CHEMOPREVENTION in BREAST CANCER

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Outline

- Risk Assessment
- Molecular Targets
- ER positive Breast Cancer
  - Tamoxifen
  - Raloxifene
  - Lasofoxifene
  - Aromatase Inhibitors
- ER negative Breast Cancer
  - Retinoids
  - Lapatinib
  - Metformin
- ASCO 2009 Guideline
Essential Elements for Breast Cancer Prevention Trials

- Population with defined, quantifiable risk
  - Gail model
  - NCI Breast Cancer Risk Assessment Tool
- A reasonable target
- An acceptable intervention
- A measurable endpoint
  - Reduction in BC incidence
  - Biomarker modulation
NCI Breast Cancer Risk Assessment Tool

Risk Calculator

(Click a question number for a brief explanation, or read all explanations.)

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?

2. What is the woman's age? This tool only calculates risk for women 35 years of age or older.

3. What was the woman's age at the time of her first menstrual period?

4. What was the woman's age at the time of her first live birth of a child?

5. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer?

6. Has the woman ever had a breast biopsy?

6a. How many breast biopsies (positive or negative) has the woman had?

6b. Has the woman had at least one breast biopsy with atypical hyperplasia?

7. What is the woman's race/ethnicity?

http://www.cancer.gov/bcrisktool/
Gail Model

Projecting individualized probabilities of developing breast cancer for white females who are being examined annually

- To assist in medical counseling, a method to estimate the chance that a woman with given age and risk factors will develop breast cancer over a specified interval.

- The risk factors used were
  - age at menarche,
  - age at first live birth,
  - number of previous biopsies,
  - number of first-degree relatives with breast cancer.

Approaches to Prevention

- Lifestyle factors
  - Diet – Weight control
  - Exercise
  - Reproductive factors
  - Exogenous hormones
- Chemoprevention
- Surgical prevention
Management Plan

- Age
- Family history
- Prior biopsy & histologic results
- Fertility history
Functional Characterization Of Molecular Targets For Breast Cancer Therapy

Tamoxifen
- Five years of tamoxifen (20 mg/d)
  - Women at increased risk of breast cancer to reduce their risk of ER positive invasive breast cancers for up to 10 years.
- The benefit of taking tamoxifen for more than 5 years is unknown.
- The greatest clinical benefit and the fewest side effects were derived from the use of tamoxifen in younger (premenopausal) women 35 to 50 years of age who are unlikely to experience thromboembolic sequelae or uterine cancer, women without a uterus, and women at high risk of breast cancer.
Four phase III randomized trials have prospectively evaluated tamoxifen compared with placebo for breast cancer risk reduction:

- NSABP-P1
- IBIS-I
- Royal Marsden Tamoxifen Prevention Trial
- Italian Randomized Tamoxifen Prevention Trial
NSABP-P1

- 13,388 women
  - 35 years or older who were at increased risk of breast cancer (ie, 35 to 59 years of age with a 1.66 risk using a modified Gail model, 60 years old, or with prior LCIS)
- Women were excluded if they were using HT, oral contraceptives or androgens, or if they had used these 3 months before randomization.
- Placebo or tamoxifen (20 mg/d) for 5 years
- The initial results were based on a median of 4.6 years of followup.
  - Invasive BC 89 vs 175
    - RR reduction of 49%
    - Absolute risk reduction of 15 invasive breast cancers per 1,000 women
  - Noninvasive cancers 50% reduction
    - Absolute risk reduction of six invasive breast cancers per 1,000 women
  - Fewer ER-positive tumors 41 vs 130
    - Overall RR reduction of 69%
    - Reduction of 16 ER-positive breast cancers per 1,000 women
  - The incidence of ER negative tumors was similar between groups, 38 vs 31

