LCA Breast Pathway 3rd Clinical Forum
High Risk Breast Cancer
24th September 2013
Welcome and Introduction

Dr Will Teh, Chair - LCA Breast Pathway Group
Update

• Metrics
• Implementation of treatment summaries
• Roll-out of Risk Stratified Pathways and Holistic Needs Assessment
• Self assessment of Best Practice Commissioning Pathways
• Guideline Publication
• Audits (ER/PR baseline and tumour bed localisation for radiotherapy boost)
• NPES
• Future clinical forum (December) – Personalised Adjuvant Systemic Treatment and Chemotherapy Closer To Home
High Risk Breast Screening
Introduction
High Risk Breast Screening

• Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary, and tertiary care (NICE Clinical Guideline CG41: partial update of CG14) 2006

• Cancer Reform Strategy 2007 – Screening to be undertaken by NHSBSP

• Protocols for the surveillance of women at higher risk of developing breast cancer. NHSBSP Publication No 74, 2013.

• Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (NICE Clinical Guideline CG164) 2013
NICE CG164 (2013) – Key Priorities for Implementation

- **Family history and carrier probability calculation method** with demonstrated acceptable performance to determine referral to a specialist genetic clinic. (BOADICEA, Manchester scoring system).
- **Individually tailored information and support**
- **Carrier probability at which genetic testing should be offered** (relative with a personal history of breast and/or ovarian cancer if that relative has a combined BRCA1 and BRCA2 mutation carrier probability of 10% or more/a person with no personal history of breast or ovarian cancer if their combined BRCA1 and BRCA2 mutation carrier probability is 10% or more and an affected relative is unavailable for testing).
NICE CG164 (2013) – Key Priorities for Implementation

• **Chemoprevention for women with no personal history of breast cancer.** Offer tamoxifen/raloxifene for 5 years to postmenopausal women with a uterus and at high risk of breast cancer unless past history/increased risk of thromboembolic disease or endometrial cancer.

• **Risk-reducing mastectomy for women with no personal history of breast cancer.** All women considering bilateral risk-reducing mastectomy should be able to discuss breast reconstruction options (immediate and delayed) with a member of a surgical team with specialist oncoplastic or breast reconstructive skills.
### 3. Surveillance protocols

<table>
<thead>
<tr>
<th>Ref</th>
<th>Risk</th>
<th>Ages</th>
<th>Surveillance Protocol</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 1   | a) *BRCA1* or 
    b) *BRCA2* carrier or 
    c) Not tested, equivalent high risk | 20-29 | n/a                           | n/a       | Review MRI annually on basis of background density                  |
|     |                               | 30-39 | MRI                           | Annual    |                                                                      |
|     |                               | 40-49 | MRI + Mammography             | Annual    |                                                                      |
|     |                               | 50+   | Mammography + MRI             | Annual    |                                                                      |
| 2   | TP53 (Li-Fraumeni)            | 20-29 | MRI                           | Annual    | Review MRI annually on basis of background density                  |
|     |                               | 30-39 | MRI                           | Annual    |                                                                      |
|     |                               | 40-49 | MRI + Mammography             | Annual    |                                                                      |
|     |                               | 50+   | Mammography + MRI             | Annual    |                                                                      |
| 3a  | A-T homozygotes               | 25+   | MRI                           | Annual    | No mammography                                                       |
| 3b  | A-T heterozygotes             | 40-49 | Mammography                   | 18 monthly| Routine screening from 50                                          |
|     |                               | 50+   | Mammography                   | Routine screening (3 yearly) |                                                                      |
| 4   | Supradiaphragmatic radiotherapy- 
    irradiated below age 30. | 30-39 | MRI                           | Annual    | Surveillance commences at 30, or 8 years after first irradiation, whichever is the later. Review MRI annually on basis of background density. |
<p>|     |                               | 40-49 | MRI + Mammography             | Annual    |                                                                      |
|     |                               | 50+   | Mammography + MRI             | Annual    |                                                                      |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Moderate risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td></td>
<td>Group 1 Moderate risk of breast cancer(^{50})</td>
<td>Group 2 High risk of breast cancer(^{51}) (with a 30% or lower probability of a BRCA or TP53 mutation)</td>
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<tr>
<td></td>
<td>Group 3 Untested but greater than 30% BRCA carrier probability(^{52})</td>
<td>Group 4 Known BRCA1 or BRCA2 mutation</td>
</tr>
<tr>
<td></td>
<td>Group 5 Untested but greater than 30% TP53 carrier probability(^{53})</td>
<td>Group 6 Known TP53 mutation</td>
</tr>
<tr>
<td></td>
<td>Group 6 Known TP53 mutation</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>Do not offer mammography</td>
<td>Do not offer mammography</td>
</tr>
<tr>
<td></td>
<td>Do not offer MRI</td>
<td>Do not offer MRI</td>
</tr>
<tr>
<td>30-39</td>
<td>Do not offer mammography</td>
<td>Consider annual mammography</td>
</tr>
<tr>
<td></td>
<td>Do not offer MRI</td>
<td>Annual MRI and consider annual mammography</td>
</tr>
<tr>
<td>40-49</td>
<td>Annual mammography</td>
<td>Annual mammography</td>
</tr>
<tr>
<td></td>
<td>Do not offer MRI</td>
<td>Do not offer mammography</td>
</tr>
<tr>
<td>50-59</td>
<td>Consider annual mammography</td>
<td>Annual mammography</td>
</tr>
<tr>
<td></td>
<td>Do not offer MRI</td>
<td>Do not offer mammography</td>
</tr>
<tr>
<td>60-69</td>
<td>Mammography as part of the population screening programme</td>
<td>Mammography as part of the population screening programme</td>
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<tr>
<td></td>
<td>Do not offer MRI</td>
<td>Do not offer MRI unless dense breast pattern</td>
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<tr>
<td>70+</td>
<td>Mammography as part of the population screening programme</td>
<td>Mammography as part of the population screening programme</td>
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<tr>
<td></td>
<td>Do not offer MRI</td>
<td>Do not offer MRI unless dense breast pattern</td>
</tr>
</tbody>
</table>
Breast Cancer Genetic Testing – Problems and solutions

Prof Nazneen Rahman
Breast Cancer Genetic Testing—problems and solutions

Dr Helen Hanson
Professor Nazneen Rahman

Cancer Genetics Unit
Royal Marsden Hospital
Two types of mutation

- Germline
- Somatic
Two types of genetic test

• **Diagnostic test**
  – Full screen of gene, normally undertaken in individual affected with condition e.g. cancer

• **Predictive test**
  – Targeted test for specific mutation identified in another family member, normally undertaken in individual unaffected with condition
**BRCA1 and BRCA2**

- Explain <5% of breast cancer cases overall.
- Explain ~16% familial risk.
- Present in ~1/900 UK general population.

