Chemo-endocrine prevention of breast cancer

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Goals of prevention

- Minimize burden of disease:
  - Psychological consequences
  - Diagnostic and staging procedures
    - Biopsies, bone scans, CT/ MRI scans, PET, etc.
  - Therapeutic intervention side effects
    - Surgery
    - Radiation
    - Chemotherapy
    - Hormone therapy
A common misinterpretation

- The purpose of cancer prevention is to avoid the trauma of cancer diagnosis and its treatment and emotional consequences.
- Mortality reduction from micrometastases eradication is the purpose of adjuvant therapy.
- Reduction of incidence, not mortality, is the primary aim of cancer prevention.
Several drugs have shown reduced cancer incidence in Phase III trials

- Breast:
  - Tamoxifen, raloxifene, losofoxifene, arzoxifene, exemestane, anastrozole, conjugated equine oestrogen

- Colon in Lynch syndrome:
  - Aspirin

- Prostate:
  - Finasteride, dutasteride

- H&N
  - 13 cis retinoic acid
Lesson from cardiology

- Placing resources on preventive therapy has resulted in a significant reduction of cardiovascular death

Jemal A et al. CA Cancer J Clin 2010;60(5):277-300 Copyright © 2010 American Cancer Society, Inc
2013 SERMs overview

- Individual subject data from 83,399 women (306,307 women-years of follow-up) from 9 double-blind trials:
  - 4 tamoxifen mainly in high risk women;
  - 3 raloxifene
  - 1 lasofoxifene
  - 1 arzoxifene

- Median follow-up 65 months (IQR 54-93)

Cuzick J et al. Lancet 2013;381(9880):1827-1834
Details of breast cancer prevention trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Recruitment period</th>
<th>Treatment groups and daily dose</th>
<th>Treatment duration (years)</th>
<th>Entry criteria</th>
<th>Present status</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsden 4,6</td>
<td>2471</td>
<td>1986-96</td>
<td>Placebo (1233) Tamoxifen 20 mg (1238)</td>
<td>5-8</td>
<td>High risk, family history</td>
<td>Blinded, further follow-up</td>
<td>171.6 (153.9-184.0)</td>
</tr>
<tr>
<td>IBIS-F 4,8</td>
<td>7109</td>
<td>1992-2001</td>
<td>Placebo (3566) Tamoxifen 20 mg (3573)</td>
<td>5</td>
<td>Greater than two times relative risk</td>
<td>Blinded, further follow-up</td>
<td>96 (80.1-117.1)</td>
</tr>
<tr>
<td>NSABP-P-110</td>
<td>13205</td>
<td>1992-97</td>
<td>Placebo (6707) Tamoxifen 20 mg (6681)</td>
<td>5</td>
<td>&gt;1.6% 5 year risk</td>
<td>Unblinded, no follow-up</td>
<td>57.6 (35.4-64.9)</td>
</tr>
<tr>
<td>Italian 11,12</td>
<td>5408</td>
<td>1992-97</td>
<td>Placebo (2708) Tamoxifen 20 mg (2700)</td>
<td>5</td>
<td>Normal risk, women with hysterectomy</td>
<td>Unblinded, further follow-up</td>
<td>139.6 (122.0-146.1)</td>
</tr>
<tr>
<td>MORE/CORE 4,8 7705/6511</td>
<td>1994-98/1998-2002</td>
<td>Placebo (2576) Raloxifene 60 mg (2557) / Placebo (2576) Raloxifene 120 mg (2572)</td>
<td>4/8</td>
<td>Normal risk, postmenopausal women with osteoporosis</td>
<td>Unblinded, no follow-up</td>
<td>71.3 (47.1-95.4)</td>
<td></td>
</tr>
<tr>
<td>RUTH 5</td>
<td>10101</td>
<td>1998-2000</td>
<td>Placebo (5057) Raloxifene 60 mg (5044)</td>
<td>5</td>
<td>Normal risk, postmenopausal women with established or risk of CHD</td>
<td>Unblinded, no follow-up</td>
<td>66.7 (60.1-72.3)</td>
</tr>
<tr>
<td>STAR 4,12</td>
<td>19490</td>
<td>1999-2004</td>
<td>Raloxifene 60 mg (9875) Tamoxifen 20 mg (9872)</td>
<td>5</td>
<td>&gt;1.6% 5 year risk, postmenopausal women</td>
<td>Unblinded, no follow-up</td>
<td>81 (60.8-96.6)</td>
</tr>
<tr>
<td>PEARL 18,19</td>
<td>8856</td>
<td>2001-07</td>
<td>Placebo (2852) Lasoxifene 0.50 mg (2852) Tamoxifen 20 mg (2852)</td>
<td>5</td>
<td>Normal risk, postmenopausal women with osteoporosis</td>
<td>Blinded, no follow-up</td>
<td>59.6 (58.8-60.1)</td>
</tr>
<tr>
<td>GENERATIONS 20,23</td>
<td>9354</td>
<td>2004-09</td>
<td>Placebo (4678) Arzoxifene 20 mg (4676)</td>
<td>4</td>
<td>Normal risk, postmenopausal with low BMD or osteoporosis</td>
<td>Unblinded, no follow-up</td>
<td>54.3 (28.3-56.1)</td>
</tr>
</tbody>
</table>

