Breast Cancer
Primary & Secondary Prevention

What (can) should (not) be done?

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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 Prevention
What should be done in 2009?

- Importance of breast cancer in Belgium
- Early onset vs late vs later onset breast cancer
- Risk estimation to optimise prevention
- Primary versus Secondary prevention
  - Stop promotion: primary prevention
    - Non-pharmacologic interventions
      - There is no harm: health management
    - Pharmacologic interventions
      - There should always be a benefit; don’t harm
  - Screening = secondary prevention

During a postmenopausal consultation

Primary prevention “prior to promotion” starts earlier in life…
Breast Cancer Disease Course
Long Window of Opportunity

Prim Prevention

Second Prevention

0 5 10 15 20 25 30 35 40
0 5 10 15 20 25 30 35 40

Number of cell doublings

Number of cells

Very early breast cancer (undetectable)

Clinical breast cancer

1 mm

1 cm

10 cm

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

2/3th happens in menopause

Postmenopausal breast cancer

Mean age is 57 years

Breast cancer ~ the ovary

Source: Vlaams Kankerregistratienetwerk, VLK

SABCS 2006 ➔ 2003: Daling van borstkankerfrequentie
Breast Cancer & Breast Cancer Evolving Model of 2 (3) Diseases

- ER - Negative
  - Decreases w/ age
  - Genetic Factors
    - BRCA 1 & 2
- Hormonally insensitive???
- Surgery, BSO
- HRT after prophylactic BSO...

- ER - Positive
  - Increases w/ age
  - Weak link to genetic factors
    - NOT BRCA - 1
    - BRCA 2, CHEK2del1100
- Hormonally sensitive
- Better prognosis?

We are/will be more successful in “prevention” of ER+ breast cancer
Cave! Postmenopausal breast cancer beyond 65-70yrs of age & nodal involvement

Relationship Between Age and Axillary Lymph Node Involvement in Women With Breast Cancer

Hans Wildiers, Ben Van Calster, Lonneke V. van de Poll-Franse, Wouter Hendrickx, Jo Roislien, Ann Smeets, Robert Paridaens, Karen Deraedt, Karin Leunen, Caroline Weliens, Sabine Van Huffel, Marie-Rose Christiaens, and Patrick Neven
What should be done?

1. Discuss breast cancer risk …also after menopause

“Very few high risk women have discussed their breast cancer risk with a physician or considered risk-reducing therapies”


The best approach is to focus preventive interventions for individuals with a substantial risk of cancer.
Risk factors for postmenopausal breast cancer: relative risk

Risk assessment after menopause

- Claus, IBIS-model (Tyler-Cuzick): ~ genetic risk
- Few models for postmenopausal
  - Modified Gail model
    - NHS-validation by Rockhill et al J Natl Cancer Inst
    - The model is well calibrated (E/O) but does not discriminate* well
  - Combining breast density and existing risk models
    - Barlow et al J Natl Cancer Inst
    - Breast density, age, race, ethnicity, FH, previous Bx


* Prediction for individual women
Tyler – Cuzick Model
If + 2 sisters with breast cancer
If + 2 sisters with breast cancer + current ccHRT
Primary prevention of breast cancer
How to stop promotion?

- Most cancers progress through the action of multiple pathways that include E-ER, COX-2, Wnt–β-catenin, MAP kinase, cytokine, and growth-factor signalling.
- Cross talk between pathways of growth
- Drugs that simultaneously block several pathways might be particularly effective as chemopreventive agents, if the clinical benefits outweigh the toxic effects.
Preventing breast cancer

Primary prevention: stop promotion

• Eliminate or prevent pre-invasive disease before invasion develops

• General health maintenance (all risk pts)
  • Eat a healthy diet
  • Reproductive issues do not affect postmenopausals as much
  • Don’t drink too much alcohol
  • Exercise/ maintain optimal weight  
  Level II evidence…

• Prophylactic breast/ ovarian surgery

• Chemoprevention  
  Level I evidence
  What can be done: NNT very high
  What should be done if high risk
Physical Activity: E-ER/Insulin/…

- The positive role of physical activity on the risk of breast cancer is a reality for all women (independent of risk)
- Supported by many epidemiologic case-control and cohort studies as well as biological mechanisms.
- There is a benefit on breast cancer, in primary prevention as well as in tertiary prevention, with a moderate physical activity of three hours, or more, per week.
- The benefit is linked to the degree of total energy expense per week.
- Physical activity has a direct action mainly on three levels:
  - the metabolism of sexual steroids,
  - the sensitivity to insulin,
  - the immunizing pathways and an indirect action through the fatty mass, which is an hormonal reserve.
Once in menopause!
Now, she is not “yet” at risk

35 years of age...