NSABP-P1: 7 yr followup

- The reduction in both invasive (RR 0.57) and noninvasive (RR 0.63) BC persisted.
  - 250 invasive breast cancers vs 145
  - 93 noninvasive breast cancers vs 60
- No statistically significant difference in stage distribution of invasive BC between the two groups.
- There was a reduction in ER+ tumors of 62% in the tamoxifen group (RR 0.38)
  - 70 vs 182
- No statistically significant difference in ER-negative tumors (RR 1.31).
- Tamoxifen consistently reduced invasive BC risk, particularly ER-positive tumors, in all age strata, all 5-year predicted risk strata for breast cancer (beginning at 1.66%), and women with atypical hyperplasia (AH) or a history of LCIS.
- The magnitude of the protective benefit in the updated results was similar to the initial report.
- NSABP-P1 trial unblinded participants in 1998, with subsequent differential rates of withdrawal from the placebo arm versus the treatment arm, and cross-over from the placebo arm to the tamoxifen arm. These circumstances may have biased the reported estimates of benefits and risks toward the null.

Fisher B, et al. JNCI 2005
IBIS-I

- 7,154 women age 35 to 70 years, who were at increased risk of BC, to receive either tamoxifen (20 mg/d) or placebo for 5 years
- Absolute risk reduction of 15 breast cancers per 1,000 women
- No difference in the risk of ER-negative invasive tumors (35 in each group)
- The risk of ER-positive invasive BC 34% lower in the tamoxifen arm (87 cases v 132 cases)
  - Absolute risk reduction of 13 ER-positive breast cancers per 1,000 women
- A decrease in DCIS but not statistically significant (17 women on tamoxifen with DCIS compared with 27 women on placebo).
- These follow-up results suggest that the risk-reducing effect of tamoxifen persists for at least 10 years.

*Cuzick J, et al. JNCI 2007*
Royal Marsden Tamoxifen Prevention Trial

- 2,494 healthy women age 30 to 70 years to receive tamoxifen (20 mg/d) or placebo for 8 years.
- Initial results showed no effect of tamoxifen on the incidence of breast cancer.
- With a median of 13.2 years of follow-up and a maximum of 20 years, also showed no statistically significant effect of tamoxifen on the overall incidence of breast cancer.
- There was also no statistically significant difference in the incidence of invasive BC.
- The incidence of ER-positive invasive BC was 39% lower in the tamoxifen group over the entire period, (53 vs 86 women).
- Absolute reduction of 26 ER-positive BC per 1,000 women over the 13.2 years median follow-up period.
- There was no effect of tamoxifen on the incidence of ER-positive BC during active treatment.
- The variable benefit of tamoxifen in reducing the incidence of ER-positive BC during and after treatment in this study is likely a reflection of a small sample size rather than a meaningful difference when compared with the benefits observed in the NSABP-P1 and IBIS-I studies.

Powles TJ, et al. JNCI 2007
Italian Randomized Tamoxifen Prevention Trial

- 5,408 women age 35 to 70 years with a prior hysterectomy and no prespecified breast cancer risk to receive tamoxifen (20 mg/d) or placebo for 5 years. Their breast cancer risk was lower than that of the general population, because 48% of participants had undergone a bilateral oophorectomy.

- No statistically significant reduction in overall breast cancer risk observed in the tamoxifen group
  \[ n \quad 62 \text{ vs } 74 \]

- A statistically significant reduction in progesterone receptor–positive tumors
  \[ n \quad 27 \text{ vs } 44 \]

- A reduction in breast cancer risk among women at high risk with at least one ovary intact

- No effect of tamoxifen on ER-negative breast cancer

*Veronesi U, et al. JNCI 2007*
Overview of the main outcomes in breast-cancer prevention trials

- The combined reduction in breast cancer incidence (invasive and DCIS) with tamoxifen use compared with placebo ranged from a relative risk of 34% to 38%.
- There was no reduction in the risk of ER-negative BC.
- The incidence of ER-positive BC decreased by 48%.
- Age had no apparent effect on the relative degree of BC risk reduction.
Adverse Events and Side Effects Related to Tamoxifen Use

- Endometrial cancer (grade I adenocarcinoma)
- Thromboembolic events (PE, DVT, retinal vein thrombosis)
- Stroke
- Cataracts
- Cognition (inconclusive)
- Gynecologic and vasomotor symptoms (vaginal discharge)
- Fractures
- Mortality
  - No overall effect of tamoxifen on all-cause mortality
  - PE was the only cause of death showing an increase with tamoxifen use
  - None of the prevention trials have demonstrated an effect of tamoxifen on breast cancer–specific mortality
For postmenopausal women at increased risk for BC, raloxifene (60 mg/d) for 5 years may be offered as another option to reduce the risk of ER positive invasive BC.

