Breast cancer chemoprevention in the high-risk patient

Pharmacological compounds to prevent the development of breast cancer

An update

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Being Diagnosed Means:

- Transformation to a patient
- You become a survivor
- End of treatment does not mean end of disease

Can we avoid this?
Breast cancer: Important enough to prevent it

Probability of developing invasive breast cancer during selected age intervals

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>by age 30</td>
<td>1 in 2,525</td>
</tr>
<tr>
<td>by age 40</td>
<td>1 in 217</td>
</tr>
<tr>
<td>by age 50</td>
<td>1 in 50</td>
</tr>
<tr>
<td>by age 60</td>
<td>1 in 24</td>
</tr>
<tr>
<td>by age 70</td>
<td>1 in 14</td>
</tr>
<tr>
<td>by age 80</td>
<td>1 in 10</td>
</tr>
</tbody>
</table>

X 50

X 5
Breast Cancer
Evolving Model of 2 Diseases

- ER - Negative
  - Decreases w/ age
  - Genetic Factors
    - BRCA 1 & 2
  - Hormonally insensitive???
  - Worse prognosis

- ER - Positive
  - Increases w/ age
  - Weak link to genetic factors
    - NOT BRCA - 1
    - BRCA 2
  - Hormonally sensitive
  - Better prognosis

We are/will be more successful in prevention of ER+ breast cancer
Prevention does work there is less heart disease & stroke

Identification of high-risk individuals by measuring BP and cholesterol levels, and offering them targeted preventive treatment

**Cholesterol lowering drugs, antihypertensives**

...breast density lowering drugs
High-risk factors for breast cancer: relative risk

Stopping (pre)malignant subclinical lesions is the key to effective prevention methods.

- **Primary prevention** = Stop promotion
  - Initiation starts earlier

- Which individuals are at risk and for what type of cancer?
  - Risk calculation = SOC
  - Information on 1(ary) (chemo)prevention= SOC

How safely and effectively “arrest” the progression of subclinical (pre) malignant disease?
Breast Cancer Disease Course
Long Window of Opportunity

*Note: 90-day doubling x 20 doublings = 1800 days (~ 5 years).
**Can vary from 25 -250 days

Preventing breast cancer

- Eliminate or prevent pre-invasive disease before invasion develops
  - General health maintenance
    - Eat a healthy diet
    - Reproductive issues
    - Don’t drink too much
    - Exercise/ maintain optimal weight
  - Prophylactic surgery
  - Chemoprevention
Chemoprevention of Breast Cancer Options for High Risk Women

- Chemoprevention with SERMs (e.g. tamoxifen (EMEA not approved))
- Participation in trials using aromatase inhibitors (IBIS-II)
- Others
  - NSAIDs, Cox 2 inhibitors
  - Vit A derivatives
  - Statins
  - Metformine
  - www.clinicaltrials
Block pre- and postmenopausal oestrogens...risk/benefit

The Tumor Cell
SERMs initiate or suppress target genes leading them to their actions
SERM activity ~ relative levels or coregulators in target cells

Riggs BL and Hartmann LC in N Engl J Med 2003;348:1192
Tamoxifen for breast cancer prevention
IBIS-I

Overall 4 tamoxifen prevention trials
Risk reduction : 38%
Tamoxifen
NSABP-P1 tam / placebo trial

Tamoxifen lowered invasive breast cancer risk by 50%
- For ER+ cancers
  - No reduction in ER- cancers
- Statistically significant
  - (95% CI 0.39-0.66)
- The trial was unblinded early

RR = 3X //3-4% over next 5 years

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of invasive breast cancer per 1000 women</td>
<td>42.5</td>
<td>24.8</td>
</tr>
<tr>
<td></td>
<td>-17/1000/5 years</td>
<td></td>
</tr>
</tbody>
</table>

NNT over 5 years: 1/80 ‘high risk’ cases
- Aclasta 3 years to prevent a hip fracture in osteoporosis
- ASA taken for 5 years reduced myocardial infarction (ARR, 0.5%, NNT 200 for 5 years), increased major haemorrhage (ARI, 0.7%, NNT 154), and did not reduce all cause mortality or cardiovascular mortality
Comparison of relative risks (with 95% confidence intervals) of benefits and undesirable effects of tamoxifen from the initial and updated results of NSABP P-1