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
HT is not indicated for the routine management of chronic disease. We need more evidence on the safety of HT for menopausal symptom control, though short-term use appears to be relatively safe for healthy younger postmenopausal women.

In relatively healthy women, cc-HRT significantly increased the risk of VTE or coronary event (after 1 yr's use), stroke (after 3 yrs), breast cancer and gallbladder disease.

Long-term E-only HT significantly increased the risk of VTE, stroke and gallbladder disease (after 1-2 yrs, 3 yrs and 7 yrs' use respectively), dementia (>65 ys) but did not significantly increase the risk of breast cancer. The only statistically significant benefits of HT were a decreased incidence of fractures and (for combined HT) colon cancer, with long-term use.

Chemoprevention of Breast Cancer Options for High Risk Women

- Chemoprevention with SERMs (e.g. tamoxifen (EMEA not approved, approved: raloxifene, lasofoxifene))

- Participation in trials using aromatase inhibitors (IBIS-II)
Block pre- and postmenopausal oestrogens...risk/benefit
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 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 

**Tamoxifen NSABP-P1 tam / placebo trial**

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

-17/1000/5 years

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

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

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! Lower NNT

What should be done!

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

Raloxifene and ER+ Breast Cancer in Low Risk Women

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

RALOXIFENE
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
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
Raloxifene is an excellent osteoporosis drug

Raloxifene is an excellent chemopreventive agent for the very high breast cancer risk patient

But, osteoporotic women are probably not at high breast cancer risk

DVT / PE
Stroke if CVD!
Hot Flashes
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
Summary: Effects of 0.5 mg/d Lasofoxifene on Bone at 5 Years

Radiographic Vertebral Fractures
Clinical Vertebral Fractures
Nonvertebral Fractures
Clinical Fractures
Moderate to Severe Fractures
Radiographic Vertebral Fractures - Prev
Nonvertebral Fractures Severe
Hip Fractures

Hazard Ratio ±95% Confidence interval (CI)

Favors Lasofoxifene
Favors Placebo
Summary: Effects of 0.5 mg/d Lasofoxifene on Breast Cancer at 5 Years

Favors Lasofoxifene

Favors Placebo

Hazard Ratio ±95% CI

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Breast Cancer</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Invasive Breast Cancer</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>ER+ Breast Cancer</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>ER+ Invasive Breast Cancer</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
## Major CHD Events Through 5 Years

<table>
<thead>
<tr>
<th>Treatment</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>
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</tbody>
</table>

- Less stroke
- Vaginal health
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
Postmenopausal patients

Aromatase Inhibitors
- Tamoxifen

Reduce Estrogen
- Aromatase Inhibitors

Block Estrogen
- SERMs (Tamoxifen, Nolvadex, Tamoplex)

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

Each AI has developed its own prevention programme
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 Mainly DCIS

Manuscripts/Abstracts:
Cognitive function study
Bone study
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.
Cyclo-Oxygenase inhibitors: Aspirine, COX-2 inhibitors, NSAIDs

so far, no randomised clinical trials of aspirin or other NSAIDs have used cancer mortality as a primary endpoint.

uncertainties remain about the minimum dose and duration to decrease breast cancer incidence, and the mixed beneficial and adverse effects on the cardiovascular and other organ systems
The Ca-Vit D story …

- adequate vitamin D stores “may” prevent breast cancer development
- Whereas circulating 25-OHD levels of >32 ng/mL are associated with normal bone mineral metabolism, data suggest that the optimal level for breast cancer prevention is >/=40 ng/mL.
- Well-designed clinical trials are urgently needed to determine whether vitamin D supplementation is effective for breast cancer chemoprevention.

- 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 HRT
- Tibolone ~ Age dependent effect
On-going trials for chemoprevention

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

www.clinicaltrials.gov
Secondary prevention

Breast Cancer
“in a menopause consultation”

What should (not) be done?

When was your last mammogram?
What should be done?