Data in parenthesis are number of randomised participants. CHD=coronary heart disease. BMD=bone mineral density. *The CORE trial was done in a subset of women originally enrolled in the MORE trial.

Table 1: Details of breast cancer prevention trials

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38% reduction, HR=0.62 (0.56-0.69) in breast cancer incidence

31% decrease of DCIS, HR=0.69 (0.53-0.90), with heterogeneity between agents

Cuzick J et al. Lancet 2013;381(9880):1827-1834
All breast cancers, invasive breast cancer and DCIS in years 0-10 according to trial

The benefit of 5 years of SERMs declines but continues up to 10 years.

2013 SERMs overview main findings - 2

- ER+ve breast cancers decreased by 51%, HR=0.49 (0.42-0.57)
- ER-ve disease non-significant increase, HR=1.14 (0.90-1.45)

Cuzick J et al. Lancet 2013;381(9880):1827-1834
2013 SERMs overview main findings - 3

- Increase in endometrial cancer with tamoxifen (HR=2.18, 1.39-3.42), but not with other SERMs
- Increase of DVT, PE or retinal vein thrombosis with all SERMs (OR=1.73, 1.47-2.05)

Cuzick J *et al.* Lancet 2013;381(9880):1827-1834
Trials

2013 SERMs overview main findings - 4

- 15% reduction in all fractures, OR=0.85 (0.80-0.89)
- 34% reduction in vertebral fractures, OR=0.66 (0.59-0.73)
- 7% reduction of non-vertebral fractures, OR=0.93 (0.87-0.99)

Cuzick J et al. Lancet 2013;381(9880):1827-1834
Trials

No effect of SERMs on death from:

- Breast cancer
- Overall mortality
- Colorectal
- Ovarian cancer
- Other cancers
- Stroke, TIA or MI

Cuzick J et al. Lancet 2013;381(9880):1827-1834
Benefit/risk indices for tamoxifen and raloxifene chemoprevention

By level of 5-year projected risk for invasive breast cancer (IBC) for white non-Hispanic women **with a uterus**, by age group (n. life threatening events prevented/10,000 over 5 years)

<table>
<thead>
<tr>
<th>5-Year Projected Risk of IBC (%)</th>
<th>Tamoxifen v Placebo (with uterus)</th>
<th>Raloxifene v Placebo (with uterus)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-59</td>
<td>60-69</td>
</tr>
<tr>
<td>1.5</td>
<td>-133</td>
<td>-310</td>
</tr>
<tr>
<td>2.0</td>
<td>-105</td>
<td>-283</td>
</tr>
<tr>
<td>2.5</td>
<td>-78</td>
<td>-255</td>
</tr>
<tr>
<td>3.0</td>
<td>-51</td>
<td>-228</td>
</tr>
<tr>
<td>3.5</td>
<td>-25</td>
<td>-202</td>
</tr>
<tr>
<td>4.0</td>
<td>3</td>
<td>-175</td>
</tr>
<tr>
<td>4.5</td>
<td>29</td>
<td>-148</td>
</tr>
<tr>
<td>5.0</td>
<td>56</td>
<td>-121</td>
</tr>
<tr>
<td>5.5</td>
<td>83</td>
<td>-95</td>
</tr>
<tr>
<td>6.0</td>
<td>109</td>
<td>-69</td>
</tr>
<tr>
<td>6.5</td>
<td>135</td>
<td>-42</td>
</tr>
<tr>
<td>7.0</td>
<td>162</td>
<td>-15</td>
</tr>
</tbody>
</table>

