Managing the Risk of Breast Cancer

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Subject identification and risk quantification

Factors Used in NCI Breast Cancer Risk Prediction Model

- Age
- Number of 1st degree female relatives with a history of breast cancer
- Age at first live birth or nulliparity
- Number of breast biopsies
- History of atypical hyperplasia
- Age at menarche
- Race

Validation of the Gail Breast Cancer Risk Prediction Model in the BCPT

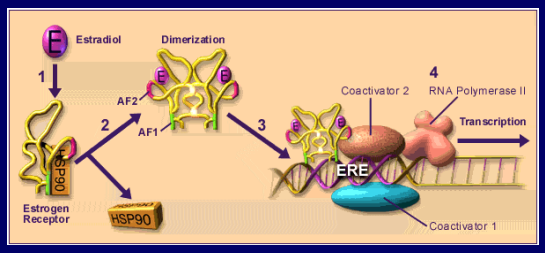
Age Group	Expected/ Observed	95% Conf. Int.
49 years or less	0.93	(0.72-1.22)
50-59 years	1.13	(0.83-1.55)
> 60 years	1.05	(0.80-1.41)
Total	1.03	(0.88-1.21)

Costantino JP et al, J Natl Cancer Inst 91:1541-1548, 1999

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

Chemoprevention

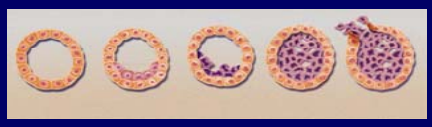
Estrogen receptor/ligand interactions



Courtesy Astra-Zeneca Pharmaceuticals

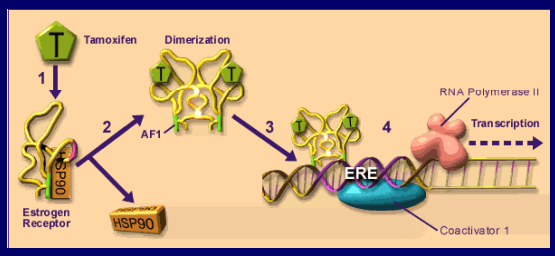
Breast Cancer Develops Over Time

One well-recognized hypothesis is that breast cancer cells progress through changes over a period of years



Normal Duct	Intraductal Hyperplasia	Intraductal Hyperplasia with Atypia	Intraductal Carcinoma In situ	Invasive Ductal Cancer

Tamoxifen action



Courtesy Astra-Zeneca Pharmaceuticals

BREAST CANCER PREVENTION TRIAL

B C NSABP T

BCPT Design

Eligible Women at High Risk
(5-yr risk ≥ 1.66%)

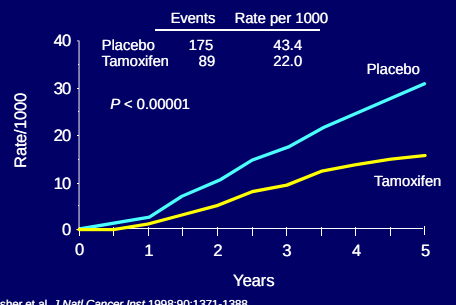
Randomization
n = 13,388

Tamoxifen
5 Years
n = 6681

Placebo
5 Years
n = 6707

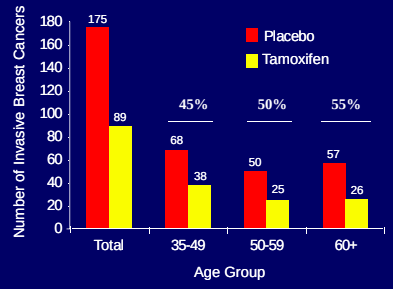
Fisher et al. *J Natl Cancer Inst* 1998; 90:1371-1388.

