; 146:643–6 e8
Risks Lynch

- Colorectal Cancer: 82% (41 X Greater Risk) vs. 2% (General Population)
- Endometrial Cancer: 71% (47 X Greater Risk) vs. 1.5% (General Population)
- Stomach Cancer: 13% vs. <1% (General Population)
- Ovarian Cancer: 12% vs. 1% (General Population)

Lynch Syndrome vs. General Population
HNPCC: effective prevention

• **Coloscopie q 1-2 jaar** vanaf 20-25
  – Zeer efficiënt
  – Mag later vanaf 30 – 35 jaar voor MSH6

• **Vaginale ultrasono** q 1-2 jaar vanaf 30 jaar + **CA125**
  – Relatief aangezien meestal stadium I

• **Urine cytologie** (als UTca in familie of MSH2 mutatie)
  – Aanbevolen, maar weinig efficiënt of specifiek
  – Vanaf 30 jaar
  – Risico: 0,2-20%

• Als te frequent ca of sterk dysplastische poliepen -> **R colectomie**

• **Low-dose aspirine**

  + hysterectomie en adnexectomie
  Na vervolledigen familie > 40
Proposal

• **Universal testing for all new CRC**
  – 1/35 CRC patient has Lynch
  – MSI

• **85% sensitivity and specificity 90%**
  – Tiwari/Lynch QJM 2015

• **Strategy**
  – All colorectal cancer
    • MSI (PCR)
    • > 90% LS zijn MSI-H
    • IHC for HNPCC genes
  – Sequencing MMR genes in all CRC > 100% sensitivity
    • +MSI

• **Offer possibility of gene panel testing to all individuals**
Breast and colon cancer genes

BRCA1/2
CDH1
PTEN
STK11
TP53
MLH1
MSH2
MSH6
PMS2
EPCAM
MUTYH
ATM
BLM
CHEK2
NBN
BRIP1
FAM175A
MEN1
MRE11A
PALB2
RAD50
RAD51C
RAD51D
XRCC2
BARD1
Red meat hysteria in perspective

![Bar chart showing data for red meat consumption in colon and lung cancer risk.]

- Series 1
- Series 2

- Rood vlees (Red meat)
- Sigaret (Cigarette)
- Hoogpenetrante genen (High-penetrance genes)

Colonic and lung cancer risks are compared across different series.
Familial risk without gene identified

- 10-15% of CRC pts have first degree relative with CRC
- 53% of CRC pts have first degree relative with cancer

*Screen all first-degree relatives with complete colonoscopy*
Lung cancer screening

- One large randomized trial reported that screening persons aged 55 to 74 years who have cigarette smoking histories of 30 or more pack-years and who, if they are former smokers, have quit within the last 15 years reduces lung cancer mortality by 20% (95% confidence interval [CI], 6.8–26.7; \(P = .004\)) and all-cause mortality by 6.7% (95% CI, 1.2–13.6; \(P = .02\)).
  - Participants were invited to undergo three screenings (T0, T1, and T2) at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. Participants

- **Magnitude of Effect:** 16% relative reduction in lung cancer–specific mortality and all-cause mortality by 6%.

- **Harms**
  - 96% of all positive low-dose helical computed tomography screening exams do not result in a lung cancer diagnosis.
  - False-positive exams may result in unnecessary invasive diagnostic procedures.
  - Average false-positive rate per screening round was 23.3%.
  - A total of 0.06% of all false-positive screening results led to a major complication after an invasive procedure performed as diagnostic follow-up to the positive screening result.
  - Over three screening rounds, 1.8% of participants who did not have lung cancer had an invasive procedure following a positive screening result.

Prostate cancer screening

• ? Benefit vs harm
  – Causes: low mortality rate and morbidity of interventions

• Yes
  – First degree family history
  – Genetic predisposition
    • BRCA2, ...
Future developments

• Screening through circulating tumor DNA (ctDNA or cfDNA)

• Panel of commonly mutated genes (KRAS, p53, PIK3CA,...)

• Sensitivity in early diagnosis, predictive value, survival impact etc remain to be established

• Early lung cancer: 50% sensitivity

• Could be applied population wide pending validation
Conclusion

• Screening is effective, most in high risk groups
• Newer methods that could be applied in general population will become available
  – cfDNA
• Prevention is most effective if etiology is clear
  – Smoking cessation
  – HPV vaccination
  – HB vaccination
  – Life style modification
  – ....
Backup
Early diagnosis (screening)

- **Clinical**
  - Monthly breast self examination ("breast awareness") from age 18
  - CBE x 2/ year

- **Breast imaging from age 25**
  - MRI, but with circular gadolinium
  - Safe if proper hydration and renal function
  - Mammography from 40-50yrs or if discrepancies