- Gene carriers
  - Approximately 80% lifetime risk breast cancer
  - Up to 50% lifetime risk ovarian cancer
Clinical utility of BRCA1/BRCA2

• Provides clinically useful information about why and how an individual got cancer.
• Provides information to improve management of second cancer risk.
• Provides information to optimise treatment.
• Provides information of potential impact to relatives.
• Identifies people at-risk of cancer before they get the disease – potential for cancer prevention.
Current model of testing

• Undertake diagnostic test in a family member affected with cancer

• If mutation identified predictive genetic test undertaken in unaffected family members
Why test an affected individual?

breast cancer 38 yrs

BRCA2

ovarian cancer 64 yrs breast cancer 54 yrs

BRCA2

breast cancer 37 yrs

ovarian cancer 57 yrs

BRCA2
Full screen- unaffected individual

breast cancer 38 yrs

ovarian cancer 64 yrs breast cancer 54 yrs

breast cancer 37 yrs

ovarian cancer 57 yrs
breast cancer 38 yrs

breast cancer 64 yrs  breast cancer 54 yrs

breast cancer 37 yrs

ovarian cancer 57 yrs

At population risk but without knowing mother had mutation still need to manage according to family history
Eligibility for testing is currently determined by risk
How to determine risk?

• Multiple BRCA mutation risk assessment models available - BRCAPro, IBIS/Tyrer-cusick, Myriad, Manchester, BOADICEA, etc.

• Calculate risk for an individual or whole family.

• Risk largely dependant on family history.
Pan-Thames *BRCA1/2* testing criteria

• In developing current guidelines we reviewed the risk assessment models for multiple pedigrees and found considerable variation dependant on extent and consistency of input information.

• Some models not practical within clinic setting.

• We integrated the information from multiple models, literature and data sets to clinical criteria.

• Two audits –SGH/RMH then Pan-Thames
Equivalent to 10% threshold

A
Woman with breast cancer who

1) has bilateral BC and both cancers diagnosed < 50 yrs
2) has triple negative BC diagnosed < 50 yrs
3) has OC
4) has bilateral BC and a relative with BC < 60 yrs
5) has a relative with BC and both diagnosed < 45 yrs
6) has relatives with cancer and a Manchester Score ≥15

B
Woman with ovarian cancer who

1) has BC
2) has a relative with OC or MBC
3) has relatives with cancer and a Manchester Score ≥15

C
Male with breast cancer who

1) has a relative with OC or MBC
2) has relatives with cancer and a Manchester Score ≥15
<table>
<thead>
<tr>
<th>Cancer, age at diagnosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer, &lt;30</td>
<td>11</td>
</tr>
<tr>
<td>Breast Cancer, 30-39</td>
<td>8</td>
</tr>
<tr>
<td>Breast Cancer, 40-49</td>
<td>6</td>
</tr>
<tr>
<td>Breast Cancer, 50-59</td>
<td>4</td>
</tr>
<tr>
<td>Breast Cancer, &gt; 59</td>
<td>2</td>
</tr>
<tr>
<td>Breast Cancer, &lt;60</td>
<td>13</td>
</tr>
<tr>
<td>Breast Cancer, &gt; 59</td>
<td>10</td>
</tr>
<tr>
<td>Ovarian Cancer, &lt;60</td>
<td>13</td>
</tr>
<tr>
<td>Ovarian Cancer, &gt;59</td>
<td>10</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Prostate Cancer, &lt;60</td>
<td>2</td>
</tr>
<tr>
<td>Prostate Cancer, &gt;59</td>
<td>1</td>
</tr>
</tbody>
</table>

- 10% risk equivalent to score of 15 or greater
- 20% risk equivalent to score of 17 or greater
What are new recommendations from CG164?
NICE CG164
Genetic testing recommendations

1. Offer *BRCA1/2* testing to women with personal history of breast and/or ovarian cancer if probability of 10% or greater of mutation detection
NICE CG164
Genetic testing recommendations

2. Offer *BRCA1/2* testing to women with **no** personal history of breast and/or ovarian cancer if probability of 10% or greater of mutation detection **and** no affected relative to test

(Full screen is undertaken in an unaffected individual – different to predictive test)
What does this mean for London centres?

• No significant change to testing offered to women with personal history of breast cancer – Pan-Thames guidelines set at 10% threshold.

• Women with epithelial ovarian cancer have 10% risk – should be eligible for testing.

• Increased number of unaffected women now eligible for testing (some London centres currently offering testing at 30% threshold)
Recommendations

1. Continue with current Pan-Thames BRCA criteria for women affected with breast cancer.
2. Test all women with non-mucinous epithelial ovarian cancer.
3. Offer testing to unaffected women at 10% risk, who have no affected relative to test.
Recommendation for full screen in an unaffected individual

- To be eligible for unaffected test
  - Manchester score for family must be 17 or greater and individual tested must have FDR with breast or ovarian cancer (20% level of risk for family -10% risk for unaffected individual)

  and

  - No affected relative available to test
Implications – RMH as example

• Increase in Genetics referrals

• Increase in number of tests (BRCA test £600-£750)
  – Patients with ovarian cancer - 300 additional tests
  – Unaffected testing harder to estimate numbers
    • Audit 2008/2009 suggests 30-50 additional tests per year, but likely underrepresentation as may not have been referred to service and all centres have seen increase in referrals
What is the bigger picture?