“Screening for breast cancer is effective”

Secondary prevention

Screening has significantly contributed to a 23.5% decline in breast cancer mortality from 1990 to 2005

NCI 2007

The absolute benefit of screening for breast cancer mortality appears to be small...

Most of the decrease in breast cancer mortality is related to better adjuvant therapies

Cochrane overview
Breast cancer screening in the average risk patient-- standard mammography

- Sensitivity to detect breast cancer is between 60% to 90%
- Less sensitive:
  - in younger women (<age 45)
  - in women with dense breasts
  - in tumors associated with BRCA1 or 2
- Positive predictive value is higher in postmenopausal women at high-risk
Breast cancer screening--harm and benefits

- Potential benefits
  - Earlier diagnosis, BCS, sentinel, less chemo
  - Decreased mortality

- Potential harms
  - False-positive results
  - Unnecessary biopsies
  - Increased anxiety
  - Increased cost
  - Inconvenience
  - Overtreatment
    - Overdiagnosis occurs mostly with DCIS
    - Less than 50% of DCIS becomes invasive, but everyone gets treated
Breast cancer screening in the average risk patient-- standard mammography

- Women age 50 to 69
  - reduces breast cancer mortality ~22%
  - Number needed to screen to prevent one breast cancer death after 14 years = 838

Breast Cancer Screening 50-69 yrs
Mammography uptake 2002-2007

Limburg: Uptake in some parts is 80% it is much lower in others....
Uptake mammographic screening

2006-2007
70% required to lower BC mortality…
## Flanders: Screening 2006-2007

Pick up rate of breast cancers

<table>
<thead>
<tr>
<th></th>
<th>Eerste screening</th>
<th>Vervolgscreening</th>
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<tbody>
<tr>
<td></td>
<td>Aantal gevonden kankers</td>
<td>Number needed to screen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>327</td>
<td>192,7</td>
</tr>
<tr>
<td>2005</td>
<td>316</td>
<td>149,3</td>
</tr>
<tr>
<td>2006</td>
<td>341</td>
<td>164,7</td>
</tr>
<tr>
<td>2007</td>
<td>236</td>
<td>190,6</td>
</tr>
</tbody>
</table>
Breast cancer screening--methods

- Self breast exam (SBE) 
  - Differs from breast awareness
- Clinical breast exam (CBE)
- Additional benefit of ultrasound?
- MRI

What should not be done!
Screening Breast Ultrasound in High-Risk Women

ACRIN Protocol 6666

Wendie A. Berg, MD, PhD, FACR
wendieberg@gmail.com
Breast Imaging Consultant and National Cancer Institute (CA80098)
Who needs US if there is mammography?

- Very high-risk women who cannot tolerate MRI
- Women at intermediate risk (personal hx, LCIS, ADH, ALH, intermediate family hx) with dense breasts
- All women with extremely dense breasts
- No proven survival benefit as yet
- Explain extreme high false positive Bx rate
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
Breast cancer prevention after menopause

What should be done?!

Secondary prevention: Mammographic screening and breast awareness
   Estimate and calculate breast cancer risk for the next 5 years
   Non-pharmacologic compounds: Life style, ...
Pharmacological compounds to prevent the development of breast cancer may become a benefit from drugs with another indication:
   Osteoporosis, CV-disease, Metabolic Syndrome, Statins,

An update

Thanks for your attention!
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
Treatment of many people to prevent a few cancers is not an efficient approach to chemoprevention. In this context, even rare side-effects can adversely affect the overall risk–benefit profile. A better approach is to focus preventive interventions for individuals with a substantial risk of cancer.
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
Comparing tamoxifen with anastrozole

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

Life style changes
Physical activity
Weight Loss
Diet
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?
Tam + other pathways

Steroid Hormones

AI

ER

HSP

The Tumor Cell

Targeted therapies
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-aromatase 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.
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

Breast cancer

Placebo: 74 events
Tamoxifen: 62 events
HR=0.84 (0.60-1.17)

5408; hysterectomy; 11 j FU; 136 events: 2,48/1000/j → 2,07/1000/j
702; 2 ovaries; tall; menarche; P0: 6,26/1000/j → 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: \[ IGFs \text{ and } Mx \text{ density} \]

II endpoint: \[ \Delta \text{ endometrial and ovarian effects} \]
\[ \Delta \text{ breast FNA (image analysis)} \]

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)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Proportion</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>