Predicted benefits vs harms for 5 years of tamoxifen per 1000 women: 74/12 FU

<table>
<thead>
<tr>
<th></th>
<th>Age 45</th>
<th>Age 55</th>
<th>Age 65</th>
<th>Age 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yr breast cancer risk</td>
<td>No FH</td>
<td>0.7</td>
<td>1.1</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>FH</td>
<td>1.6</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td># of invasive breast cancers avoided</td>
<td>No FH</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>FH</td>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Hip fractures avoided</td>
<td>&lt;1</td>
<td>3</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Endometrial cancer caused</td>
<td>2</td>
<td>12</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Strokes caused</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>PE caused</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>DVT caused</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>7</td>
<td>22</td>
<td>42</td>
<td>64</td>
</tr>
</tbody>
</table>

Less side effects <50 years  
Hot flushes and night leg cramps not considered
Tamoxifen FDA Approved

**But ...**

- Less than 3% of eligible candidates for primary prevention of breast cancer are taking tamoxifen
- 10 million women meet high risk status
- 2 million would derive an overall benefit, especially 40 - 50 year olds
- >28,000 invasive breast cancers prevented / 5 years

Tamoxifen and LCIS or ADH in P1 trial

**LCIS**
- 829 women included: 413, 416
- Events at 7 yrs FU: 29, 16
- Incidence of event n/1000/Y: 11.7, 6.3

**ADH**
- 1196 women included: 615, 581
- Events at 7 yrs FU: 38, 9
- Incidence of events n/1000/Y: 10.4, 2.5

First, do not Harm! Menopausal women are at risk for toxicity! Lower NNT

Circulating oestrogens do not predict benefit from tamoxifen
More Trials

- Multiple Outcomes of Raloxifene Evaluation (MORE trial)
  - 7705 postmenopausal with osteoporosis
  - Raloxifene vs placebo, 3 years
  - Increased bone density; reduced risk of vertebral (not hip) w/o risk of uterine ca
  - Decreased risk of invasive BC (RRR 76%)
    - For ER+ tumors, RRR 90%
  - But did increase risk of VTE, RR 3.1

Raloxifene
Raloxifene and ER+ Breast Cancer in Low Risk Women

Incidence per 1000 woman-yrs

- Placebo
- Raloxifene

- RUTH
  - 44% reduction
- MORE
  - 71% reduction
- CORE
  - 56% reduction

High risk population
**NSABP P2 Breast Cancer Prevention**

**STAR Schema**

- **Risk-Eligible Post-Menopausal Women**

**STRATIFICATION**
- Age
- Relative Risk
- Race
- History of LCIS

**TAMOXIFEN**
- 20 mg/day x 5 years

**RALOXIFEN**
- 60 mg/day x 5 years

- Age 35 +
- No history of:
  - Cancer
  - Clotting
  - DM & HTN
P-2 STAR: raloxifene vs tamoxifen
Primary endpoint: Breast cancer prevention
Baseline Characteristics

- 19474 women randomized (risk = NASBP-P1)
- 47.3 months follow-up
- Mean age, 58.5 years
- Mean 5-year predicted risk of breast cancer, 4.03%
- History of lobular carcinoma in situ (LCIS)*
  - Tamoxifen: 9.2%  Raloxifene: 9.2%
- History of breast atypical hyperplasia
  - Tamoxifen: 22.5%  Raloxifene: 23.0%

*Women with history of ductal carcinoma in situ (DCIS) were excluded

Vogel VG et al. JAMA 2006;295:2727-41
P-2 STAR
Age Distribution of Participants

- <49: 9%
- 50-59: 50%
- 60-69: 32%
- 70+: 9%

Vogel VG et al. JAMA 2006;295:2727-41
P-2 STAR
First-Degree Relatives with Breast Cancer

Vogel VG et al. JAMA 2006;295:2727-41
STAR Average Annual Rate & Number of Invasive Breast Cancers

- **Gail Model Projection**
  - N= 9726
  - Av Ann Rate per 1000: 312*

- **TAM**
  - N= 9745
  - Av Ann Rate per 1000: 163*

- **Raloxifene**
  - N= 9745
  - Av Ann Rate per 1000: 168*

* # of events

Population: 4% over 5 yrs will get breast cancer (normal: 2%)
Tamoxifen vs Raloxifene

- Comparable efficacy to prevent invasive breast cancer and osteoporotic fractures
- Raloxifene had fewer thromboembolic events, endometrial hyperplasia hysterectomies, cataracts, and less uterine cancer
- Similar risk of MI, stroke, hot flashes, leg cramps
Clear Winner?