Equally efficacious to tamoxifen in reducing BC risk in postmenopausal women.

Not as effective in reducing the incidence of noninvasive BC compared with tamoxifen.

In the STAR trial, raloxifene was associated with a more favorable side-effect profile compared with tamoxifen, including a statistically significant lower risk of thromboembolic disease, benign uterine complaints, and cataracts as compared with tamoxifen.

Not known to have an effect on overall or breast cancer–specific mortality in women at increased risk of BC.

Raloxifene may be used for longer than 5 years in women with osteoporosis in whom BC risk reduction is an additional potential benefit.
**Raloxifene**

- Four randomized prospective trials have evaluated the influence of raloxifene on breast cancer risk.
- Risk reduction was the primary end point of two trials,
  - STAR and RUTH trials,
- A secondary end point of the
  - MORE trial.
- Also the primary end point of the
  - CORE trial, which followed a subgroup of participants from the MORE trial.
MORE and CORE Trials

- 7,705 postmenopausal women with osteoporosis who were \( \leq 80 \) years of age
- Raloxifene (60 or 120 mg/d) or placebo for 4 years.
- Participants were entered regardless of BC risk, which was not formally assessed at study entry, although information on breast cancer family history was collected and presented.
  - Breast cancer was a secondary outcome.
- 78 cases of BC in 7,682 women (44/2571 placebo vs 34/5111 Raloxifene)
  - 59 were invasive BC and 19 were noninvasive.
  - Women treated with raloxifene had a statistically significant reduced risk of invasive BC compared with women on placebo particularly ER positive invasive BC
MORE and CORE Trials

- After the completion of the MORE trial, consenting participants were observed under an amended design called the CORE trial, which reconsented 4,011 MORE trial participants (52%).
- CORE participants had 5-year breast cancer risk assessed at study entry with the Gail model.
- 4 years of additional raloxifene use reduced invasive BC by 59% compared with placebo and ER-positive invasive BC by 66% compared with placebo.
- Through 8 years of randomization from the MORE trial to the end of the CORE trial, raloxifene continued to significantly reduce the risk of overall BC, invasive BC, and ER-positive BC.
- The incidence of ER-negative invasive BC was similar in the two treatment groups throughout the 8 years of treatment.
Raloxifene (60 mg/d) vs placebo in 10,101 postmenopausal women with coronary heart disease or multiple risk factors for coronary heart disease.

The two primary outcome measures were coronary events and invasive BC.

Participants were entered regardless of BC risk, and only 41% had a 5-year predicted BC risk of 1.66%.

Not influence the risk of primary coronary events

Significantly reduced invasive BC risk primarily due to reduced ERpositive BC
NSABP STAR

- 19,747 postmenopausal women with a 5-year increased risk of BC
- Tamoxifen (20 mg/d) or raloxifene (60 mg/d) for 5 years.
- The same risk assessment used in NSABP-P1.
- The primary end point was a reduction in BC risk.
- Baseline characteristics were substantially different from the prior NSABP-P1 tamoxifen prevention trial.
  - 5-year projected breast cancer risk was higher (58.7% had a 3% 5-year projected breast cancer risk in the STAR trial, compared with 44% in the NSABP-P1 trial).
  - More than 51% of STAR participants had a prior hysterectomy as compared with 37% of participants in the NSABP-P1 tamoxifen prevention trial.
  - More than 32% of STAR participants had a history of breast LCIS or AH compared with 15% of NSABP-P1 participants.
- The incidence of invasive breast cancer in the tamoxifen and raloxifene groups were not significantly different.
- More noninvasive breast cancers in the raloxifene (n80) group than in the tamoxifen (n57) group, not statistically significant.
- Findings were also comparable for women diagnosed with ER-positive tumors
Adverse Events and Side Effects Related to Raloxifene Use