Proportion of disease prevalence attributable to obesity

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 ≥ 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>
</tr>
</tbody>
</table>

P-value = 0.01
Lasofoxifene, a SERM

- Lasofoxifene is a selective estrogen receptor modulator (SERM) with high affinity for the estrogen receptor.
The PEARL Trial

- Randomized, placebo-controlled trial
- 2 daily doses (0.25 mg or 0.5 mg)
  - All received 400-800 IU vitamin D₃ and 1 g of calcium daily
- 3-year trial with 2-year extension
Participants

- 8556 women aged 59-80 years
- Bone mineral density (BMD) T-score ≤ –2.5 and ≥ –4.5 at the femoral neck or spine
- < 4 radiographic vertebral fractures
Endometrial Polyps at 3 Years (TVU-P)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lasofoxifene, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Patients at risk</td>
<td>360</td>
<td>354</td>
</tr>
<tr>
<td>Events (%)</td>
<td>12 (3.3)</td>
<td>31 (8.8)</td>
</tr>
<tr>
<td>Incidence rate/1000 patient-years</td>
<td>7.4</td>
<td>20.1</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>7.4</td>
<td>20.1</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.41–5.51</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.003&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- All lasofoxifene endometrial polyps were atrophic/inactive
- Similar to raloxifene, OR=1.7<sup>b</sup>

<sup>a</sup>P value significant vs placebo
Vaginal Bleeding

- More subjects in the lasofoxifene groups vs the placebo group experienced vaginal bleeding
  - Lasofoxifene 0.25 mg/d: 2.2%
  - Lasofoxifene 0.5 mg/d: 2.6%
  - Placebo: 1.3%

- The excess vaginal bleeding in the lasofoxifene groups may be attributed to concomitant related adverse events such as endometrial polyps or thickening, and
Vulvar and Vaginal Atrophy

- Compared with placebo at 3 years, treatment with lasofoxifene decreased vaginal pH
  - pH log units $-0.27 \ (P = 0.001)$ for 0.25 mg/d; and
  - $-0.13 \ (P = 0.001)$ for 0.5 mg/d

- Lasofoxifene demonstrated favorable effects on maturation index with an increase in superficial cells relative to
Breast cancer screening in the average risk patient--SBE

- Most women do not regularly perform
- If they do perform, most do it incorrectly
- The practice of regular breast self-exam by trained women does not reduce breast cancer mortality

- Evidence from 2 large RCTs
Breast cancer screening in the average risk patient---SBE

- Cochrane review 2003
  - Conclusions
    - SBE has no beneficial effect
    - Increases the number of biopsies
    - Evidence of harm
  - Recommendation
    - Women should NOT perform SBE
Breast cancer screening in the average risk patient-- SBE

- USPSTF 2007
  - Insufficient evidence to recommend for or against breast self-examination

- ACS 2007
  - Monthly breast self-examination optional at any age 20 or older
Breast cancer screening in the average risk patient-- SBE

- “If women choose to perform breast self-examination after being informed of the lack of benefit and potential harms, the physician should train the patient in appropriate technique, timing, and follow-up.”

Breast cancer screening in the average risk patient--SBE

- Self breast-exam at any age
  - Not supported by the evidence
  - Physicians should discourage, or at least not encourage
  - If patients want to perform, should be taught the appropriate way to perform the exam

Breast cancer screening in the average risk patient -- CBE

- Sensitivity 50% at best
- 5% to 10% of breast cancers detected only by CBE
  - (not detected by mammogram)
- USPSTF 2007
  - Insufficient evidence to recommend for or against CBE
- ACS 2007
  - CBE every 3 yrs ages 20 to 39
  - CBE annually age 40 and older
Breast cancer screening in the average risk patient -- CBE

- Age 20 to 39
  - Even necessary?
  - Every 3 years?
- Age 40 to 49
  - Benefits and harms approximately equal
  - May discuss, but do not need to actively encourage
  - Every 1 to 2 years, if at all
- Age 50 to 70
  - Encourage every year
  - Every 2 years acceptable
- After age 70
  - Balance of benefits and harms uncertain, take patients general health and life expectancy into consideration

How safely and effectively “arrest” the progression of subclinical (pre) malignant disease?