- Tamoxifen not widely accepted
  - Primary care physicians less familiar with its use
  - Serious adverse effects
- Raloxifene as effective
  - More widespread use by primary physicians
  - Less adverse effects
Raloxifene is an excellent chemopreventive agent for the very high breast cancer risk patient. But, osteoporotic women probably not at high breast cancer risk.
The ideal treatment for postmenopausal women would:

- Decrease vertebral fractures
- Decrease non-vertebral fractures
- Decrease CHD
- Decrease Stroke
- Decrease Breast Cancer
- Decrease Vulvo-Vaginal Atrophy
- Decrease hot Flashes
- No increase in DVT / Endometrial Cancer

No current therapy meets these needs but… Lasofoxifene is not far from being the ideal SERM
Lasofoxifene

- High affinity for the estrogen receptor
- Previous clinical studies
  - Decreases bone turnover
  - Decreases bone loss
  - Decreases LDL-cholesterol
  - Relieves vulvovaginal atrophy

Indication: Treatment of osteoporosis and vaginal atrophy with breast cancer reduction as a consequence

Presented at FDA & ASBMR-Canada Sept 2008
The PEARL Trial – 5 year results
Double Blind RCT: Plac vs Laso

- Randomized placebo-controlled trial
- Two daily doses (0.25 mg or 0.5 mg)
  - All received Vit D3 and calcium daily
- 5 year results
- 8,556 women 59 to 80 years old
- BMD T-score ≤ -2.5 and ≥ -4.5 at the femoral neck or spine
- < 4 radiographic vertebral fractures

* Postmenopausal Evaluation and Risk-reduction with Lasofoxifene*
Endpoint

- Adjudication committees (blinded):
  - Fractures: Vertebral, Non-vertebral, Hip
  - Breast cancer (ER+ cancer co-1° at 5 yrs)
  - Gynecologic: endometrial cancer, hyperplasia
  - Cardiovascular
    - Stroke, TIA, VTE, major CHD events*
    - Cause of death

*Composite of coronary death, non-fatal MI, new ischemic heart disease, hospitalization for unstable angina, revascularization procedures
Nonvertebral Fracture at 5 Years

First SERM with Non-vertebral fracture Risk reduction

- Pbo: 0.90 (0.76, 1.06)
- 0.25 mg: 0.76 (0.64, 0.91)
- 0.5 mg: 0.76 (0.64, 0.91)

Cumulative %

- Pbo: 10.4%
- 0.25 mg: 9.4% (P = 0.19)
- 0.5 mg: 8.1% (p < 0.01)

n = 296
n = 269
n = 230

Lasofoxifene - First SERM with Non-vertebral fracture Risk reduction
ER+ Breast Cancer at 5 years

<table>
<thead>
<tr>
<th>Incidence Rate per 1000 Patient Years (95% CI)</th>
<th>Placebo</th>
<th>0.25 mg</th>
<th>0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 21</td>
<td>1.7</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>n = 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Placebo: 0.52 (0.25, 1.08)
- 0.25 mg: 0.19 (0.07, 0.56)
- 0.5 mg: 0.38 (0.07, 0.56)

48% (p = 0.073) for 0.25 mg
81% (p < 0.001) for 0.5 mg
Major CHD Events Through 5 Years

<table>
<thead>
<tr>
<th>Drug</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laso 0.25 mg</td>
<td>0.76</td>
<td>(0.56, 1.03)</td>
<td>0.077</td>
</tr>
<tr>
<td>Laso 0.5 mg</td>
<td>0.68</td>
<td>(0.50, 0.93)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Placebo</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