- **MRI is key exam**
  - Low sensitivity of mammography
  - BRCA-associated cancer often benign looking
  - **Cancers detected are small and N0**
  - *Problem: many false positives*

- **In BRCA1 mutation carriers screening is an unsafe method**
Preventive surgery

• Complete mastectomy is 100 % effective

• Diep-flap is very efficiënt and has made preventive surgery much more effective
  – 3% residual risk
  – No additional imaging needed

• Discussion of screening versus preventive surgery?
  – Respecting autonomy, supported decision
  – Highly influenced by family history
  – Encouraged in young BRCA1 mutation carriers
Total preventive mastectomy is 100% effective, but traumatizing.

The younger, the higher the impact.

Bilateral salpingo-oöophorectomie (BSO)

- With tuba
- After completion of desired family
- Can be done concomitantly with mastectomy
- Low dose hormone substitution until age 50
  - Combination preps such as Femoston (1/10, 2/10, conti, low)
  - In combination with Mirena spiral (of na hysterectomie) transdermal Oestrogel
Reproductive options

• Male and female carriers

• BRCA1/2 or other moderate to high risk genes

• Prenatal diagnose
  – Psychologically less acceptable

• Preimplantation Genomics Diagnosis (PGD) and IVF
  – Preferred
  – BRCA-negative embryo’s can be implanted
Information dissemination is highly deficient.
Informatiedoorstroming is deficiënt

BRCA1 en CHEK2
Information dissemination is highly deficient
Interventional counseling in families is efficiënt and safe

Diagnostische Strategie voor HNPCC

Traditionele strategie

Criteria
1. Amsterdam I/II criteria
2. Revised Bethesda Guidelines
3. Gekende mutatie in de familie
4. Persoonlijke voorgeschiedenis endometrium carcinoom < 50 jaar

Universele testing

Colorectale kanker

MSI testing
PCR
Normal

MSI-high

IHC testing MMR protein expressie

MLH1 verlies (often with PMS2)

Verlies andere MMR proteins

Presence of BRAF mutation (or MLH1 promoter hypermethylation)

BRAF testing (of promoter hypermethylation testing)

Afwezigheidf BRAF mutatie (of MLH1 promoter hypermethylation)

Germline testing

Tiwari/Lynch QJM 2015

Geen verdere testing of verder genetisch onderzoek

Nee
Ja
Effective prevention

• **Volledige colonoscopie en bovenste digestieve tractus**
  – Detecteren dysplasie

• **Totale proctocolectomie einde puberteit < 20 jaar**
  – Ileo-anale anastomose met ileale pouch
  – Dietist, stoma nurse, psycholoog, genetische counseling, sociale verplegenden

• **Ileo-rectale anastomose bij AFAP**
  – Levenslange opvolging overblijvend rectum om de 6 maand
  – Minder sexuele dysfunctie

• **Endoscopie om de 1 à 2 jaar vanaf 10-12 jaar tot 50 jaar**
  – Als geen colectomie
  – Eerste graadsverwanten die geen testing hebben ondergaan
  – later (18-20) als aFAP

• **Als geen mutatie (en ook geen Lynch)**
  – intensieve follow-up en coloscopie bij alle eerstegraadsverwanten
ctDNA

• To date, two main mechanisms for releasing ctDNA have been postulated: “passive” and “active”.

• It is important to consider that ctDNA may represent a small proportion of the total cfDNA, at levels corresponding to one genome equivalent in 5 mL of plasma (0.01% allele fraction), and thus it may be undetectable with routine sampling.

• Apart from this, ctDNA levels can vary according to tumor burden and stage, anatomical proximity to vasculature, and biological features like apoptotic rate and metastatic potential.
ctDNA
Applications

Future developments

Sensitivity in early diagnosis, predictive value, survival impact etc remain to be established

Could be applied population wide pending validation
## Risks Lynch

<table>
<thead>
<tr>
<th>Type Kanker</th>
<th>Risico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectale kanker</td>
<td>30-80%</td>
</tr>
<tr>
<td>Endometriumkanker</td>
<td>25-70%</td>
</tr>
<tr>
<td>Eierstokkanker</td>
<td>3-13%</td>
</tr>
<tr>
<td>Maagkanker</td>
<td>2-13%</td>
</tr>
<tr>
<td>Urinewegenkanker</td>
<td>1-12%</td>
</tr>
<tr>
<td>Dunne darmkanker</td>
<td>4-7%</td>
</tr>
<tr>
<td>Hersentumor</td>
<td>1-4%</td>
</tr>
<tr>
<td>Galwegenkanker</td>
<td>2%</td>
</tr>
</tbody>
</table>