- Endometrial cancer (Tmx > Ral)
- VTE (Tmx > Ral)
- Ischemic Heart Disease (no increase) (Tmx = Ral)
- Stroke (women with underlying vascular disease should not be treated with raloxifene)
- Cataracts (no increase)
- Cognition (inconclusive)
- Gynecologic and vasomotor symptoms (Tmx > Ral)
- Fractures (reduced)
- Mortality
  - No effect of raloxifene on the incidence of death in these trials
  - None of the prevention trials have demonstrated an effect of raloxifene on breast cancer–specific mortality
Lasofoxifene

- Third generation SERM
- The randomised, placebo-controlled Postmenopausal Evaluation and Risk-Reduction With Lasofoxifene (PEARL) study
  - 8,556 otherwise healthy women aged 59 to 80 years
  - 0.5 mg/day vs placebo or 0.25 mg/day vs placebo, for 5 years
  - The primary endpoints were incidence of oestrogen receptor-positive (ER+) breast cancer and vertebral fracture (at 3 years) and nonvertebral fracture (at 5 years)
  - Increased protection against BC in postmenopausal women with osteoporosis and a high risk of BC

Powles T, et al. St Gallen 2009
SERMs in the Prevention of Breast Cancer

- 35% reduction in BC
- 53% reduction in ER+ BC

Cuzick J. SABCS, 2009
Adverse Events and Side Effects Related to SERM Use

- Inc endometrial cancer (Tmx)
- No effect on colorectal, ovarian or other cancer
- Inc DVT, PE & retinal vein thrombosis
- Dec fractures (Las)
- Inc hysterectomy (Tmx)
- No effect on mortality, incidence of stroke, TIA, MI, cataract

*Cuzick J. SABCS, 2009*
Aromatase Inhibitors

- The effects of aromatase inhibitors (anastrozole, letrozole) and inactivators (exemestane) on contralateral BC risk support further evaluation of these agents for BC risk reduction.

- A meta-analysis of adjuvant breast cancer trials evaluating aromatase inhibitors identified a 48% relative reduction in contralateral BC risk with five of the six comparators being tamoxifen.

*Cuzick J. J Clin Oncol, 2005*
Contralateral Tumors in AI Trials

Cuzick J. SABCS, 2009
The concept of using aromatase inhibitors as a BC risk reduction agent was strengthened by the recent update of the ATAC trial, in which, with 100 months of follow-up, 5 years of anastrozole was associated with fewer contralateral breast cancers as a first event compared with 5 years of tamoxifen (for hormone receptor-positive patients).

IBIS-II

6,000 postmenopausal women at increased breast cancer risk to 5 years of placebo or anastrozole (1 mg/d)
ExCel

4560 postmenopausal women either at increased BC risk or age 60 years to 5 years of exemestane (25 mg/d) or placebo
Direct Effects of Hormonal Manipulation

- **In vitro**
  - Growth inhibition
  - No effect

- **In vivo**
  - Oestrogen drives micrometastasis
  - Tamoxifen inhibits micrometastasis
  - Tamoxifen inhibits tumour growth and survival
  - Tamoxifen inhibits CXCL12 production and therefore reduces micrometastasis

Nature Reviews | Cancer
Prevention of ER-negative Breast Cancer

![Diagram showing novel targets for the prevention of ER-negative Breast Cancer](image-url)
ER-Negative Breast Cancer

- All of the breast cancer risk reduction trials using SERMs demonstrate that these agents are effective in reducing the risk of only ER-positive breast cancer.
- They do not prevent the development of ER-negative breast cancer, which accounts for 30% of all breast cancers.
- Tamoxifen did, however, seem to increase the sensitivity of mammography for the detection of ER-negative tumors in the NSABP-P1 trial.
  - ER-negative tumors were found earlier and were smaller in women treated with tamoxifen in comparison with women on placebo.
- There is a need to develop agents that also prevent ER-negative breast cancer.
ER-Negative Breast Cancer

