Patient and clinician decision-making in the context of chemoprevention

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Breast cancer incidence

Breast Cancer (C50): 1979-2013
European Age-Standardised Incidence Rates per 100,000 Population, Females, Great Britain

Prevention is becoming a priority
Worldwide incidence trends

Age-standardised rate per 100,000 women

- Denmark
- Finland
- France*
- Slovakia
- Spain*
- England
Worldwide incidence trends

International Agency for Research on Cancer
World Health Organization

Age-standardised rate per 100,000 women

- China*
- India*
- Japan*
- Philippines*
- Singapore
- Thailand*

Chemoprevention

- Also known as preventive therapy
- ‘The use of natural, synthetic, or biologic chemical agents to reverse, suppress or prevent carcinogenic progression to invasive cancer’

Examples
- Vaccinations
- Dietary supplements
- Oral medications
Selective Oestrogen Receptor Modulators (SERMs)

- Nine randomised trials\(^1\)
- Median 5 year follow up
- 38% reduction (breast cancer)
- 51% reduction (ER+)
- Thromboembolic events
- Endometrial cancer
- Menopausal side-effects
- Preventive effect lasts 20 years (Tamoxifen)\(^2\)
- No mortality reduction…

Breast cancer: NHS to offer tamoxifen to at-risk women

By Michelle Roberts
Health editor, BBC News online

Thousands of women across Britain with a family history of breast cancer are to be offered drugs on the NHS to help prevent the disease.

The National Institute for Health and Care Excellence says tamoxifen or raloxifene taken daily for five years can cut breast cancer risk by 40%.

Its guidance for England and Wales means 500,000 women now have a choice other than mastectomy.
- **Offer** tamoxifen or raloxifene* for 5 years to women at high risk of breast cancer

- **Consider** offering either tamoxifen or raloxifene* for 5 years to women at moderate risk

*Anastrozole to replace SERMs for post-menopausal women*
Implementation problems

Uptake

Prescribing

Adherence
Implementation problems

Uptake
Systematic review - Uptake

- 31 studies reported uptake data
- 14 studies reported 1+ correlate of uptake
- 26 studies included in meta-analysis (n=21,423)
- Uptake ranged from 0-54.9%
Uptake: Meta-analysis

Smith et al., 2016 Ann Oncol
Important factors (uptake)

Clinical
- Abnormal breast biopsy
- Clinician recommendation
- Higher risk

Demographic
- No consistent findings

Psychological
- Concerns about medications
- Perceived risk & worry
- 100% quali studies mentioned risk
Conclusions - uptake

- Uptake is low in trials and likely to be lower in clinical practice

- Communication important for informed uptake

- Evidence (perhaps) insufficient to promote, but are patients being offered the opportunity?
Implementation problems

- Uptake
- Prescribing
- Adherence
Implementation problems

Prescribing
Implementation problems

- Qualitative study - GPs, genetic counsellors, breast physicians, surgeons (n=25)

- Reluctant to discuss and prescribe:
  - Tamoxifen not licensed for prevention
  - Familiarity
    - Geneticists unfamiliar with prescribing, GCs not medically trained
    - GPs unfamiliar with chemoprevention

- No clear prescribing pathway
- Not in British National Formulary

Smith et al., 2016 Public Health Genomics
‘I think particularly in this day and age, GPs, all doctors are so worried about getting sued, that people would be concerned if something adverse happened and it came back and it wasn’t licensed, that that could be another thing levied at them.’ (D.D., GP, female)

‘I suppose the main issue is obviously with it being off-licence. But if it had come from secondary care and I had a letter, discussed it with her and discussed that it was off-licensed, I feel happy that the responsibility is kind of a, you know, they’ve taken the primary decision, and we are supporting it by prescribing.’ (D.D., GP, female)
We [clinical genetics] are not willing to take [prescribing] on and we can’t, the breast team don’t want to and I suspect the GPs don’t want to either…you’re relieved when they say they’re not interested.’ (FHCG clinician, Female)

‘One of their [clinical genetics] representatives had come to explain how the service was going to be set up and [they] started talking about [chemoprevention] as well because she’d suggested that GPs would initiate prescriptions. And the whole place was roaring with horror.’ (GP, Female)
National survey

- National survey (n=1007 GPs) in 2016
- Vignette describing hypothetical patient
  - Manipulated risk level and initial prescriber

928 GPs

- High risk GP first prescriber
- Moderate risk GP first prescriber
- High risk SCC first prescriber
- Moderate risk SCC first prescriber

Smith et al., 2017. BJGP
Sarah is a 45-year-old woman with a family history of breast cancer. A family history clinician assessed her as having a high risk of breast cancer. This means she has a lifetime risk of \( \geq 30\% \). Sarah has discussed the potential harms and benefits of taking tamoxifen. Sarah is premenopausal with no menstrual dysfunction, is not planning pregnancy, has no contraindications, and is taking no other medications. The family history clinician supports her decision to take tamoxifen and has also referred her for additional screening. The family history clinician requested that you write the first prescription and continue to act as the main prescriber.
Results - Awareness

- 52% aware of prevention indication for tamoxifen
- 24% aware of NICE guideline (CG164)

Majority of GPs:
- willing to prescribe (77.4%)
- comfortable managing patient (66.4%)
- comfortable discussing harms / benefits (58.3%)

- Attitudes vary significantly by context…
Willingness to prescribe for patient (% willing) (N=928)

Prescriber: p<0.001
Risk: N.S
Interaction: N.S.