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates

Combining RR from BCPT and STAR using WHI baseline rates

- **Strong evidence of benefits outweighing risks**
- **Moderate evidence of benefits outweighing risks**
- **Benefits do not outweigh risks**

NCIC CTG MAP.3 Prevention Trial

Eligibility
- Postmenopausal women ≥ 35yrs
- With at least 1 of these risk factors for BrCa:
  - >60 years old
  - Gail score >1.66%
  - Prior ADH, ALH, LCIS
  - DCIS with prior mastectomy

Stratification
- Aspirin use
- Gail score (<2.0 vs. ≥ 2.0)

Double-blind
- Exemestane
  - 25 mg/day x 5 years
  - n = 4560
  - February 2004 – March 2010
- Placebo
  - 1 mg/day x 5 years

Placebo vs. Exemestane

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Annual incidence rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemestane</td>
<td>0.19% (0.08-0.30%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.55% (0.36-0.73%)</td>
</tr>
</tbody>
</table>

Hazard Ratio 0.35 (95% CI=0.18–0.70)
Stratified log rank   p-value=0.002

No. at risk
Placebo 2275 1905 1468 986 477 82
Exemestane 2285 1902 1468 980 464 77

Mean percent change in bone mineral density over time

The International Breast cancer Intervention Study II (IBIS-II)

- Study Design

3864 postmenopausal women
10 yr risk >5%

RANDOMISATION

Anastrozole
1 mg/day
(n=1920)

Placebo/day
(n=1944)

for 5 years
IBIS-II breast cancer Incidence

IBIS-II breast cancer Incidence in subgroups analysis

### IBIS-II cancers other than breast according to treatment allocation

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (N=1920)</th>
<th>Placebo (N=1944)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin cancer</strong></td>
<td>14</td>
<td>27</td>
<td>0.53 (0.28-0.99)*</td>
</tr>
<tr>
<td>Non-melanoma skin</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>4</td>
<td>12</td>
<td>0.34 (0.11-1.04)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>3</td>
<td>5</td>
<td>0.61 (0.15-2.54)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>40 (2.1%)</td>
<td>70 (3.6%)</td>
<td>0.58 (0.39-0.85)**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01

Treatment specificity: Number needed to treat

NNT over 5 years, preventive drug vs. placebo

- 8 Tamoxifen recurrence
- 22 Rosuvastatin CVD JUPITER
- 25 Tamoxifen prevention ADH
- 25 Exemestane MAP3
- 27 Tamoxifen P-1 IBC
- 67 Raloxifene CORE IBC
- 71 Aspirin Meta-analysis (CV events)

333 women*
270 men*

*6.4 years follow-up for aspirin

Consider prescribing tamoxifen for 5 years to pre-menopausal women at moderate risk of developing breast cancer within the next 10 years. [new 2013]

Offer tamoxifen for 5 years to pre-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer. [new 2013]

Offer tamoxifen or raloxifene for 5 years to post-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer. [new 2013]

Consider prescribing tamoxifen or raloxifene for 5 years to post-menopausal women at moderate risk of developing breast cancer within the next 10 years. [new 2013]

Discuss all the options for preventive treatment (including side effects of drugs and the extent of risk reduction) to women at high or moderate risk. [new 2013]
<table>
<thead>
<tr>
<th>Breast cancer risk category</th>
<th>Lifetime breast cancer risk from aged 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near population risk</td>
<td>Lifetime risk of less than 17% (equivalent to less than 1 in 6)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Lifetime risk of 17% or a greater but less than 30% (equivalent to greater than 1 in 4)</td>
</tr>
<tr>
<td>High risk</td>
<td>Lifetime risk of 30% or greater (equivalent to greater or equal to 1 in 3)</td>
</tr>
</tbody>
</table>
The Gail Model

Gail risk factors
- Menarche: 12 yrs
- 1st live birth: 22 yrs
- # biopsies: 2
- # 1st degree rel.: 2
- Atypical hyperplasia: +

Redrawn from National Surgical Adjuvant Breast and Bowel Project (NSABP)
**NEW Recommendations†**

