Angelina Jolie’s high publicity bilateral mastectomy has done much to raise awareness of the risk of familial breast cancer and was closely followed by the release of these new NICE guidelines which hit the headlines with the promise of “drug treatment to offer a 50% reduction in the risk of breast cancer for high risk women”. I suspect many of us have had a number of consultations in the light of this and I hope to clarify our responsibilities in primary care as well as a summary of the evidence that led to the NICE recommendations.

### Familial breast cancers
- 49 000 women and 400 men are diagnosed with breast cancer each year.
- 1 in 5 of them will have a family history – the majority will not.
- 5% of all breast cancers are attributable to specific mutations in BRCA1, BRCA2 and TP53 genes.
- The cause of most breast cancers is not known and is likely to be a combination of environmental, lifestyle and lower level genetic susceptibilities.

### The role of primary care
NICE are not asking us to proactively establish all women’s family history of breast cancer but rather to respond to those women who present with concerns. I think our role is:
- To identify women at greater than population risk and refer them to secondary care for assessment.
- To use consultations where no increased risk is identified as an opportunity for high impact lifestyle advice – “teachable moments”.

### Definitions
Before we look at the NICE guidelines it is important to clarify some definitions which we will need to take an accurate family history:

#### Family history definitions:
- **First degree relatives:** mother, father, brother, sister, son, daughter
- **Second degree relatives:** grandmother, grandfather, aunt, uncle, niece, nephew, grandchild, half-sibling
- **Third degree relatives:** great-grandparent, great aunt/uncle, first cousin, great grandchild, great niece or great definition.

#### Definitions of breast cancer risk categories as used by NICE:
(The percentage risk is worked out by the geneticists using a computer programme)

<table>
<thead>
<tr>
<th>Lifetime risk from age 20</th>
<th>Near population risk</th>
<th>Moderate risk</th>
<th>High risk (includes BRCA1/2 and TP53 carriers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 17%</td>
<td>&gt;17% but &lt;30%</td>
<td>30% or greater</td>
</tr>
<tr>
<td>Risk between ages 40 and 50</td>
<td>Less than 3%</td>
<td>3-8%</td>
<td>&gt;8%</td>
</tr>
</tbody>
</table>
Who should be referred from primary care for further assessment by clinical genetics?

- Take a personal history of cancer and take a first and second degree family history to assess risk.
- Refer immediately anyone with a known cancer predisposing gene in the family (BRCA1, BRCA2 or TP53).
- Refer any patient who meets any of the following criteria:

<table>
<thead>
<tr>
<th>Female breast cancers:</th>
<th>Male breast cancers:</th>
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</thead>
<tbody>
<tr>
<td>One 1st degree relative diagnosed with breast cancer &lt;40y</td>
<td>One 1st degree male relative diagnosed with breast cancer at any age</td>
</tr>
<tr>
<td>Two 1st or one 1st and one 2nd degree relative diagnosed with breast cancer at any age</td>
<td></td>
</tr>
<tr>
<td>Three 1st or 2nd degree relatives diagnosed with breast cancer at any age</td>
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</table>

<table>
<thead>
<tr>
<th>Bilateral breast cancers:</th>
<th>Breast &amp; ovarian cancers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>One 1st degree relative with bilateral breast cancer, where the first cancer was diagnosed aged &lt;50y</td>
<td>One 1st or 2nd degree relative diagnosed with breast cancer AND one 1st or 2nd degree relative with ovarian cancer diagnosed at any age</td>
</tr>
</tbody>
</table>

- If none of these criteria are present, ask if there are any additional special risk factors (if present seek written advice from secondary care):
  - Presence of bilateral or male breast cancers anywhere in family history.
    - Jewish ancestry
    - Unusual cancers: sarcoma in a relative aged <45 years, gliomas or childhood adrenocortical carcinomas.
    - Complicated patterns of multiple cancers at a young age
  - Paternal history of breast cancer (two or more relatives on fathers side of the family)
  - All other patients can be managed in primary care e.g. those with one first or second degree relative diagnosed with breast cancer aged >40.

What happens after referral to clinical genetics?

Risk stratification:
- A more detailed family history will be taken, this will be used to determine whether an individual is moderate (>17 but <30% lifetime risk) or high risk (30% or greater lifetime risk).
- Counselling and information about the advantages and disadvantages of determining risk.