• Increasing number of individuals eligible for genetic testing

• Increased appetite for genetic testing
  – Media
  – Increased awareness of clinical utility

• How will Genetics services cope with increased demand?
A Wellcome Trust funded, cross-disciplinary, translational initiative to develop the assays, informatics, clinical infrastructure, education, ethics and evaluation that will allow implementation of (germline) cancer genetic testing into routine clinical care of cancer patients and their relatives.

www.mcgprogramme.com
Aspire for any cancer patient that can benefit to have access to gene testing
Strong clinical and economic rationale for greater genetic testing of cancer predisposition genes
Limitations of current clinical cancer genetics

• Highly complex referral and testing eligibility criteria.
• Clinically and molecularly a low-throughput system.
• **New sequencing technologies allow fast, cheap, large-scale, high-throughput gene testing**
• Not serving the needs of cancer patients well. Value of testing in cancer patients under-appreciated.
• Inequity at many points.
MCG Workstreams

1. Technical
2. Analytical
3. Interpretation
4. Implementation
5. Education & Engagement
6. Evaluation & Ethics

Genetic Testing
1. Technical
2. Analytical
3. Interpretation
4. Implementation
5. Education & Engagement
6. Evaluation & Ethics

Genetic Test
How can we implement large scale, routine testing?
Models for routine gene testing in cancer patients

1. All testing could be done in Genetics (current UK model)

2. Testing could be done by non-genetic clinicians e.g. Oncologists (?direct-to-consumer)

Mixed Model

- Medical testing (i.e. in cancer patients) done through routine Oncology in most patients, (with support from Genetics).
- Negative tests – valuable information and will likely not require genetic input.
- Positive tests – patient seen in genetics.
- Predictive testing (i.e. in unaffecteds) done in Genetics.
Medical genetics in people with disease vs Predictive genetics in healthy individuals
MCG implementation plan

1. Pilot BRCA testing by non-Geneticists in ovarian cancer patients (July 2013).
2. Pilot BRCA testing by non-Geneticists in breast cancer patients (Sept 2013).
3. Pilot TruSight Cancer testing alongside standard testing in Genetics in patients already eligible for testing (Jan 2014).
4. Implement clinical testing of all relevant genes in broader patient groups at Marsden (2014).
5. Roll out to more genes / centres the NHS (2014).
Gynae unit direct BRCA testing protocol

Patient with:
- Serous Ovarian Cancer <65 years

*Actions by approved clinician
1. Information sheet (MS IS1) given to patient.
2. BRCA testing discussed.
3. Consent obtained and scanned onto EPR.
4. Blood (2xEDTA) and request form sent to lab.
5. EPR notification to Genetics ‘Thank you for accepting X for BRCA testing’.

Genetics review results and issues report to clinician.

Mutation
- Clinician gives result to patient.
- *Genetic appt letter sent 3 weeks after report issued.

No Mutation
- Clinician gives result and information sheet (MS IS2) to patient.
- *Genetic appt offered if required.

More discussion required
- Refer to Genetics
Gynae unit direct BRCA testing protocol

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More discussion required

Refer to Genetics

Genetics send letter to offer patient telephone consult
How to become approved

• Have to complete training (~35 mins)
• 5 short e-learning modules (on YouTube)
  – Background to mainstreaming
  – BRCA1 and BRCA2
  – Gynae direct testing Protocol
  – Taking consent
  – Sending a sample to the lab
• Read documentation (IS1, IS2, FAQ)
• Complete checklist
• Receive certificate.
First 50 patients

• All patients offered the test has accepted it.
• No patient has been referred to Genetics for ‘extra’ discussion.
• No patient has called Genetics.
• No one with a negative result has requested a Genetics appointment.
• 7 patients with positive result (only 2 with FH).
• No detailed mutation reports requested.
Breast unit direct BRCA testing protocol

*Patient with:
- Bilat BC and both cancers diagnosed <50yrs
- Triple negative BC diagnosed <50yrs
- BC and OC at any age

*Actions by approved clinician
1. Information sheet (MS IS1) given to patient.
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Breast unit direct BRCA testing protocol

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MUTATION
Cliniclan gives result to patient.
*Genetic appt letter sent 3 weeks after report issued.

NO MUTATION
Cliniclan gives result and information sheet (MS IS2) to patient.
*Genetic appt offered if required.

*Patients that do not meet direct testing criteria may still be eligible for testing through genetics. E.g. patients with:
  • BC + relative with OC
  • Bilat BC + relative with BC
  • BC + 2 relatives with BC
Summary

• There is strong medical and economic rationale for increased cancer gene testing.
• New sequencing technologies can provide high-throughput, cost-effective testing.
• Reorganisation of existing clinical infrastructures can deliver increased testing, and maintain clinician and patient confidence.
Summary (2)

• Implement revised NICE guidance
  – 10% threshold for breast cancer patients based primarily on family history (no change)
  – Non-mucinous ovarian cancer (new recommendation)
  – Unaffected women at 10% (new recommendation)

• ICR/RMH to circulate updated protocols and rationale – can be used in discussions regarding funding

• Spearhead simplified, more cost-effective, more equitable testing pathway.
Many people are involved in the MCG consortium

Clare Turnbull (deputy chair) + Daniel Riddell (programme manager)
Shazia Mahamdallie, Elise Ruark, Helen Hanson, Angela George, Ingrid Slade, (workstream coordinators)

UK Cancer Genetics Consultation Group

WTCHG - Gerton Lunter, Chris Holmes, Andrew Rimmer, Márton Münz, Anna Fowler

Programme Committee and Advisory Board
Surveillance and risk: recommendations and evidence

Professor Stephen Duffy
Surveillance and risk: recommendations and evidence

Stephen W. Duffy
Wolfson Institute of Preventive Medicine

Barts and The London
School of Medicine and Dentistry
NICE recommendations

• Based on risk definitions and recommendations in NICE Clinical Guideline 164
• Will not deal with personal history of breast cancer
• Let us remind ourselves of the results of surveillance in the general population
RCTs of screening mammography:
Overall results in terms of breast cancer mortality

Overall RR = 0.79 (95% CI: 0.73, 0.86)
Heterogeneity p = 0.3
## RR (mortality) and RR (node positive cancer)