- Should be offered to reduce the risk of ER-positive invasive BC in premenopausal women who are ≥ 35 years of age with a 5-year projected BC risk ≥ 1.66%, a or with LCIS or atypical hyperplasia. Risk reduction benefit continues for at least 10 years b
- Should be offered to reduce the risk of ER-positive invasive BC in postmenopausal women who are ≥ 35 years of age with a 5-year projected BC risk ≥ 1.66%, a or with LCIS. Risk reduction benefit continues for at least 10 years b
- Risks and benefits should be given careful consideration during the decision-making process c
- Is not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack. Tamoxifen is contraindicated in women who are pregnant, women who may become pregnant, and in nursing mothers
- Combined use of tamoxifen for BC prevention and hormone therapy is currently not recommended
- Follow-up should include a timely work-up of abnormal vaginal bleeding.
- **DOSAGE:** 20 mg/d for 5 years

U.S. Preventive Services Task Force medications for risk reduction of primary breast cancer in women

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic women aged ≥35 years without a prior diagnosis of breast cancer who are at increased risk for the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Engage in shared, informed decision making and offer to prescribe risk-reducing medications, if appropriate. Grade: B*</td>
</tr>
<tr>
<td>Preventive medications</td>
<td>Tamoxifen and raloxifene have been shown to reduce the incidence of invasive breast cancer in women who are at increased risk for the disease. Tamoxifen has been approved for this use in women age 35 years or older, and raloxifene has been approved for this use in postmenopausal women. The usual daily doses for tamoxifen and raloxifene are 20 mg and 60 mg, respectively, for 5 years</td>
</tr>
<tr>
<td>Balance of benefits and harms</td>
<td>There is a moderate net benefit from use of tamoxifen and raloxifene to reduce the incidence of invasive breast cancer in women who are at increased risk for the disease</td>
</tr>
</tbody>
</table>

*Grade B= There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.*
Key Ingredients in cancer preventive medicine: The **ABC** paradigm

1. Effective non-toxic **Agents**

2. Effective for individuals based on **Biomarker** response →

3. Better identification of high-risk **Cohorts**
The ABC paradigm in future breast cancer prevention

- **Novel Agents:**
  Low-dose tamoxifen, metformin, bisphosphonates, others?

- **Putative Biomarkers:**
  Mx density, E2, T, SHBG, IGF-I, adiponectin

- **At risk Cohorts:**
  Gail, intra epithelial neoplasia, BRCA, family history
### Predictive markers in prevention

#### The case for mammographic density and tamoxifen

**OR for developing breast cancer for tamoxifen versus placebo arm overall and by breast density reduction category in specific subgroups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of control subjects/No. of case subjects</th>
<th>Tamoxifen, all</th>
<th>Tamoxifen, breast density reduction &lt;10%</th>
<th>Tamoxifen, breast density reduction ≥10%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)†</td>
<td>No. of case subjects</td>
<td>OR (95% CI)‡</td>
</tr>
<tr>
<td>Overall</td>
<td>929/120</td>
<td>0.73 (0.49, 1.08)</td>
<td>35</td>
<td>1.13 (0.72, 1.77)</td>
</tr>
</tbody>
</table>

Redrawn from Cuzick J et al. J Natl Cancer Inst 2011;103(9):744-752
Possible scenario for a validated efficacy biomarker for prevention

- >10% reduction of mx density after 1 year: **continue tamoxifen**
- <10% reduction of mx density after 1 year: **stop tamoxifen**
Tamoxifen at lower doses has similar effects on KI-67 change in a 4-week presurgical trial.

Median % change and 95% CI

- Tam vs. control: P<0.0001
- Dose-response: P=0.81

Conclusions-1

- SERMs can decrease breast cancer risk by 40% in at-risk subjects. For all SERMs, incidence of ER+ breast cancer was reduced both during treatment and for at least 5 years after completion.

- AIs are even more effective than SERMs in reducing breast cancer risk in postmenopausal women, but they may lose the favorable estrogenic effects on bone and blood vessels.

- Similar to other preventive interventions in medicine, SERMs and AIs should be offered to women at high risk for breast cancer after careful consideration of risks and benefits.
Conclusions-2

- We should learn from the cardiologists that identification of high risk individuals and use of prophylactic treatments is a better strategy than passively waiting for disease to appear. This paradigm shift will hopefully find increasing consensus among the young generations of medical oncologists.

- A crucial issue for the future will be the validation of efficacy biomarkers that allow an early selection of responders versus non-responders.

- With the increasing costs of cancer therapy, there is a reason for optimism that inexpensive preventive therapy for high risk women will become a key strategy for global breast cancer control.
Thank you!