+ less stroke
## Adverse Events: VTE / Flushes

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.25</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EndCan</strong></td>
<td>3 (0.1%)</td>
<td>2 (0.1%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td><strong>Endhyperpl</strong></td>
<td>0</td>
<td>3 (0.1%)</td>
<td>2 (0.1%)</td>
</tr>
<tr>
<td><strong>Vaginal Bleeding</strong></td>
<td>36 (0.3%)</td>
<td>70 (0.5%)</td>
<td>90 (0.7%)</td>
</tr>
<tr>
<td><strong>Hot Flushes</strong></td>
<td>158 (1.2)</td>
<td>372 (2.9)</td>
<td>365 (2.8)</td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td>18 (0.6%)</td>
<td>48 (1.7%)</td>
<td>37 (1.3%)</td>
</tr>
</tbody>
</table>

Endometrial Texture = Tam Like (20%)

Subepithelial changes and More Atrophic E-Polyps
The Ideal SERM?
Tamoxifen, Raloxifene
Arzoxifene, Lasophoxifene, Bazedoxifene
Much more data to come

Agonist
- Bone
- CVS

Antagonist
- Breast
- Uterus

More evidence than before

Time is ripe for reassessment of the rapidly changing SERM concept
Barriers To Chemoprevention

- Women and physicians perceptions
  - 89 of 345 w/ breast lump were high risk
  - Counseled on increased risk and prevention
  - Encouraged to discuss with family physician
  - Physicians educated on chemoprevention
  - F/U by telephone interviews

< 3% of eligible women take pills to prevent breast cancer

Results

- 1/89 decided to take Tamoxifen for prevention of breast cancer
  - Only 49% discussed with MD
  - MD recommended T for only 3 (3.4%)
  - MD made NO recs for 8 (9.1%)
  - MD advised against use for 37 (42%)

- Reasons against use
  - Fear of adverse events (47%), MD’s recommendation (34%), perceived low breast cancer risk (34%)

And Physicians?…

- Survey 822 primary care docs
- Six patient scenarios with varying breast cancer risks (0.7% - 8.2%)
- Almost all endorse mammography and lifestyle behavior counseling
- Many underestimate the BC risk
  - Overemphasize FH but neglect other factors
- Under-use genetic counseling or primary chemoprevention
Conclusions SERMs

- Physicians must become more familiar with breast cancer risk assessment
- Both tamoxifen and raloxifene decrease breast cancer risk in high risk women
- Both have adverse effects which must be weighed against benefits
- We must improve communication of risk and benefits to patients and be aware of their perceptions, especially for minority patients
- New SERMs: Laso, Basedoxifene, Arzoxifene
Breast Cancer Prevention
Combining SERMs with other agent

- Clinical trials with retinoids for breast cancer chemoprevention. Fenretinide
- Tamoxifen + Vit A analogue in premenopausals
  - DCIS, LCIS, 4 arm trial
- Hot trial, 2 arm trial
- LHRH-agonist + Tibolone/Raloxifene
- Raloxifene + Omega – 3 FA

STEAR: Tibolone
Aromatase Inhibitoren (Arimidex, Femara, Aromasin) block estrogen.

Postmenopausal patients:

- Reduce Estrogen
  - Aromatase Inhibitors

- Block Estrogen
  - SERMs (Tamoxifen, Nolvadex, Tamoplex, etc.)

NO OESTROGENS AT ALL!
Incidence of Contralateral Breast Cancers
Tamoxifen versus Oral Aromatase Inhibitor

Each AI has developed its own prevention programme
## Comparing tamoxifen with anastrozole

<table>
<thead>
<tr>
<th></th>
<th>Completion analysis (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td><strong>Hot flushes</strong></td>
<td>35.7</td>
<td>40.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Vaginal bleeding</strong></td>
<td>5.4</td>
<td>10.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Vaginal discharge</strong></td>
<td>3.5</td>
<td>13.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td>0.2</td>
<td>0.8</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Ischaemic cerebrovascular event</strong></td>
<td>2.0</td>
<td>2.8</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Venous thromboembolic events</strong></td>
<td>2.8</td>
<td>4.5</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Deep venous thromboembolic events</strong></td>
<td>1.6</td>
<td>2.4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Joint symptoms</strong></td>
<td>35.6</td>
<td>29.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Total fractures</strong></td>
<td>11.0</td>
<td>7.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