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (node positive)</th>
<th>RR (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP</td>
<td>0.85</td>
<td>0.78</td>
</tr>
<tr>
<td>Malmo</td>
<td>0.83</td>
<td>0.78</td>
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<tr>
<td>2-county</td>
<td>0.73</td>
<td>0.68</td>
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<tr>
<td>Edinburgh</td>
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<td>Stockholm</td>
<td>0.82</td>
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<tr>
<td>NBSS-1</td>
<td>1.20</td>
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<tr>
<td>NBSS-2</td>
<td>1.09</td>
<td>1.02</td>
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<tr>
<td>Gothenburg</td>
<td>0.80</td>
<td>0.79</td>
</tr>
<tr>
<td>UK Age</td>
<td>0.89</td>
<td>0.83</td>
</tr>
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Mortality benefit

• The UK independent review estimated that being screened for twenty years at ages 50-69 prevents one breast cancer death per 180 women screened

• Higher estimates of overdiagnosis but this tends to be less of a concern in high risk groups
Guideline 164 risk definition

<table>
<thead>
<tr>
<th>Denominator for risk</th>
<th>Near population risk</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime from age 40</td>
<td>&lt;17%</td>
<td>17-29%</td>
<td>30% +</td>
</tr>
<tr>
<td>Between ages 40 and 50</td>
<td>&lt;3%</td>
<td>3-8%</td>
<td>&gt;8%</td>
</tr>
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</table>

Recommendations also take into account mutation status and mutation probabilities
Recommendations- annual mammography

• Annual mammography for
  – Age 40-49, moderate risk
  – Age 40-59, high risk but <30% probability of BRCA/TP53
  – Age 40-49, no genetic test but 30% or more chance of BRCA
  – 40-69 with known BRCA mutation
Consider annual mammography

- 30-39 at high risk, or with various combinations of mutation status/mutation probability
- 50-59 at moderate risk
Population programme surveillance

- 50+ with >30% chance of TP53
- 60+ at high risk but <=30% chance of BRCA/TP53
- 60+ at moderate risk
- 60+ with >30% chance of BRCA
- 70+ with BRCA mutation
No mammography

• Age <30
• 30-39 moderate risk
• 30-49 with >30% chance of TP53
• Known TP53
Evidence- annual mammography

• Major source for women under age 50 with enhanced familial risk is FH01
  – Duffy et al, HTA 2013; 17 (11): 1-95
• 6710 women, 94% aged <45 at recruitment, annual mammography
• Predicted 10-year breast cancer risk 6.3% (Tyrer-Cuzick)
FH01 design and analysis

- FH01 was a single arm study, with all subjects receiving the intervention
- External comparison with no intervention made possible by:
  - Age Trial control group
  - Dutch tumour series with family history but no surveillance
  - Risk prediction programmes (e.g. Tyrer-Cuzick)
  - Strong relationship of survival in breast cancer with tumour size, node status etc.
FH01 primary result

• 165 breast cancers
• From NPI, 19 expected deaths in ten years
  – Compared to 31.9 expected from Age Trial, adjusted for different risk status (RR=0.60)
  – RR=0.55 compared to Dutch series
Other studies

- Other UK (notably Manchester) and international studies also suggest a substantial mortality reduction with mammography in women in their 40’s at moderate familial risk
- For women under age 40, ongoing FH02 study
More detailed recommendations

• In some cases, NICE had to make recommendations on limited information
• Mammography is contraindicated in known TP53 carriers
• How strong is the evidence that in women with a >30% chance of TP53
  – Mammography is permissible above age 50?
  – Contraindicated below age 50?
MRI Surveillance

- 30-49 with BRCA mutation or >30% probability of BRCA mutation
- 20-49 with TP53 mutation or >30% probability of TP53 mutation
- Consider at ages 50-69 with TP53 mutation
- NOT at ages 50-69 with BRCA or >30% chance thereof unless dense breast tissue
- NOT at ages 50-69 with >30% chance of TP53, unless dense breast tissue
Evidence

• Major sources of evidence include UK (MARIBS), Canada and Netherlands studies
  – Leach et al, Lancet 2005; 365: 1769
  – Kriege et al, NEJM 2004; 351: 427

• Various other sources, notably from US, Germany Norway and Italy
Evidence

• Guidelines reflect that in mutation carriers and those at high risk of mutation, studies have consistently observed MRI to have substantially higher sensitivity than mammography.

• The evidence is less clear for the age-specific recommendations, but they reflect that for the majority of women at any risk, fatty replacement takes place with ageing and menopause.
Other issues

• Ultrasound is generally not encouraged, however
  – No imaging tool is right for all breasts and all tumours
  – Ultrasound is not a single technological entity-automated tomosonography may well have a role, particularly in dense breasts

• X-ray tomosynthesis is on the way
Conclusions

• The guidelines are prudent and reasonable, and backed up by observational evidence where this is available

• They will necessarily evolve with technological advances

• They may change as more effective and acceptable primary preventive measures are developed
Chemoprevention of women at high risk of breast cancer

Professor Paul Pharaoh
Chemoprevention for women at high risk of breast cancer

Professor Paul Pharoah
Department of Public Health and Primary Care
University of Cambridge
## Breast cancer risk categories

<table>
<thead>
<tr>
<th></th>
<th>Near population</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime risk from age 20</td>
<td>&lt;17%</td>
<td>17-29%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Risk between ages 40 and 50</td>
<td>&lt;3%</td>
<td>3-7.9%</td>
<td>≥8%</td>
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24th September 2013 LCA Forum
Clinical question

• What is the effectiveness of chemoprevention for the reduction of the incidence of breast cancer in women with a family history of breast, ovarian or related cancer?
The evidence: benefits 1

• Breast cancer incidence
• Reduced incidence with tamoxifen compared to placebo
  – Relative risk reduction of 35 per cent (high quality)
• Raloxifene less effective than tamoxifen
  – Relative risk R vs T = 1.24 (high quality)
• Reduced incidence with exemestane compared to placebo
  – Low quality
The evidence: benefits 2