BCPT Results: Cumulative Rate of Invasive Breast Cancer



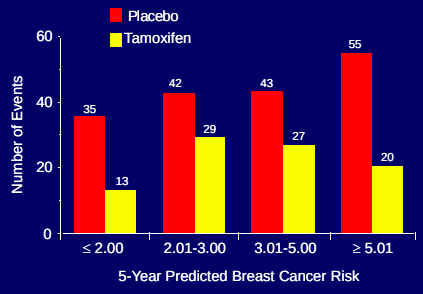
Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

BCPT Results: Invasive Breast Cancer Cases by Age Group



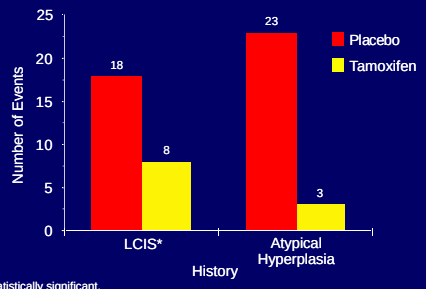
Fisher et al. *J Natl Cancer Inst* 1998; 90:1371-1388.

BCPT Results: Invasive Breast Cancer Cases by Risk Level



Fisher et al. *J Natl Cancer Inst* 1998; 90:1371-1388.

BCPT Results: Invasive Breast Cancer Cases by Previous Pathology



*Not statistically significant.

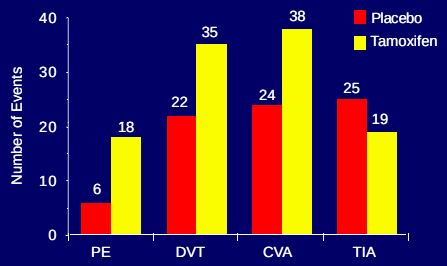
Fisher et al. *J Natl Cancer Inst* 1998; 90:1371-1388.

BCPT Results: Invasive Endometrial Cancer

Age (yr)	Placebo n	Tamoxifen n	Risk Ratio
≤ 49	8	9	1.21
≥ 50	7	27	4.01
Total	15	36	2.53

Fisher et al. *J Natl Cancer Inst* 1998;90:1371-1388.

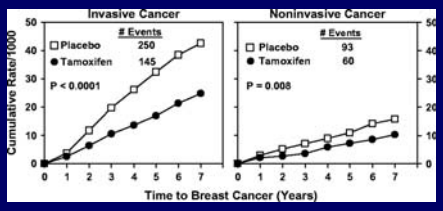
BCPT Results: Vascular Events



PE = pulmonary embolism; DVT = deep vein thrombosis; CVA = cerebral vascular accident (stroke); TIA = transient ischemic attack

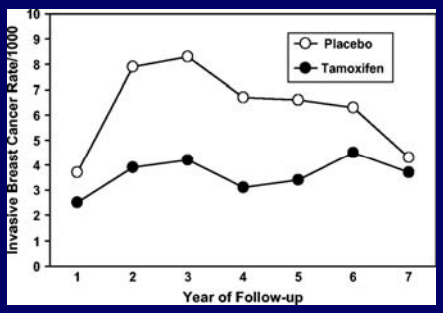
Fisher et al. *J Natl Cancer Inst* 1998; 90:1371-1388.

Cumulative rates per 1000 women of invasive and noninvasive breast cancers in NSABP P-1 participants by treatment group



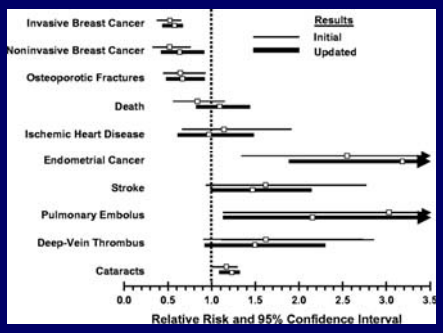
Fisher, B. et al. J. Natl. Cancer Inst. 2005 97:1652-1662

Annual rates of invasive breast cancer per 1000 women by year of follow-up and treatment group in NSABP P-1