IBIS-II: 5 years anti-E therapy
Current status

- Prevention: Anastrozole versus Placebo
  - N = 2284/6000
- ER+ DCIS: Anastrozole versus Tamoxifen
  - N = 1686/4000

19 countries

- UK: 1764
- Germany: 511
- ANZ: 390
- Italy: 357
- France: 298
- Belgium: 124

Manuscripts/Abstracts:
- Cognitive function study
- Bone study

Mainly DCIS
Preventing ER- Breast Cancers?


NSAIDs, COX-2 inhibitors, retinoids, statins

Triple-negative breast cancers express receptors for GHRH and respond to GHRH antagonists with growth inhibition.
Three potential mechanisms through which growth-hormone-releasing hormone (GHRH) antagonists mediate the inhibition of tumor growth

Nat Clin Pract Endocrinol Metab 4: 33–43 doi:10.1038/ncpendmet0677
Life style changes
Physical activity
Weight Loss
Diet
Premenopausal breast cancer
She is not “yet” at risk

Anovulatory cycle and less progestins
but once in the menopause
Doctors Seek To Prevent Breast Cancer Recurrence by Lowering Insulin Levels

Insulin in the adjuvant breast cancer setting: a novel therapeutic target for lifestyle and pharmacologic interventions?

BMJ 330:1304-1305, 2005
Metformin and reduced risk of cancer in diabetic patients.

Galega officinalis has been known since the Middle Ages for relieving the symptoms of diabetes.
On-going trials for chemoprevention

- Phyto-Oestrogens, Omega-3 FA, …
- Weight bearing exercises,…
- Letrozole, Exemestane
- Celecoxib
- LHRH + Raloxifene
- Atorvastin
- cHCG

www.clinicaltrials.gov
Case #1

- A 40 yrs patient presents for her annual physical exam. Last year she had a wide excision for LCIS right breast. On her history, she has a paternal grandmother, and two paternal aunts who had breast cancer, all after age 50. Her father has had prostate cancer at 55 years and he tested negative for the BRCA mutation.

- *Is she a high breast cancer risk patient?*
- *Would you suggest 5 years of tamoxifen?*
- *What if she is 55, has no uterus and if she is not obese*
  - *IBIS-II trial?*
  - *Or do you already give tamoxifen?*
Case #2

- A 45 yrs female patient had a mastectomy and breast reconstruction for ER-positive right breast.
  - Is she a high-risk patient for CL breast cancer?
  - Would you suggest 5 years of tamoxifen?
  - What if she is 55
    - IBIS-II prevention trial?
    - Or do you already give tamoxifen?
    - If osteoporosis: Raloxifene
Case #3

- A 40 yrs patient presents for her check up. On family history, her mother died at age 35 from breast cancer. She is BRCA-2 positive. The patient has already seen a genetic counselor, and informs she does not want prophylactic surgery and opts for self examination, a yearly mammogram, breast ultrasound and MRIs

- Should she be offered chemoprophylaxis?

- Type of preventive treatment:
- Which tumor do we want to prevent:
- Durability of the preventive effect:
- Influence on mortality
- Subsets who really benefit from treatment
- Interaction with HR
- Preventive effect in BRCA1/2 carriers
Breast cancer chemoprevention in the high-risk patient

Pharmacological compounds to prevent the development of breast cancer

An update

Belgian Breast Meeting 2008

Thanks for your attention!
The Tumor Cell

Targeted therapies

Tam
The highest risk factor for breast cancer is having a gene mutation in either *BRCA1* or *BRCA2*

- Both are autosomal dominant, high-penetrance genes
- Normally function as a tumor suppressor
- Over 30 known mutations
- 35% to 85% lifetime risk of breast cancer
- 10% to 50% lifetime risk of ovarian cancer
Hormonal Preventive Effect in BRCA1/2 Carriers

- Early reports suggested that there is a loss of ER and PgR in tumors with BRCA1 mutations, whereas tumors with BRCA2 mutations are often ER positive\(^1\).