• Fractures
• Reduced incidence with tamoxifen or aromatase inhibitors compared to placebo
  – Tam relative risk reduction 32 per cent (8 – 49)
  – AI relative risk reduction 32 per cent (24 – 40)
  – High quality evidence
• Tamoxifen equivalent to raloxifene
The evidence: harms 1

- Endometrial cancer
- Tamoxifen associated with increased risk compared to placebo
  - High-quality evidence from systematic review
  - Relative risk = 2.1 (1.4 – 3.3)
- Effect of raloxifene compared to placebo uncertain
- Raloxifene associated with lower risk than tamoxifen
  - Relative risk reduction 45 per cent (16 – 54) (high quality)
- Aromatase inhibitors associated with lower risk than tamoxifen
  - Relative risk reduction 78 per cent (54 – 89) (high quality)
The evidence: harms 2

- Thrombo-embolism
- Tamoxifen and raloxifene associated with increased risk of thrombo-embolic event
  - High quality evidence from systematic review
  - Tamoxifen relative risk = 1.9 (1.4 – 2.6)
  - Raloxifene relative risk = 1.6 (1.2 – 2.2)
- Raloxifene lower risk than tamoxifen
  - relative risk = 0.75 (0.60 – 0.93)
- AI lower risk than tamoxifen
  - relative risk = 0.57 (0.46 – 0.64)
Issues

• No evidence for long term benefits/harms (>10 years)
• No reduction in overall mortality
• Evidence of adverse events also utilized data from adjuvant breast cancer therapy trials
• Limited evidence for specific aromatase inhibitors
• Tamoxifen and raloxifene do not have UK marketing authorisation for chemoprevention
• Full health economic analysis not carried out
Chemoprevention for women with no personal history of breast cancer

1.7.20 Healthcare professionals within a specialist genetic clinic should discuss and give written information on the absolute risks and benefits of all options for chemoprevention to women at high risk or moderate risk of breast cancer. Discussion and information should include the side effects of drugs, the extent of risk reduction, and the risks and benefits of alternative approaches, such risk-reducing surgery and surveillance. [new 2013]

1.7.21 Offer tamoxifen\(^7\) for 5 years to premenopausal women at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [new 2013]

1.7.22 Offer tamoxifen\(^7\) for 5 years to postmenopausal women without a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or they have a past history of endometrial cancer. [new 2013]

1.7.23 Offer either tamoxifen\(^7\) or raloxifene\(^8\) for 5 years to postmenopausal women with a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [new 2013]
1.7.24 Do not offer tamoxifen or raloxifene to women who were at high risk of breast cancer but have had a bilateral mastectomy. [new 2013]

1.7.25 Consider prescribing tamoxifen for 5 years to premenopausal women at moderate risk of developing breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [new 2013]

1.7.26 Consider prescribing tamoxifen for 5 years to postmenopausal women without a uterus and at moderate risk of developing breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or they have a past history of endometrial cancer. [new 2013]

1.7.27 Consider prescribing either tamoxifen or raloxifene for 5 years to postmenopausal women with a uterus and at moderate risk of developing breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [new 2013]

1.7.28 Do not continue treatment with tamoxifen or raloxifene beyond 5 years. [new 2013]

1.7.29 Inform women that they should stop tamoxifen at least:

- 2 months before trying to conceive
- 6 weeks before elective surgery. [new 2013]
Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Chemoprevention for women with no personal history of breast cancer

- Offer either tamoxifen\(^1\) or raloxifene\(^2\) for 5 years to postmenopausal women with a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. [new 2013]
Questions?
Chemoprevention of women with breast cancer – managing non-breast cancer outcomes

Miss Jo Marsden
CHEMOPREVENTION OF BREAST CANCER: MANAGING NON-BREAST CANCER OUTCOMES

Miss Jo Marsden
Consultant Surgeon
Kings College Hospital
Foundation Trust
London
OUTSTANDING ISSUES FOR CHEMOPREVENTION PLANNING

NICE recommends discussion about chemoprevention limitations and side effects:

• Where should this take place and who should do it?
  – Demand for specialist genetics services in UK is high
    • Usually only high risk women offered appointment for genetic counselling
    • Where should moderate risk women be counselled?

• Little practical advice about non cancer outcomes
  – Seek referral in the event of post-menopausal bleeding
  – Report symptoms of osteoporosis (this usually is a fracture!)
  – Oestrogen modulation impacts on multiple chronic health conditions

• Benefits may be outweighed by chemoprevention-associated risks in
  – BRCA1 mutation carriers (more likely to be diagnosed with ER-ve cancer)
  – Moderate risk women
Oestrogen promotes glucose and lipid homeostasis. Deficiency or resistance in tissues predisposes to the metabolic syndrome, type 2 diabetes, and obesity.
MANAGEMENT OF NON-CANCER OUTCOMES

Vasomotor symptoms and vulvo-vaginal atrophy
• Many women at increased risk who discuss chemoprevention will already have or be very likely to develop vasomotor symptoms and vulvo-vaginal atrophy as a consequence of a natural menopause
  – Vasomotor symptoms usually improve with time
  – Vulvo-vaginal atrophy gets progressively worse

Health conditions affected by oestrogen modulation
• Bone health
• Cardiovascular, VTED, glucose metabolism
• Endometrial cancer risk
• Tamoxifen activity is influenced by menopausal status
VASOMOTOR SYMPTOMS

SWAN Study: Reported Prevalence of Vasomotor Symptoms in Perimenopausal Women

Ages 40 to 55 Years

Race/Ethnicity - n
- African American – 3650
- Hispanic – 1712
- Caucasian – 5746
- Chinese – 542
- Japanese – 707

% of Women Reporting Hot Flushes/Night Sweats

n = 12,357. SWAN = Study of Women's Health Across the Nation.