Fisher, B. et al. J. Natl. Cancer Inst. 2005 97:1652-1662

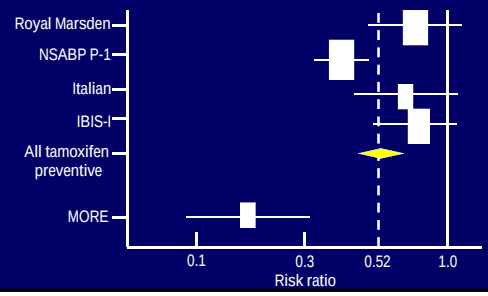
Comparison of relative risks of benefits and undesirable effects of tamoxifen from the initial and updated results of NSABP P-1



Fisher, B. et al. J. Natl. Cancer Inst. 2005 97:1652-1662

Meta-analysis of ER-positive breast cancer risk reduction trials using SERMs

Cuzick J et al. Lancet 361:296-300, 2003



Risks and benefits of tamoxifen

Benefits

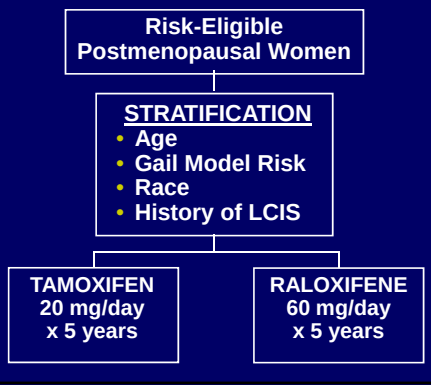
- 34% to 49% reduction in the risk of breast cancer in high-risk women
- 86% risk reduction in women with atypical hyperplasia
- 55% reduction in risk in women with lobular carcinoma *in situ* (LCIS)
- 50% reduction in risk of ductal carcinoma *in situ* (DCIS)

Risks

- Increased risk of thromboembolic events in postmenopausal women ONLY
- 2.5-fold risk of uterine malignancy in postmenopausal women ONLY
- 10% increased risk of cataracts and cataract surgery
- Increased risk of menopausal symptoms

Vogel et al. JAMA 2006;295:2727-2741

NSABP STAR Schema



STAR Trial Primary Objective

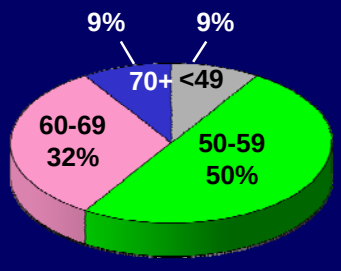
Evaluate the effect of raloxifene vs. tamoxifen in reducing the incidence of Invasive breast cancer

STAR Trial Objectives

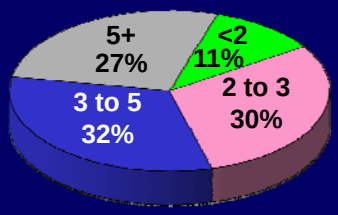
Secondary objectives:

- Noninvasive breast cancer
- Endometrial cancer
- Ischemic Heart Disease
- Fractures of the:
  - Hip
  - Spine
  - Wrist (Colles')