Consideration of genetic testing:
- An assessment of probability that an individual is a carrier of a defined risk gene using a validated computerised tool e.g. BOADICEA (this is available for all to download – see useful websites).
- Genetic testing may be offered if probability of being a carrier is ≥10% however, if possible, this will be offered to an affected relative first to establish the specific mutation.

Discussion of a surveillance plan:
- No surveillance is recommended for women aged <30.
- From 30 years, a combination of mammography and MRI screening is recommended depending on whether moderate or high risk and whether a specific genetic mutation has been identified.
- Annual mammography will be offered to women aged 40-49 at moderate risk and women aged 40-59 at high risk.
- MRI is reserved for those with confirmed or high probability of BRCA1/2 and TP53 mutations.
Risk reduction strategies for all women

- **Hormonal contraception (combined oral contraceptive pill (COCP))**
  - Up to the age of 35 women with a family history of breast cancer can take the COCP in line with standard guidance.
  - Women aged >35 with a family history should be given information that there may be a slight increased risk associated with COCP use given that absolute risk increases with age – consider alternative?
  - For women with BRCA1 mutations the slight increased risk of breast cancer with COCP use must be balanced against the lifetime protection of COCP use for ovarian cancer.
  - Women should not be prescribed the COCP purely to prevent ovarian cancer.

- **Breastfeeding**
  - Women with a family history of breast cancer should be encouraged to breast feed.
  - Having children at a younger age appears to be protective.

- **Hormone replacement therapy**
  - HRT use in women with a family history of breast cancer should be restricted to the shortest duration and lowest dose possible. Where possible, use oestrogen only HRT.
  - Risks should be discussed with women.
  - Women who experience premature menopause either naturally or artificially (due to prophylactic oophorectomy) can be offered HRT until age 50 – though I suspect many women may be reluctant to take it in this situation!

- **Alcohol**
  - Alcohol may increase the risk of breast cancer in women with a family history – a ‘safe’ level of consumption is not known.

- **Smoking**
  - All women should be advised to stop smoking.

- **Body weight and exercise**
  - Maintain a healthy BMI (20-25) as particularly post-menopausal obesity increases the risk of breast cancer.
  - Physical exercise reduces breast cancer risk.

Chemoprevention of breast cancer

NICE now recommend that certain women be offered the option of taking tamoxifen or raloxifene to reduce their risk of developing breast cancer. This is an unlicensed indication at present and should be discussed and initiated by secondary care service. This partly because other preventative treatments may be more effective and appropriate e.g. prophylactic mastectomy/oophorectomy and because there are risks as well as benefits (see below).

If prophylactic surgery is unsuitable or unacceptable, the following women may be offered chemoprophylaxis:

- Offer chemoprophylaxis to all high risk women who are not at increased risk of endometrial cancer or thromboembolism:
  - Premenopausal women – tamoxifen for 5 years
  - Postmenopausal women – tamoxifen or raloxifene for 5 years if uterus intact, tamoxifen for 5 years if no uterus.
- Consider 5 years of chemoprophylaxis for moderate risk women.
- Women should be advised to stop tamoxifen
  - 2 months before trying to conceive
  - 6 weeks before elective surgery

So if that is the NICE guidance, what is the evidence around chemoprophylaxis?

The evidence for tamoxifen and raloxifene as chemoprophylaxis

Tamoxifen and raloxifene are selective oestrogen receptor modulators (SERM’s). There potential role in the prevention of breast cancer has been an evolving story that we have covered over recent years in the handbook. The state of current evidence was well
summarised by a comprehensive meta-analysis of available RCTs (AnnIntMed 2009;151:703) which showed that:

- Tamoxifen and raloxifene reduced oestrogen receptor positive breast cancer by 7-10 cases per 1000 women per year if taken for 5 years.
- They did not reduce oestrogen receptor negative disease (as is typically seen in BRCA1).
- Tamoxifen was equally effective in pre and post-menopausal women.
- However, both drugs were associated with harms:
  - VTE risk was increased in tamoxifen users by about 4 extra cases per 1000 women over 7 years.
  - Endometrial cancer risk was increased in tamoxifen users with an extra 11 cases per 1000 women over 7 years.
  - VTE was increased in the raloxifene group but to a lesser extent.