- The critical question is whether breast cancer prevention, specifically hormone-therapy, would also reduce incidence of invasive BC among cancer-free women with inherited BRCA1 or BRCA2 mutations.

\(^1\)Johannsson et al., Eur J Cancer 33: 362-371; 1997
Study participants who developed BC in 288 genotyped cases (NSABP-P1, JAMA, Nov 14, 2001)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TAM</th>
<th>Risk Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mut.</td>
<td>3</td>
<td>5</td>
<td>1.67 (0.32-10.70)</td>
</tr>
<tr>
<td>BRCA2 mut.</td>
<td>8</td>
<td>3</td>
<td>0.38 (0.06-1.56)</td>
</tr>
<tr>
<td>BRCA WT</td>
<td>182</td>
<td>87</td>
<td>0.48 (0.37-0.61)</td>
</tr>
<tr>
<td>All participants*</td>
<td>211</td>
<td>109</td>
<td>0.52 (0.41-0.65)</td>
</tr>
</tbody>
</table>

Includes 288 genotyped cases and 32 cases without DNA available.
Preventive effect in BRCA1/2 carriers

- In BC treatment, oophorectomy, tamoxifen, or anti-aromatase agents are effective.
- If oophorectomy, performed before 35 years, is effective in reducing BC incidence among women with BRCA1 mutations (Rebbeck et al., JNCI, 1999), then TAM or anti-aromatase agents might be effective in cancer-free women with BRCA1 mutations.
- It is possible that early in the course of BRCA1 tumors, hormone-therapy might still have a role to play.
Chemopreventive trials in BRCA mutated carriers

- Which treatment?
  - Tamoxifen.
  - LH-RH agonists & aromatase inhibitors (premenopausal women).
  - Aromatase inhibitors (postmenopausal women).
Exemestane:
Rationale for Use in BC Prevention

- Exemestane inhibits in situ aromatase by more than 95%.
- It also reduces endogenous oestrogen concentrations in BC. The treatment with irreversible aromatase inhibitors has been demonstrated to completely abrogate estrogen production, at the level of mammary gland.
- Suppressing local estrogen production may be important, as suggested by the discovery of a unique transcriptional promoter of aromatase gene expression in breast adipose tissue.
Exemestane: Rationale for Use in BC Prevention

- Preventive effect in preclinical models
- Decreased levels of aromatase enzyme (instead of the increase observed after non-steroidal anti-arommatase agents)
- Activity in advanced breast cancer
- Improved tolerability vs TAM
- No negative effects on lipids
- Preclinical and clinical favourable bone data
ApreS (Aromasin® Prevention Study)

- Double-Blind, Placebo-Controlled Study of Exemestane for the Prevention of Breast Cancer in Postmenopausal Unaffected Carriers of BRCA1/2 Mutations

- Participating Italian Institutions (partial list):
  - Italian Consortium HB/OC (G. Bevilacqua)
  - Cooperative group for the identification of families at BC risk in Italy (V. Silingardi, S. Venuta)
  - IRE Rome (F. Cognetti, M. Lopez, E. Terzoli), University of Napoli (A.R. Bianco, S. De Placido, A. Contegiacomo), University of Modena (M. Federico), University of L’Aquila (C. Ficorella, P. Marchetti), University of Chieti (S. Iacobelli, R. Mariani Costantini), University of Padova (Chieco Bianchi, E. D'Andrea, Monfardini), University of Messina (M. Mesiti), University of Ancona (R. Cellerino, A. Piga), University of Torino (P. Sismondi), Catholic University, Roma (G. Scambia, D. Terribile), Medical Oncology, Terni (F. Di Costanzo).
  - Participation of 4 more European cooperative groups is pending.
ApreS
Primary End-Point

The efficacy of the irreversible aromatase inhibitor exemestane in preventing breast cancer by significantly reducing the incidence rate of invasive breast cancer in unaffected postmenopausal women carriers of BRCA1/BRCA2 inactivation.
Defining the target: Lowering NNT

5408; hysterectomy; 11 j FU; 136 events: 2,48/1000/j $\Rightarrow$ 2,07/1000/j
702; 2 ovaries; tall; menarche; P0: 6,26/1000/j $\Rightarrow$ 1,50/1000/j