- Several classes of chemopreventive agents have been shown to prevent ER-negative breast cancer in animal models.
  - Retinoids and rexinoids (9-cis retinoic acid, bexarotene, and LG100268),
  - Cox-2 inhibitor (celecoxib)
  - Tyrosine kinase inhibitors (gefitinib and lapatinib).
- Several of these agents are now being tested in early-phase risk reduction trials involving biomarker modulation.
- In the future, these cancer risk reduction drugs will be combined with hormonal agents (such as SERMs or aromatase inhibitors) to reduce the risk for both ER-positive and ER-negative breast cancer.
Retinoids

- Fenretinide is the only retinoid that has been evaluated in a phase III study for secondary BC prevention.
- 3,000 women age 30 to 70 years with a diagnosis of DCIS or stage I BC
- 5 years of fenretinide (200 mg/d) or no treatment, in addition to standard tx
- The primary end point of this study was the incidence of second BC
- At a median follow-up time of 97 months, there was no statistically significant difference in overall BC incidence between the two arms.
- Further follow-up of a subset of women (59%) over a median of almost 15 years continued to observe no difference in overall BC incidence between the two groups. In a subset analysis, a statistically significant reduction in second primary BC was observed among the premenopausal women treated with fenretinide
- No difference was observed in overall mortality between the study arms.
- Dermatologic and dark-vision adaptations were the most common adverse events.
ER-Negative Breast Cancer

A new subclassification scheme for ER-negative breast cancer based upon kinome-wide gene expression profiling, potentially relevant for both treatment and clinical outcome.

Panel of Kinases Define Four ER-negative Breast Cancer Sub-sets

<table>
<thead>
<tr>
<th>ER-Neg / Her2-Neg</th>
<th>ER-Neg / Her2-Pos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER (-), Her2 (-)</strong></td>
<td><strong>ER (-), Her2 (+)</strong></td>
</tr>
<tr>
<td>Mitotic checkpoint cluster</td>
<td>MAPK signaling cluster</td>
</tr>
<tr>
<td>S6 Kinase pathway cluster</td>
<td>Immunomodulatory cluster</td>
</tr>
</tbody>
</table>

- BUB1
- CHK1 checkpoint homolog
- TTK protein kinase
- serum/glucoc. reg. kinase
- SFRS protein kinase 1
- maternal embryonic leucine zipper kinase
- RYK tyrosine kinase
- phosphoglycerate kinase
- selenophosphate synthetase
- uridine-cytidine kinase 2
- UDP-glucose pyrophosphorylase 2
- adenylate kinase 2
- S6 kinase
- SMG-1 kinase
- EPH receptor B4
- ser/thr kinase 38 like (NDR2)
- DAPK 1
- pim-1 oncogene
- LIM domain kinase
- Phosphoribosyl pyrophosphate synthetase
- MAP3K5
- MAP2K6
- c-raf-1
- PTK7
- myelin protein zero-like 1
- guanylate kinase
- tyrosine 3-monooxygenase - activation protein
- phosphofructokinase
- CDC2-related protein kinase
- chemokine ligand 10
- interleukin-1 receptor-associated kinase 1
- LYN
- LCK
- lymphocyte-specific PTK
- toll-like receptor 1
- chemokine ligand 4
- serine/threonine kinase 17b
- pyridoxal/Vit B6 kinase
- Yes-1

*Speers et al. Clin Cancer Res 2009*
Lapatinib

Prevention of Mammary Tumors by Lapatinib

- **Randomize**
  - Lapatinib (75 mg/kg) N = 20
  - Lapatinib (30 mg/kg) N = 20
  - Vehicle N = 20

- **Endpoints:**
  - Time to Tumor Formation
  - Tumor Number
  - Biomarker Expression

**MMTV-erbB2 Mice**

- **3 mos**
- **16 mos**

**Survival**

- P < 0.001

- 70%

T. Strecker, JNCI, 2009
Lapatinib Suppresses Mammary Tumorigenesis: Incidence of Early Lesions after 5 Months of Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Glands Examined</th>
<th>Number of Lesions</th>
<th># MG Showing Any Lesion</th>
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<tr>
<td>Vehicle</td>
<td>20</td>
<td>16</td>
<td>3</td>
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<tr>
<td>Lapatinib</td>
<td>20</td>
<td>8</td>
<td>1</td>
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<tr>
<td>P Value</td>
<td></td>
<td>0.02</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