Hot Flushes may continue for many years after the menopause

*Number of years women report having hot flushes as estimated by a survey of 501 untreated women who experienced hot flushes
Aged 29-82 yrs

Mean age of natural menopause was 45.5 years; mean age of surgical menopause was 43.7 years.
Kromberg F. Ann NY Acad Sci. 1990;592:52-86.
VAGINAL DRYNESS, DYSPAREUNIA AND SEXUAL DYSFUNCTION

Prevalence of Superficial Dyspareunia and Vulvovaginal Atrophy by Menopausal Age

- Superficial Dyspareunia
- Atrophy

Effect of Menopausal Transition on Parameters of Sexual Functioning

Cross-sectional Data Reported From a Longitudinal, Population-based Cohort of Australian Women, 45–55 Years of Age

- Sexual Responsivity
- Sexual Frequency
- Libido
- Vaginal Dyspareunia
- Partner Problems

Atrophy increased significantly with increase in menopausal age (P < .001).

Mean Change in SFRQ (Sexual Domain)

-0.17 *
-0.14 *
-0.20 *
0.27 *
0.15 *

n = 438; SFRQ = Shortened version of the Personal Experiences Questionnaire.
*P < 0.05 for postmenopausal compared with perimenopausal women.
STAR TRIAL TAMOXIFEN VS RALOXIFENE
SELF-REPORTED GYNAECOLOGICAL SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom/severity level</th>
<th>Tamoxifen (n = 4693)</th>
<th>Raloxifene (n = 4669)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes bothersome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>670</td>
<td>774</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Slightly / moderately</td>
<td>1712</td>
<td>1943</td>
<td></td>
</tr>
<tr>
<td>Quite a bit / extremely</td>
<td>2311</td>
<td>1952</td>
<td></td>
</tr>
<tr>
<td>Vaginal discharge bothersome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1765</td>
<td>2673</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Slightly / moderately</td>
<td>2114</td>
<td>1678</td>
<td></td>
</tr>
<tr>
<td>Quite a bit / extremely</td>
<td>614</td>
<td>328</td>
<td></td>
</tr>
<tr>
<td>Vaginal dryness bothersome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1432</td>
<td>1315</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Slightly / moderately</td>
<td>1839</td>
<td>1715</td>
<td></td>
</tr>
<tr>
<td>Quite a bit / extremely</td>
<td>1422</td>
<td>1639</td>
<td></td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3548</td>
<td>4042</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Slightly / moderately</td>
<td>899</td>
<td>543</td>
<td></td>
</tr>
<tr>
<td>Quite a bit / extremely</td>
<td>247</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

- Vaginal dryness worse with raloxifene
- Hot flushes, vaginal discharge and bleeding worse with tamoxifen

Runowicz et al Am J Obstet Gynecol 2011
MANAGEMENT OF VASOMOTOR SYMPTOMS
ALTERNATIVES TO HRT: PRESCRIPTION MEDICINES

- NICE guidance (symptomatic breast cancer patients)
  - Fluoxetine, paroxetine
    - RCTs show no better than placebo with longer-term follow-up
    - Some SSRIs attenuate tamoxifen (cytochrome P450)
  - Clonidine – ineffective and troublesome side effects

<table>
<thead>
<tr>
<th>Gabapentin</th>
<th>Pre-gabapentin</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>300mg od for 2/12</td>
<td>50mg od for 1/52</td>
<td>37.5mg bd for 3/12</td>
</tr>
<tr>
<td>300mg bd for 2/12</td>
<td>50mg bd for 2/52</td>
<td>75mg od for 3/12</td>
</tr>
<tr>
<td>300mg tds for 3/12</td>
<td>75mg bd for 3/12</td>
<td>75mg bd for 3/12</td>
</tr>
<tr>
<td>Weight gain</td>
<td>¬ Orgasm</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>¬ Appetite</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>¬ Mood</td>
<td></td>
</tr>
<tr>
<td>↓ Appetite</td>
<td>↓ Dizziness</td>
<td></td>
</tr>
<tr>
<td>↓ Concentration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Dizziness
- ↓ Appetite
**MANAGEMENT OF VASOMOTOR SYMPTOMS**

**ALTERNATIVES TO HRT**

- Limited / no evidence for effectiveness
- * some oestrogen activity

<table>
<thead>
<tr>
<th>Complementary / herbal interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil of Evening Primrose</td>
</tr>
<tr>
<td>Phyto-oestrogens*</td>
</tr>
<tr>
<td>Wild yam cream*</td>
</tr>
<tr>
<td>Chinese herbal mixture</td>
</tr>
<tr>
<td>Vitamin E</td>
</tr>
<tr>
<td>Dong Quai*</td>
</tr>
<tr>
<td>Korean ginseng*</td>
</tr>
<tr>
<td>Agnus castus (Chasteberry)*</td>
</tr>
<tr>
<td>Licorice root*</td>
</tr>
<tr>
<td>Ginko Biloba*</td>
</tr>
<tr>
<td>Black Cohosh</td>
</tr>
<tr>
<td>Acupuncture</td>
</tr>
<tr>
<td>Aromatherapy</td>
</tr>
<tr>
<td>Relaxation, massage</td>
</tr>
<tr>
<td>Homeopathy</td>
</tr>
</tbody>
</table>
VAGINAL DRYNESS

• Vaginal dryness is associated with SERMs
  – Worse with raloxifene than tamoxifen

• Use of vaginal oestrogen
  – Limited systemic absorption
  – Safe to use if taking tamoxifen?
  – ? Avoid if using raloxifene

• Non-hormonal alternatives
  – Trial of each in sequence for 2 months
    • Replens
    • Sylk
    • Astroglide
    • YES!
TAMOXIFEN ACTIVITY IS INFLUENCED BY MENOPAUSUAL STATUS

- Bone health
- Risk markers for cardiovascular disease
- Risk of diagnosis of:
  - Thrombo-embolic events
  - Cardiovascular disease
  - Stroke
  - Endometrial cancer
  - Metabolic syndrome

- Most chemoprevention trials (including meta-analyses) have failed to stratify outcomes according to menopausal status
TAMOXIFEN-INDUCES BONE LOSS IN HEALTHY PREMENOPAUSAL WOMEN

% change in lumbar spine BMD from pre-treatment value after 3 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>0.63</td>
<td>-1.86 *</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.27</td>
<td>-3.64 *</td>
</tr>
<tr>
<td>Year 3</td>
<td>-0.5</td>
<td>-3.26 *</td>
</tr>
</tbody>
</table>

% change in hip BMD from pre-treatment value after 3 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>Year 2</td>
<td>1.07</td>
<td>-0.3</td>
</tr>
<tr>
<td>Year 3</td>
<td>2.68 *</td>
<td>-1.59 *</td>
</tr>
</tbody>
</table>

*statistically significant

- Is the effect of tamoxifen reversible following cessation?