J Natl Cancer Inst. 2007 May 2;99(9):727-37.
LCIS/ADH

- IBIS I (n=7152):
  - 88/201 Vrouwen
  - Geen stratificatie
- NSABP-P1: (n=13338)
  - 826/1193 pre- en postmenopauzale vrouwen
  - 56% en 75% Vermindering ER+ Borstkanker

IBIS-II: 6000 postmenopauzale vrouwen met hoog risico
LCIS/ ADH/ DCIS and mastectomy
Familial history
Anastrazole versus Placebo
Low-dose tamoxifen and fenretinide

Premenopausal women
DCIS, LCIS

Gail ≥ 1.3% in 5 yrs

I endpoint:  Δ IGFs and Mx density

II endpoint:  Δ endometrial and ovarian effects
Δ breast FNA (image analysis)

Sample size:  300 subjects
The HOT (Hormone Replacement Therapy and Tamoxifen) Study

HRT users
(de novo or current users)

R

Placebo/day

Tamoxifen 5 mg/day

Sample size: 8500 subjects (4250 per arm)

Endpoint: Breast cancer incidence (IBC and DCIS)
### Proportion of disease prevalence attributable to obesity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>57%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>17%</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>30%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>14%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>11%</td>
</tr>
<tr>
<td>Uterine cancer</td>
<td>11%</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>11%</td>
</tr>
</tbody>
</table>

Approach to the high-risk patient

- Increased surveillance
  - Recommended for all patients
- Referral to genetic counseling if high-risk due to family history
  - BRCA testing
- Prevention
  - Prophylactic medication (chemoprevention)
    - Selective estrogen receptor modulators (SERMs)
      - Tamoxifen
      - Raloxifene
      - Aromatase inhibitors
  - Prophylactic surgery
    - Bilateral mastectomy
    - Bilateral oophorectomy
Risk assessment tools

- **Gail model**
  - Uses predominantly clinical history
  - Estimates 5-yr and lifetime breast cancer risk
  - [www.breastcancerprevention.org](http://www.breastcancerprevention.org)
    - National Surgical Adjuvant Breast and Bowel Project
  - [www.cancer.gov/bcrisktool](http://www.cancer.gov/bcrisktool)
    - National Cancer Institute

- **Claus model**
  - Uses family history only

- **Tyrer-Cuzick model**

- **BRCAPRO**
Risk assessment tools-- Gail model

- Most commonly used by clinicians
- Least accurate
- Based on
  - National Surgical Adjuvant Breast and Bowel Project
  - Breast Cancer Detection and Demonstration Project
- Looks at
  - Current age, age at menarche, age at first live birth, number of prior breast biopsies, biopsy results, # of first degree relatives with breast cancer, and race
- Limitations
  - Does not account for extended family history, history of chest radiation, breast density
  - A calculated 5-year risk of breast cancer of $\geq 1.67\%$ is high-risk
    - Women age 35 or older with a 5-yr breast cancer risk of 1.67% or more were included in the first breast cancer chemoprevention trial
Sample Gail model calculation

- Hx of breast cancer, DCIS, or LCIS: No
- Woman’s age: 36
- Age of menarche: 12 to 13
- Age at first birth of child: >30
- First-degree relatives with breast cancer: 0
- Hx of breast biopsy: No
- Race: White

- 5 year risk
  - This patient: 0.5%
  - Average patient: 0.3%

- Lifetime risk
  - This patient: 13.8%
  - Average patient: 12.5%
Tamoxifen

- Selective Estrogen Receptor Modulator (SERM)
  - Competes with estrogen for estrogen receptors on breast cancer cells
    - Blocks estrogen uptake
    - Prevents cell growth
- FDA-labeled for breast cancer prophylaxis in high-risk patients
  - >35 yo with a Gail model 5-yr risk of ≥1.67%
- Dose 20 mg orally daily for 5 years
Tamoxifen