P-2 STAR
Age Distribution



P-2 STAR
5-year Predicted Risk of Breast Cancer among Participants at Entry

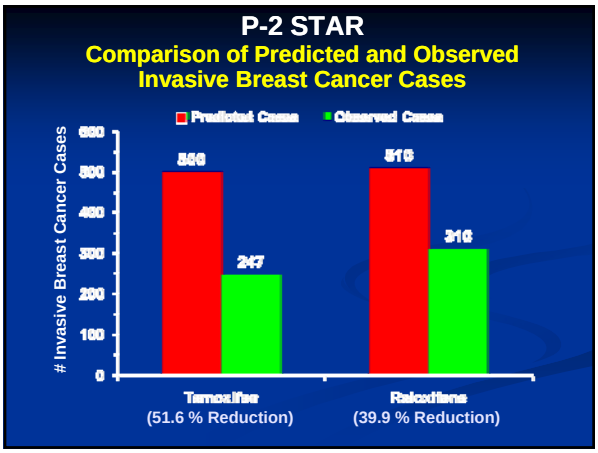


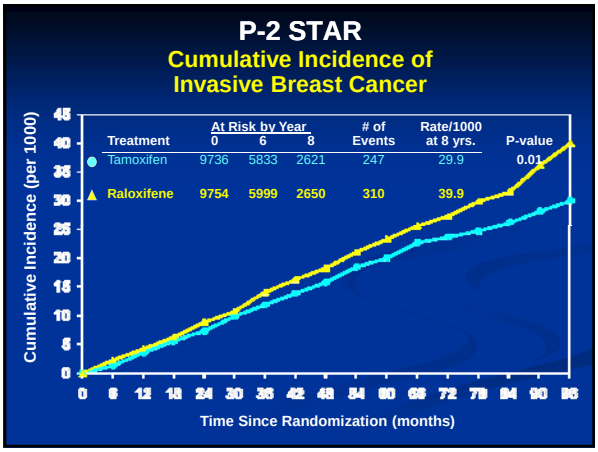
P-2 STAR

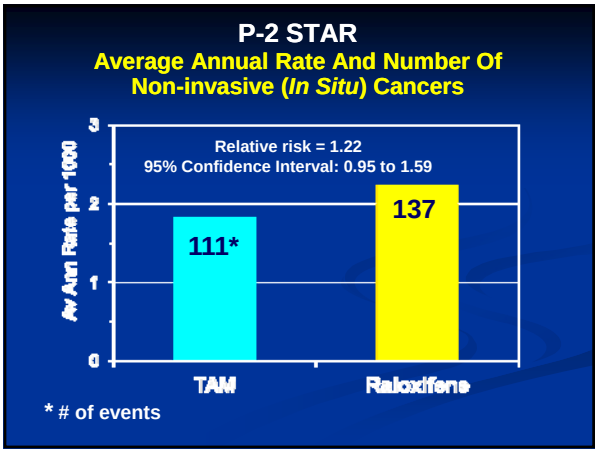
	LCIS	Atypical Hyperplasia
Total Number	1,789	4,426
% of Randomized	9.2	22.7

STAR trial results through March 2010

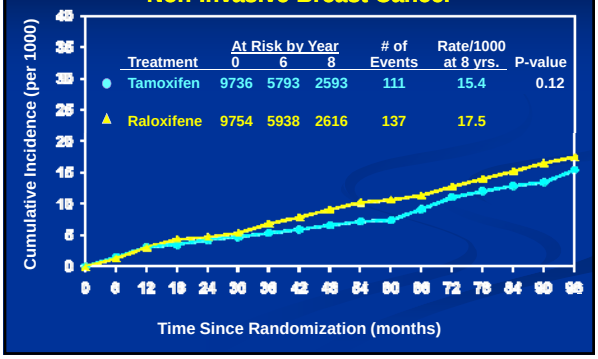
(Vogel et al, Cancer Prev Res 2010;3:696-706)


P-2 STAR
Comparison of Predicted and Observed
Invasive Breast Cancer Cases
Predicted Cases
Observed Cases
Invasive Breast Cancer Cases
556
247
516
316
Tamoxifen
(51.6 % Reduction)
Raloxifene
(39.9 % Reduction)


P-2 STAR
Cumulative Incidence of
Invasive Breast Cancer
Cumulative Incidence (per 1000)
At Risk by Year
Treatment 0 6 8 # of Events Rate/1000 at 8 yrs. P-value
Tamoxifen 9736 5833 2621 247 29.9 0.01
Raloxifene 9754 5999 2650 310 39.9
Time Since Randomization (months)

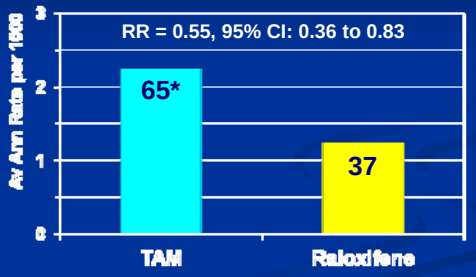

P-2 STAR
Average Annual Rate And Number Of
Non-invasive (In Situ) Cancers
Relative risk = 1.22
95% Confidence Interval: 0.95 to 1.59
Av Ann Rate per 1000
111*
137
TAM
Raloxifene
* # of events