Powles et al JCO 1996
MANAGING BONE HEALTH IN PREMENOPAUSAL WOMEN

• Should high risk pre-menopausal women have screening for low BMD prior to commencing tamoxifen?

• Who is at risk?
  – Low BMD and history of low trauma 
  – BMD Z score ≤ 2.0

• What monitoring should be done if low BMD?
  – Repeat BMD after 1 to 2 years to determine if further bone loss or BMD stable

• What interventions are appropriate?
  – Weight-bearing exercise
  – Nutrition and lifestyle modifications (stop smoking, reduce excessive alcohol)
  – Anti-resorptive agents?
    • Limited data (no RCTs) on efficacy in premenopausal women with low BMD
    • Not for isolated low BMD without low trauma 
    • Consider if on-going secondary cause (e.g. tamoxifen?)
ESTIMATING FRACTURE RISK: THE FRAX TOOL

• Developed by WHO to evaluate individual fracture risk of patient (40 to 90yrs)
  – 10-year probability of hip fracture
  – 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)

• Based on clinical risk factors and BMD at the femoral neck (using T-scores)
  – ? Z-score more reliable indicator of risk in pre-menopausal women

• Relies on specialist clinical interpretation
# BREAST CANCER CHEMOPREVENTION:

## All Cardiac Events HR / RR (95% CI)
(Fatal and non-fatal MI, Arrhythmia, Angina, HT)

<table>
<thead>
<tr>
<th>Tamoxifen trials</th>
<th>All patients</th>
<th>Premenopausal (≤ 49 yrs)</th>
<th>Postmenopausal (≥ 50 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- RMH Trial</td>
<td>NS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- IBIS I</td>
<td>0.9 (0.63-1.28)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- Italian Trial</td>
<td>Arrhythmia or AF: 1.73 (1.01-2.98)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- NSABP-P1</td>
<td>1.03 (0.79-1.36)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Previous CHD: 1.39 (0.73-2.67)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>No previous CHD: 0.96 (0.63-1.46)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

| Meta-analysis ‘13 All SERMs combined | No increased or decreased risk reported for individual SERMs (i.e. tamoxifen, raloxifene, lasofoxifene, arzoxifene) but no data provided |

| Ruth Trial ’06 (Raloxifene) | No increased or decreased risk for cardiovascular events except possible benefit in women aged < 60yrs (this was post hoc analysis) |

- Null effect on cardiovascular outcomes
  - Follow-up too short?
  - Differential impact for tamoxifen if analysis according to menopausal status?
BREAST CANCER CHEMOPREVENTION:

<table>
<thead>
<tr>
<th>VTE Events HR / RR (95% CI)</th>
<th>All patients (DVT, PE, retinal thrombosis)</th>
<th>Premenopausal (≤ 49 yrs)</th>
<th>Postmenopausal (≥ 50 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMH Trial</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>IBIS I</td>
<td>2.26 (1.36-3.87)</td>
<td>1.63 (1.02-2.62)</td>
<td></td>
</tr>
<tr>
<td>Italian Trial</td>
<td>1.44 (0.91-2.30)</td>
<td>DVT: 0.76 (0.59-3.10)</td>
<td>DVT: 1.49 (0.84-2.68)</td>
</tr>
<tr>
<td>NSABP-P1</td>
<td>PE: 2.15 (1.08-4.51)</td>
<td>PE: 2.01 (0.29-22.19)</td>
<td></td>
</tr>
<tr>
<td><strong>Meta-analysis ‘2013</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All SERMs combined</td>
<td>1.73 (0.55-2.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(tamoxifen, raloxifene, lasofoxifene, arzoxifene)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Thromboembolic risk restricted to postmenopausal women?
## BREAST CANCER CHEMOPREVENTION:

### Cerebrovascular Events HR / RR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Premenopausal (≤ 49 yrs)</th>
<th>Postmenopausal (≥ 50 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- RMH Trial</td>
<td>Stroke: NS</td>
<td>Stroke: 1 (0.33-3.06)</td>
<td>Stroke: 3.11 (0.63-15.4)</td>
</tr>
<tr>
<td></td>
<td>TIA: 0.44 (0.1-1.59)</td>
<td>TIA: 1.24 (0.38-4.08)</td>
<td>TIA: 1.13 (0.39-3.36)</td>
</tr>
<tr>
<td>- IBIS I</td>
<td>Stroke: 3.11 (0.63-15.4)</td>
<td>Stroke: 1.42 (0.97-2.08)</td>
<td>Stroke: 1.47 (0.97-2.22)</td>
</tr>
<tr>
<td>- Italian Trial</td>
<td>TIA: 1.24 (0.38-4.08)</td>
<td>TIA: 0.91 (0.54-1.52)</td>
<td>TIA: 0.99 (0.56-1.76)</td>
</tr>
<tr>
<td>- NSABP-P1</td>
<td>Stroke: 1.42 (0.97-2.08)</td>
<td>Stroke: 1.13 (0.39-3.36)</td>
<td>Stroke: 1.47 (0.97-2.22)</td>
</tr>
<tr>
<td></td>
<td>TIA: 0.91 (0.54-1.52)</td>
<td>TIA: 0.57 (0.12-2.25)</td>
<td>TIA: 0.99 (0.56-1.76)</td>
</tr>
</tbody>
</table>

### Meta-analysis ‘13
All SERMs combined

No increased or decreased risk reported for individual SERMs (i.e. tamoxifen, raloxifene, lasofoxifene, arzoxifene) but data not provided in publication

### Ruth Trial ‘06
(Raloxifene)

Risk of stroke not increased but risk of dying from stroke RR 1.49 (1.0-2.24)

- Tamoxifen null effect on stroke / TIA
- Raloxifene stroke diagnosis not increased but risk of death from stroke elevated
BREAST CANCER CHEMOPREVENTION:

<table>
<thead>
<tr>
<th>Endometrial cancer events HR / RR (95% CI) / number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td><strong>Tamoxifen trials</strong></td>
</tr>
<tr>
<td>- RMH Trial</td>
</tr>
<tr>
<td>- IBIS I</td>
</tr>
<tr>
<td>- NSABP-P1</td>
</tr>
<tr>
<td><strong>Meta-analysis ’2013</strong></td>
</tr>
<tr>
<td>Tamoxifen After tamoxifen cessation</td>
</tr>
<tr>
<td>Raloxifene</td>
</tr>
</tbody>
</table>

- Risk of endometrial cancer diagnosis restricted to post-menopausal women?
- NICE recommends avoiding tamoxifen in women with a history of endometrial cancer
  - No evidence add-back oestrogen has adverse impact on survival in women with previous endometrial cancer
METABOLIC SYNDROME

Definition

**Three of the following present (AHA)**
- Elevated waist circumference (>88cm in women)
- Elevated triglycerides
- Reduced HDL cholesterol
- Elevated blood pressure (or use of anti-hypertensives)
- Elevated fasting serum glucose

**Elevated waist circumference (>80cm in women)**

At least two of the following (IDF)
- Elevated triglycerides
- Reduced HDL cholesterol
- Elevated blood pressure (or use of anti-hypertensives)
- Elevated fasting serum glucose

CVD
- Type 2 diabetes
- Non-alcoholic steatosis
- ↑risk of breast cancer and recurrence
CHEMOPREVENTION AND METABOLIC SYNDROME

- Oestrogen modulation modifies glucose metabolism
- What is the impact of SERMs?

<table>
<thead>
<tr>
<th>SERMs</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Promotes steatosis (43%)</td>
</tr>
<tr>
<td></td>
<td>Premenopausal women with BMI &gt; 25</td>
</tr>
<tr>
<td></td>
<td>- Increases insulin resistance</td>
</tr>
<tr>
<td></td>
<td>- Promotes adverse lipid profile (↑ HDL-C, TG)</td>
</tr>
<tr>
<td></td>
<td>- May increase insulin requirements if pre-existing metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>Older postmenopausal women may increase risk DM (24%)</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Inconsistent results from RCTs</td>
</tr>
<tr>
<td></td>
<td>- No adverse effect on glucose metabolism (+/- diabetes)</td>
</tr>
<tr>
<td></td>
<td>- Reduces insulin sensitivity in non diabetics</td>
</tr>
<tr>
<td></td>
<td>Effect dependent on metabolic status?</td>
</tr>
<tr>
<td></td>
<td>- Only cardiovascular benefit if obese (i.e. insulin resistant)?</td>
</tr>
</tbody>
</table>
OUTSTANDING ISSUES FOR CHEMOPREVENTION PLANNING

Uptake of chemoprevention

• Uptake of chemoprevention will depend on:
  – Individual baseline risk
  – Personal experience of breast cancer
  – Alternative risk management options
  – Perceptions / knowledge of SERM side effect and risk profile

• NICE estimates 25% uptake of chemoprevention
  – Optimistic!
  – USA data:
    • 2/1000 of the 15% of eligible women in general population take up offer of chemoprevention
  – Clinical trial data - uptake in eligible women is estimated to be < 5%
  – Women and health professionals’ unfavourable perception of risk-benefit profile
OUTSTANDING ISSUES FOR CHEMOPREVENTION PLANNING

Adherence with chemoprevention

- Risk reduction is dependent on:
  - Individual baseline risk
  - Treatment adherence

- Meta-analyses of studies evaluating tamoxifen adherence

<table>
<thead>
<tr>
<th>Treatment discontinuation</th>
<th>Tamoxifen % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 year</td>
<td>13.6 (11.4–16.2)</td>
</tr>
<tr>
<td>At 2 years</td>
<td>22.1 (18.8–25.9)</td>
</tr>
<tr>
<td>At 3 years</td>
<td>32.1 (27.5–37.2)</td>
</tr>
<tr>
<td>At 4 years</td>
<td>37.7 (32.5–43.4)</td>
</tr>
<tr>
<td>At 5 years</td>
<td>47.1 (41.1–53.5)</td>
</tr>
</tbody>
</table>

- Lack of information on modifiable determinants and feasible interventions to improve this
  - Socio-demographic
  - Treatment-related factors
  - Lower perceived benefit of treatment
  - Perception of less than optimal role in the treatment-decision making
  - Low social and/or material support.

- Emphasis on ‘good toxicity’ profile of tamoxifen and raloxifene

Murphy et al Breast Cancer Treat Res 2012; 134
Huiart et al Breast Cancer Treat Res 2013
MANAGING HEALTH IN THE CONTEXT OF CHEMOPREVENTION

Impact of chemoprevention
Baseline;
- Breast cancer risk
- Cardiovascular risk
- Metabolic syndrome
- Quality of life
- Bone health

Ideally:
- Multi-disciplinary input and co-ordination

Individualised
Risk / benefit assessment
- Who should do it?
- Who should interpret data
- Who makes final decision?
Surveillance / monitoring

Oestrogen deficiency symptoms
Cardiovascular disease
Vaginal dryness
Metabolic syndrome
Bone Health
Weight / obesity
Cancer surveillance
Psycho-logical support
Uptake and adherence

Patient centred
Who should co-ordinate?
Cancer genetics service?
Breast clinics?
Primary care?
Gynae-endocrine?
BREAST CANCER CHEMOPREVENTION

• Oestrogen modulation will impact on the pathophysiology of multiple chronic health conditions in women

• Implications for uptake and adherence if adequately counselled

• Management needs to be multi-disciplinary

• Apply same principles for chemoprevention as for survivorship planning in breast cancer patients
  – How do we plan, predict and manage competing health risks?
Pathology of High-Risk Breast Lesions

Professor Louise Jones
Table Discussions:
Preparation for panel discussion

Please use the paper on the table to submit questions
Panel Discussion on the Implementation of NICE Guidelines

Chair: Dr Rebecca Roylance
Thank you for coming today

Presentations will be on the website
www.londoncanceralliance.nhs.uk