This was then updated by a further meta-analysis which looked at all available SERM’s, published after the NICE guidelines were issued (Lancet 2013;381:1827). The vast majority of studies included were for tamoxifen and raloxifene. This meta-analysis showed that in women taking SERM’s:

- There was a 38% reduction in breast cancer incidence (HR 0.62 (CI 0.56-0.69).
- **NNT=42** – 42 women would have to be treated with a SERM for 5 years to prevent 1 breast cancer over 10 years.
- The reduction in incidence was mainly in invasive oestrogen receptor positive breast cancer and ductal carcinoma in situ – there was no impact on oestrogen receptor negative disease.
- There was an increased risk of VTE with all SERMs (OR 1.73 (CI 1.47-2.05)
- There was an increased risk of endometrial cancer with tamoxifen (HR 1.56 (CI 1.13-2.14)
- The benefits persisted beyond the first 5 years of treatment though were smaller in magnitude whilst the harms were all mainly seen during active treatment.
- There was no difference in overall mortality.

A single well designed RCT compared tamoxifen v raloxifene and demonstrated that tamoxifen was significantly better at preventing breast cancer than raloxifene but had more side effects, particularly the risk of endometrial cancer (JAMA 2006;295:2727).

NICE therefore recommend tamoxifen first line for women without a uterus and in pre-menopausal women at high risk who stand most to gain from breast cancer prevention. However in high risk post-menopausal women with a uterus a choice of raloxifene or tamoxifen is offered.

**What about aromatase inhibitors?**

This US based double blind RCT compared the incidence of breast cancer in 4500 post-menopausal women of moderate to high risk taking exemestane v placebo. Women with the BRCA mutation or previous history of breast cancer were excluded. They found that:

- Exemestane significantly reduced invasive breast cancer over 3 years (HR 0.35 (CI 0.27-0.79))
- **NNT=96** women need to take exemestane for 3 years to prevent 1 breast cancer.
There was no difference in other cancers, fractures, CV events or mortality between the two groups.
Discontinuation rates were 15% in exemestane group v 10% in placebo – usually due to hot flushes and arthralgia.

NICE commented that the quality of this study was not sufficient to make specific recommendations because of its relatively short follow up and the fact that it excluded women with BRCA. Other studies which have considered aromatase inhibitors have “lumped them together” making it difficult to make specific recommendations.

NICE are waiting for an RCT comparing tamoxifen (for which we have more, better quality evidence in this setting) with specific aromatase inhibitors before making any recommendation.

However, if aromatase inhibitors prove to be equally or more effective than tamoxifen, they will be an attractive option for breast cancer prevention in post-menopausal women because they do not present the increased risk of endometrial cancer. Remember aromatase inhibitors cannot be used in pre-menopausal women because their action is on preventing the conversion of androgens to oestrogens. They do not affect ovarian oestrogen production which is the main source in pre-menopausal women.

NICE on familial breast cancer

- 1 in 5 cases of breast cancer occur in women with a significant family history.
- In concerned women, take a first and second degree family history and consider other risk factors such as ovarian cancer, male breast cancer, Jewish ancestry.
- Refer all women who meet the criteria for genetics assessment.
- Offer all women who do not meet the criteria for referral written information about breast awareness, lifestyle choices and the impact of COCP, HRT and breast feeding.
- Women who are determined to be moderate or high risk will be offered additional screening and some will be offered chemoprophylaxis with tamoxifen or raloxifene if prophylactic surgery is unsuitable or unacceptable.
- Tamoxifen reduces the risk of breast cancer by 38% with a NNT of 42 women taking the drug for 5 years to prevent 1 case of breast cancer over 10 years.
- This is at a cost of an increased risk of VTE and endometrial cancer.
- There is insufficient evidence at present to recommend aromatase inhibitors though they may be used in the future.

Reflect on your last 3 consultations about family history of cancer:
- Did you feel confident in taking a family history and considering other risk factors?
- How could you have improved the opportunity to make it a teachable moment- i.e. to give high impact lifestyle advice.

NICE patient information leaflet:
This is a useful online tool for patients (and GPs!) to assess genetic risk in women with a family history of breast and ovarian cancer:
http://www.macmillan.org.uk/Cancerinformation/Causesriskfactors/Genetics/OPERA.aspx
The BOADICEA tool was developed by CRUK and Cambridge to calculate and assess an individual’s risk of being a carrier of a cancer gene – it is free to download and access:
http://ccge.medschl.cam.ac.uk/boadicea/
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<td>Oxford</td>
<td>Friday September 27</td>
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<td>Southampton</td>
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<td>Leeds</td>
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<td>Glasgow</td>
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