T. Strecker, JNCI, 2009
Metformin

- Managing breast cancer with a diabetes drug?
- Epidemiological data:
  - Lower cancer rates in diabetics taking metformin
  - Potentially better response to chemotherapy
- Plausible biologic mechanism
- Growing preclinical data
  - Animal models
  - Increased apoptosis in cell culture
Metformin use associated with lower risk of cancer in 11,876 newly dx diabetics

- Any metformin use associated with significantly lower risk of cancer

(OR 0.77; 95% CI 0.64-0.92)

Evans, JM. BMJ, 2005
Metformin use associated with decreased cancer-related mortality

- 10,309 new users of metformin or sulfonylureas; 5.4 years median follow up

<table>
<thead>
<tr>
<th>Oral antidiabetics</th>
<th>Total n</th>
<th>Cancer deaths</th>
<th>Cancer mortality rate (per 1,000 person-years) (%)</th>
<th>Adjusted HR (95% CI)*</th>
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</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>6,969</td>
<td>243 (3.3)</td>
<td>6.3</td>
<td>1.0†</td>
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<tr>
<td>Sulfonylurea</td>
<td>3,340</td>
<td>162 (4.9)</td>
<td>9.7</td>
<td>1.3 (1.1–1.6)</td>
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<td>Insulin use</td>
<td></td>
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<tr>
<td>No insulin use</td>
<td>8,866</td>
<td>323 (3.6)</td>
<td>6.8</td>
<td>1.0†</td>
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<tr>
<td>Insulin use</td>
<td>1,443</td>
<td>84 (5.8)</td>
<td>9.9</td>
<td>1.9 (1.5–2.4)</td>
</tr>
</tbody>
</table>
Metformin
Preclinical and Clinical Studies

NCIC MA-32

N: 3582 breast cancer patients
- Completed with primary therapy
- Within 12 months of definitive surgery

Primary Outcome: Invasive Disease Free Survival

Metformin: 850mg/BID for 5 years
Placebo

Randomize
ASCO Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction

<table>
<thead>
<tr>
<th>Agent</th>
<th>2009 Recommendation</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>May be offered to reduce the risk of ER-positive invasive BC for premenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown. May be offered to reduce the risk of ER-positive invasive BC for postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool), or with LCIS. Risk reduction benefit continues for at least 10 years. Impact on BC mortality is unknown. Is not recommended for women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack. Combined use of tamoxifen for BC prevention and hormone therapy is currently not recommended. Follow-up should include a baseline gynecologic examination before initiation of treatment and annually thereafter, with a timely work-up of abnormal vaginal bleeding. Risks and benefits should be given careful consideration during the decision-making process.</td>
<td>20 mg/d for 5 years</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>May be offered to reduce the risk of ER-positive invasive BC in postmenopausal women with a 5-year projected BC risk ≥ 1.66% (according to the NCI Breast Cancer Risk Assessment Tool) or with LCIS. Impact on BC mortality is unknown. May be used longer than 5 years in women with osteoporosis, in whom BC risk reduction is a secondary benefit. Should not be used for BC risk reduction in premenopausal women. Is not recommended for use in women with a prior history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack. Risks and benefits should be given careful consideration during the decision-making process.</td>
<td>60 mg/d for 5 years</td>
</tr>
<tr>
<td>Fenretinide</td>
<td>Use is not recommended outside of the clinical trial setting to lower BC risk.</td>
<td>NA</td>
</tr>
<tr>
<td>Aromatase Inhibitors</td>
<td>Use is not recommended outside of the clinical trial setting to lower BC risk.</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; BC, breast cancer; NCI, National Cancer Institute; LCIS, lobular carcinoma in situ; NA, not applicable.

Visvanathan K, et al. JCO 2009
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