P-2 STAR
Cumulative Incidence of Non-Invasive Breast Cancer

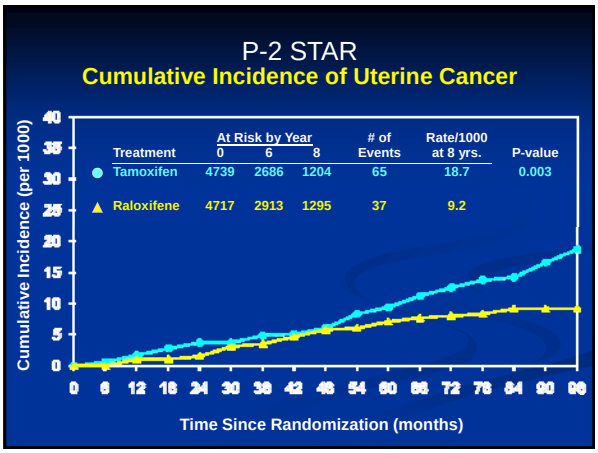


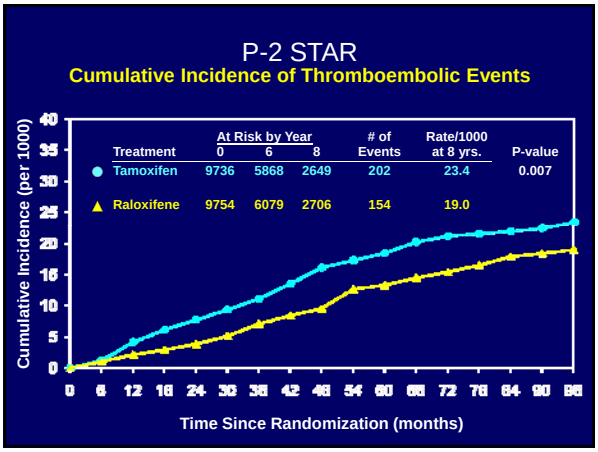
Tamoxifen and raloxifene-associated toxicities

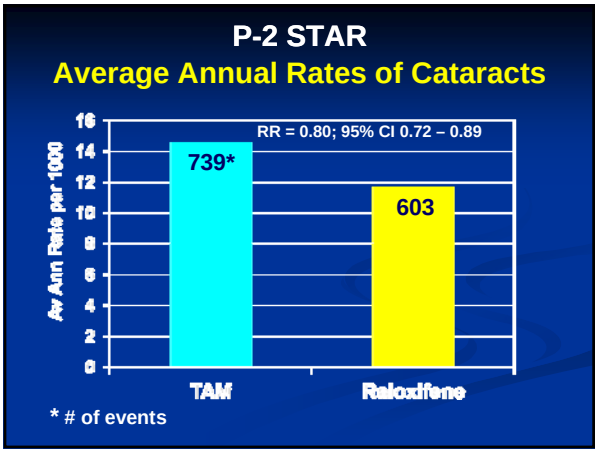
P-2 STAR
Average Annual Rate and Number of Uterine Cancers



* # of events


P-2 STAR
Cumulative Incidence of Uterine Cancer
Cumulative Incidence (per 1000)
Treatment | At Risk by Year 0 | 6 | 8 | # of Events | Rate/1000 at 8 yrs. | P-value
Tamoxifen | 4739 | 2686 | 1204 | 65 | 18.7 | 0.003
Raloxifene | 4717 | 2913 | 1295 | 37 | 9.2
Time Since Randomization (months)


P-2 STAR
Cumulative Incidence of Thromboembolic Events
Cumulative Incidence (per 1000)
Treatment | At Risk by Year 0 | 6 | 8 | # of Events | Rate/1000 at 8 yrs. | P-value
Tamoxifen | 9736 | 5868 | 2649 | 202 | 23.4 | 0.007
Raloxifene | 9754 | 6079 | 2706 | 154 | 19.0
Time Since Randomization (months)