- Only acts on estrogen receptor positive tumors (ER+)
  - BRCA2 gene mutation carriers can have estrogen receptor positive or negative tumors
    - Tamoxifen is effective only in the subset of patients who are ER+
  - BRCA1 gene mutation carriers are usually estrogen receptor negative
    - Tamoxifen is ineffective for most of these patients
    - Oophorectomy is effective …
Tamoxifen

- Increased risks of
  - Uterine cancer
  - Stroke
  - Myocardial infarction
  - Thromboemboli (DVT, PE)
  - Cataracts

- Decreased risks of
  - Osteoporosis
  - Hyperlipidemia

- Side effects
  - Hot flashes, night sweats, irregular menses
Chemoprophylaxis of breast cancer

- **Best for**
  - Women in their 40s who are at increased risk for breast cancer and have no predisposition to thromboembolism
  - Women in their 50s who are at increased risk for breast cancer, have no predisposition to thromboembolism, and do not have a uterus.

- **Less beneficial for**
  - Women in their 30s (less risk of breast cancer)
  - Women > age 60 (increased risk of thromboembolism)
Aromatase inhibitors

- Block the peripheral conversion of androstenedione to estrone and testosterone to estradiol
- Not yet approved for prophylaxis
- Anastrazole, Tamoxifen, Alone or in Combination (ATAC) trial (Lancet 2002)
  - Multicenter, international, double-blind, RCT
  - 9,366 postmenopausal women with early stage breast cancer
  - After 33 months statistically significant >50% reduction in contralateral primary invasive breast cancers in the anastrazole alone group
Prophylactic oophorectomy

- In women who have a known BRCA mutation, prophylactic oophorectomy can decrease breast cancer incidence by 50%

- Insufficient evidence regarding mortality benefit

- Adverse effects
  - Premature menopause
    - Increased risks of osteoporosis, cardiovascular disease
Identifying high-risk patients in clinic

- Any FH of breast or ovarian cancer?
  - Any 1º or 2º relative with both breast and ovarian cancer?
  - Any male relatives with breast cancer?
  - Any 1º relative with cancer in both breasts?
  - Two or more 1º relatives?
  - Three or more 1º or 2º relatives?
  - Both breast and ovarian cancer in 1º or 2º relatives?
  - Two or more 1º or 2º relatives with ovarian cancer?
  - Has a relative tested positive for a BRCA gene mutation?
  - Has the patient tested positive for a BRCA gene mutation?

- Gail model 5-yr risk ≥ 1.67%?
- Lifetime risk ≥ 20%
- Therapeutic chest radiation ages 10-30?
- HRT ≥ 10 yrs?
- Dense breast tissue?
- Atypical hyperplasia, LCIS, or prior breast cancer?
Summary--Management options for high-risk women

- Surveillance
  - SBE?
  - CBE yearly (? or q 6 mos)
  - Annual mammogram (? age to start)
    - Once determined high-risk
    - 10 years younger than age of youngest affected first degree relative
    - Age 25 if BRCA mutation carrier
- Annual MRI
  - Starting at age 30 if they meet the ACS criteria
    - Known BRCA mutation
    - 1º relative with a BRCA mutation, and patient untested
    - 20% or greater lifetime risk of breast cancer
    - Chest radiation exposure between ages 10 and 30 yrs
  - And consider even if they don’t meet ACS criteria…
    - Lifetime breast cancer risk 15-20%
    - Mammographically dense breasts
    - Personal history of atypia, LCIS, breast cancer
Summary--Management options for high-risk women

**Genetic testing**
- If high-risk based on family history
  - To help guide surveillance and prophylaxis

**Chemoprophylaxis**
- If *BRCA* mutation carrier
- If Gail 5-yr risk ≥ 1.67%
- Use of tamoxifen or raloxifene

**Surgical prophylaxis**
- If *BRCA* mutation carrier
  - Mastectomy and/or oophorectomy
References

P-2 STAR
Annual Rate and Number of Invasive Breast Cancers by 5-year Predicted Risk*

*Determined using Gail Model
†No. of events

Vogel VG et al. JAMA 2006;295:2727-41
<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726 6682 814</td>
<td>141</td>
<td>21.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745 6764 836</td>
<td>100</td>
<td>16.0</td>
<td></td>
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</tbody>
</table>

P-value = 0.01