- GP 1st: 69.1%
- Moderate: 63.7%
- Family history clinician: 83.7% (High risk) 85.6% (Moderate)
Source of information about tamoxifen (N=243)

- Training days: 32%
- GP magazines: 31%
- National guidelines: 31%
- Academic journals: 15%
- Patient: 15%
- Colleagues: 14%
- National media: 14%
- Local guidelines: 8%
- Other: 7%
- Practice meetings: 6%
- Unsure: 2%
Lynch Syndrome (LS)

- Inherited defect in one of 4 DNA mismatch repair genes
- LS characterised by development of colorectal, endometrial and other cancers at unusually young age
- ~3% of CRC attributable to LS (~1200 pa in UK)
- No UK guidance on aspirin use, but...European guidelines recommend low-dose aspirin for gene carriers (European Guidelines for the clinical management of Lynch Syndrome, 2013)
Lynch Syndrome

N=937

Aspirin 600mg (N=427)

Matching placebo (N=434)

- ITT analysis (HR 0.63, 95% CI 0.35-1.13, p=0.12)
- Per-protocol analysis taking into account multiple cancers (IRR 0.56, 95% CI 0.32-0.99, p=0.05)
- Promising effects on other cancers associated with LS
Expert consensus aspirin should be offered to gene carriers, but debate regarding dose.

- Aspirin 100mg
- Aspirin 300mg
- Aspirin 600mg

2 years on therapy

Open-label (same dose)
Results

Before today, had you heard of Lynch Syndrome, HNPCC, Muir Torre Syndrome?

- Yes, Lynch Syndrome: 27.3%
- Yes, HNPCC: 61.2%
- Yes, Muir Torre Syndrome: 4%
- No, hadn't heard of any: 29.2%

Multiple answers permitted
Imagine the CAPP3 study shows that 100mg/300mg/600mg of aspirin is the optimal dose for reducing the incidence of cancer in Lynch Syndrome carriers. How willing would you be to prescribe aspirin for a patient with Lynch Syndrome?
Conclusions - prescribing

**Recommendations:**
- GP education
  - Standardised pro-formas for secondary care
- ‘Shared care’ agreements for prescribing
  - CCGs, Medicines Management Groups
- List prevention as indication for tamoxifen and aspirin in BNF
  - Possibly happening for tamoxifen, watch this space

[www.cancerresearchuk/chemoprevention](http://www.cancerresearchuk/chemoprevention)
Implementation problems

Uptake

Prescribing

Adherence
Implementation problems

Adherence
IBIS-1 adherence

- **Aim:** To investigate adherence to tamoxifen in a clinical trial context and the role of participant-reported symptoms

- **Methods:** IBIS-1 (tamoxifen vs. placebo) (n=4279)

- **Inclusion criteria:**
  - UK women aged 35-70
  - Increased risk of developing breast cancer

- 4.5 years defined as adherent for analysis (yes / no)

Smith, Sestak et al., 2017. Journal of Clinical Oncology
Long-term persistence in IBIS-1 trial
Annual drop-out rates: IBIS I

<table>
<thead>
<tr>
<th>Follow-up time [years]</th>
<th>Placebo</th>
<th>Tamoxifen</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>150</td>
<td>220</td>
</tr>
<tr>
<td>1</td>
<td>127</td>
<td>181</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>136</td>
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<td>3</td>
<td>93</td>
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<tr>
<td>4</td>
<td>76</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>89</td>
</tr>
</tbody>
</table>
## Symptoms at 6-months

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild (%)</th>
<th>Moderate (%)</th>
<th>Severe (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea / vomiting</td>
<td>4.0</td>
<td>0.8</td>
<td>0.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Headache</td>
<td>4.3</td>
<td>1.5</td>
<td>1.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>17.7</td>
<td>8.7</td>
<td>5.1</td>
<td>31.5</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>16.8</td>
<td>3.1</td>
<td>1.0</td>
<td>20.9</td>
</tr>
</tbody>
</table>
Adherence also decreased with increasing symptom severity (p<0.001 for trend)
IBIS-1 adherence

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Odds Ratio (95% CI)</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>0.55 (0.35-0.86)</td>
<td>P=0.98</td>
</tr>
<tr>
<td></td>
<td>0.54 (0.36-0.82)</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>0.59 (0.40-0.86)</td>
<td>P=0.23</td>
</tr>
<tr>
<td></td>
<td>0.83 (0.57-1.19)</td>
<td></td>
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<tr>
<td>Hot flashes</td>
<td>0.99 (0.76-1.30)</td>
<td>P=0.48</td>
</tr>
<tr>
<td></td>
<td>0.88 (0.71-1.08)</td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>0.99 (0.73-1.35)</td>
<td>P=0.21</td>
</tr>
<tr>
<td></td>
<td>0.77 (0.61-0.96)</td>
<td></td>
</tr>
</tbody>
</table>

Smith, Sestak et al., 2017. Journal of Clinical Oncology
Conclusions – common themes

- Moderate adherence among IBIS trials
  - Rates outside trial context unknown, but likely to be lower

- Trial drop-out fastest in first 12-18 months
  - Implications for intervention timing

- Some side-effects associated with adherence
  - Sometimes bodily symptoms are misattributed to drug (‘nocebo’)
  - Dose-response relationship with severity and adherence
  - Other (psychological?) factors likely to be at play too

- Interventions to manage and prevent symptoms are important for ensuring adequate adherence and QoL
Conclusions - overall

- A mixture of patient and clinician factors affecting the effective use of breast cancer chemoprevention

- Most barriers can be addressed through interventions

- Breast cancer chemoprevention implementation issues have implications for other clinical groups and disease sites:
  - Lynch syndrome and aspirin
  - Secondary prevention (e.g. tamoxifen / AIs in breast cancer)
  - Many other trials in progress
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