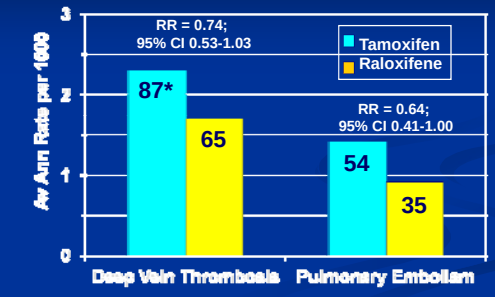

P-2 STAR
Average Annual Rates of Cataracts
RR = 0.80; 95% CI 0.72 – 0.89
Av Ann Rate per 1000
739*
603
TAM
Raloxifene
* # of events

Number of Hysterectomies for Non-Cancer Reasons

TAM	RAL
244	111

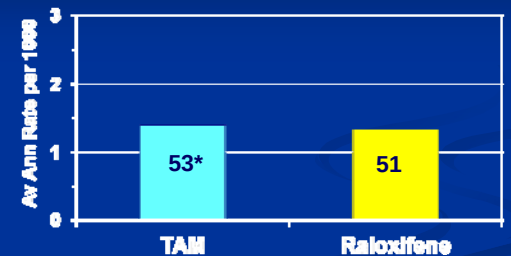
RR = 0.44, 95% CI, 0.35 – 0.56

P-2 STAR
Average Annual Rate and Number of Deep Vein Thromboses and Pulmonary Emboli



* # of events

P-2 STAR
Average Annual Rate and Number of Strokes



* # of events

P-2 STAR
Conclusions

- Raloxifene is as effective as tamoxifen in the prevention of primary invasive breast cancer
- Raloxifene is less effective than tamoxifen in the prevention of non-invasive breast cancer (LCIS & DCIS)
- Compared to tamoxifen, raloxifene use results in:
  - Fewer thromboembolic events
  - Fewer endometrial cancers and
  - Fewer cataracts

Using SERMs in the management of breast cancer risk

Risk management prescription

- Quantitative risk assessment
- [Genetic counseling]
- [Genetic testing]
- Re-evaluation of risk over time
- Chemoprevention
- Imaging strategies or protocols
- Prophylactic surgery
- Regular follow-up visits for screening, monitoring and education

Women in whom SERMs should be considered (1)

- History of lobular carcinoma *in situ* (LCIS)
- History of ductal carcinoma *in situ* (DCIS)
- History of atypical ductal or lobular hyperplasia

Atypia and tamoxifen use in the STAR Trial

- In the STAR trial, ½ of women who submitted risk assessments were eligible for the trial BUT only 20% of the eligible women enrolled
- Women with a diagnosis of atypical lobular or ductal hyperplasia in STAR were 70% more likely to agree to undertake SERM therapy than were women without these lesions, probably reflecting their more positive risk/benefit profiles

Vogel VG, et al. J Natl Cancer Inst 2002;94:1504.

Women in whom SERMs should be considered (2)

- Women with mutations in either the *BRCA1* or *BRCA2* genes (other predisposing genetic mutations?)
- Women with Gail model 5-year probability of breast cancer ≥ 1.66% and significant benefit:risk profile

Women in whom caution should be used when considering the use of SERMs

- History of stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolus
- History of cataracts or cataract surgery
- Current use of hormone replacement therapy

Summary and challenges

Barriers to use of tamoxifen

- Uptake of tamoxifen for breast cancer risk reduction has been poor (5 to 45 percent of eligible women)
- Most common reason for refusing use of tamoxifen is ***fear of serious side effects*** such as uterine malignancy and thrombosis
- Non-life threatening toxicities (e.g., weight gain and depression) that do not occur with greater frequency with tamoxifen are ***widely misunderstood*** and ***inaccurately attributed*** to the drug contribute to its lack of use

Reasons women do not use SERMs to reduce breast cancer risk

- Use of hormone replacement therapy
- Fear of adverse effects (including uterine cancer)
- Medication costs
- Lack of reasonably accurate and feasible methods for assessing personal, individual risk
- Lack of established risk thresholds that maximize benefit and minimize harms

Waters EA, et al. Cancer Epidemiol Biomarkers Prevent 2010;19:443-446

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