- Primary prevention = Stop promotion
  - Initiation starts earlier
- Which individuals are at risk and for what type of cancer?
  - Risk calculation = SOC
  - Information on 1\textsuperscript{ary} (chemo)prevention = SOC
Breast cancer screening in the average risk patient-- standard mammography

- Cochrane review (2001)
  - Meta-analysis concluded that screening for breast cancer with mammography is unjustified

- USPSTF (2007)
  - Meta-analysis using many of the same trials
  - For women of average risk, recommended screening mammography (B recommendation)
    - Every one to two years for women ages 40 to 49
    - Every year for women age 50 and older
      - Little evidence to suggest this is better than every 2 yrs

- ACS (2007)
  - Every year for women age 40 and older
Breast cancer screening in the average risk patient-- mammogram

- **Age 40 to 49**
  - Benefits and harms approximately equal
  - May discuss, but do not need to actively encourage
  - Every 1 to 2 years, if at all

- **Age 50 to 70**
  - Encourage
  - Every 2 years acceptable

- **After age 70**
  - Balance of benefits and harms uncertain, take patients general health and life expectancy into consideration

Breast cancer screening-- MRI

- Not recommended for average risk patients
  - Too expensive for screening all patients
  - Availability issues
- More sensitive (but less specific) than mammography in high-risk women
  - Sensitivity of 71% to 100% vs 16% to 40% for mammogram in high-risk women
    - Particularly more sensitive with dense breasts
  - Tumors found are smaller and earlier
- Combination of mammography and MRI is better than either alone for detection
- No data yet on mortality reduction
ACS indications for annual breast cancer screening with MRI

- Women age 30 or older with any of the following should be screened yearly:
  - Patient with BRCA1 or BRCA2 mutation
  - First degree relative with BRCA1 or BRCA2 mutation
    - *If the patient has not yet been tested*
  - History of therapeutic chest radiation between the ages of 10 to 30 years
  - Lifetime risk of breast cancer of 20% or greater, based on a risk assessment calculation tool that depends largely on family history
ACS indications for annual breast cancer screening with MRI

- Of note what is NOT included:
  - Insufficient evidence to recommend for or against MRI screening with other risk factors
    - Lifetime risk of breast cancer 15-20%
    - Hx of atypia/CIS/breast cancer
    - Dense breasts
  - These above items should be discussed individually
    - MRI screening may be recommended by expert opinion, but not endorsed by ACS
Breast cancer screening in the high-risk patient

- SBE?
- CBE
  - Annually or every 6 months?
- Mammogram
  - Yearly
  - ? Age to start
    - ?Once determined they are high-risk
    - If high-risk due to family history, start 10 years earlier than youngest affected first-degree relative
    - If BRCA 1 or 2 mutation in patient (or in family and patient not tested), start age 25
- MRI
  - Yearly, starting at age 30, if meet ACS criteria
    - (And consider screening if other high-risk factors present that don’t yet meet criteria, such as dense breasts)
Tamoxifen for breast cancer prevention

IBIS-I

Overall 4 tamoxifen prevention trials
Risk reduction: 38%
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

P-2 STAR
Age Distribution of Participants

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

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
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
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
Nonvertebral Fracture at 5 Years

First SERM with Non-vertebral fracture Risk reduction

Cumulative %

Pbo 0.25 mg 0.5 mg Lasofoxifene

n = 296 n = 269 n = 230

10.4
9.4
8.1

10% (P = 0.19) 24% (p < 0.01)

0.76 (0.64, 0.91) 0.90 (0.76, 1.06)
ER+ Breast Cancer at 5 years

Incidence Rate per 1000 Patient Years (95% CI)

- Placebo: 1.7 (0.25, 1.08)
- 0.25 mg: 0.9 (0.07, 0.56)
- 0.5 mg: 0.3

- Lasofoxifene:
  - n = 21, 48% (p = 0.073)
  - n = 11, 81% (p < 0.001)
Major CHD Events Through 5 Years

<table>
<thead>
<tr>
<th>Treatment</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>Lasofoxifene, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>EndCan</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>Endhyperpl</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal Bleeding</td>
<td>36 (0.3%)</td>
</tr>
<tr>
<td>Hot Flushes</td>
<td>158 (1.2)</td>
</tr>
<tr>
<td>VTE</td>
<td>18 (0.6%)</td>
</tr>
</tbody>
</table>

Endometrial Texture = Tam Like (20%)
Subepithelial changes and More Atrophic E-Polyps