# Therapy for Non-Invasive Breast Cancer & Prevention

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No Disclosures

# Objectives

1) Differentiate local and systemic therapy for LCIS from DCIS.

2) Evaluate who should we consider for chemoprevention.

3) Compare and contrast SERMs and Aromatase Inhibitors.

4) Understand the importance of lifestyle on Breast Cancer risk.

# Epidemiology: Breast Cancer Incidence and Mortality

- Most common cancer in women
- 29% of all new cancers
- 2nd leading cause of cancer death in US
- 249,260 cases diagnosed
- 40,890 died of breast cancer

American Cancer Society. Breast Cancer Facts & Figures at www.cancer.org. Surveillance, Epidemiology, and End Results Program, 1976-2006, Division of Cancer Control and Population Sciences, NCI 2009. http://seer.cancer.gov. Combined data from National Program of Cancer Registries as submitted to CDC and from SEER as submitted to NCI in November 2014. http://www.cdc.gov/cancer/breast/statistics/race.htm

# Notable Risk Factors

| Factor | Relative risk (RR) |
|---|---|
| Female sex | 100 |
| Age (30 vs. 70) | 10 |
| Atypia or Intraepithelial neoplasia (DCIS, LCIS, ADH, etc.) | 2 to 10 |
| Prior breast/ovarian cancer | 2 to 10 |
| 1° relative <60 at diagnosis | 2 |
| Germ-line mutations responsible for hereditary breast cancer | Up to 20 |
| Breast Density (heterogeneous vs. extremely dense) | 1.79 to 4.64 |

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

# Modifiable Factors with Increased Risk

| Factor | Relative risk (RR) or Effect |
|---|---|
| Combined Hormone Therapy | ~26% increase |
| Ionizing radiation to chest < 30 | 5 to 20 |
| Obesity (>82 kg vs. <59 kg) | 2.85 |
| Alcohol intake (4 drinks/day vs. non-drinkers) | 1.32 |
| Parity (Nulliparous vs. parous) | 2 |

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

# Modifiable Factors with Decreased Risk

| Factor | Magnitude of Effect |
|---|---|
| Early pregnancy | 50% decrease in risk compared to nulliparous women or women who give birth >35 years |
| Breast Feeding | 4.3% decrease in RR for every 12 months, in addition 7% for every birth |
| Exercise<br>(strenuous exercise ≥ 4 hrs/week) | Average RR reduction is 30% to 40%. The effect may be greatest for premenopausal women of normal or low body weight. |

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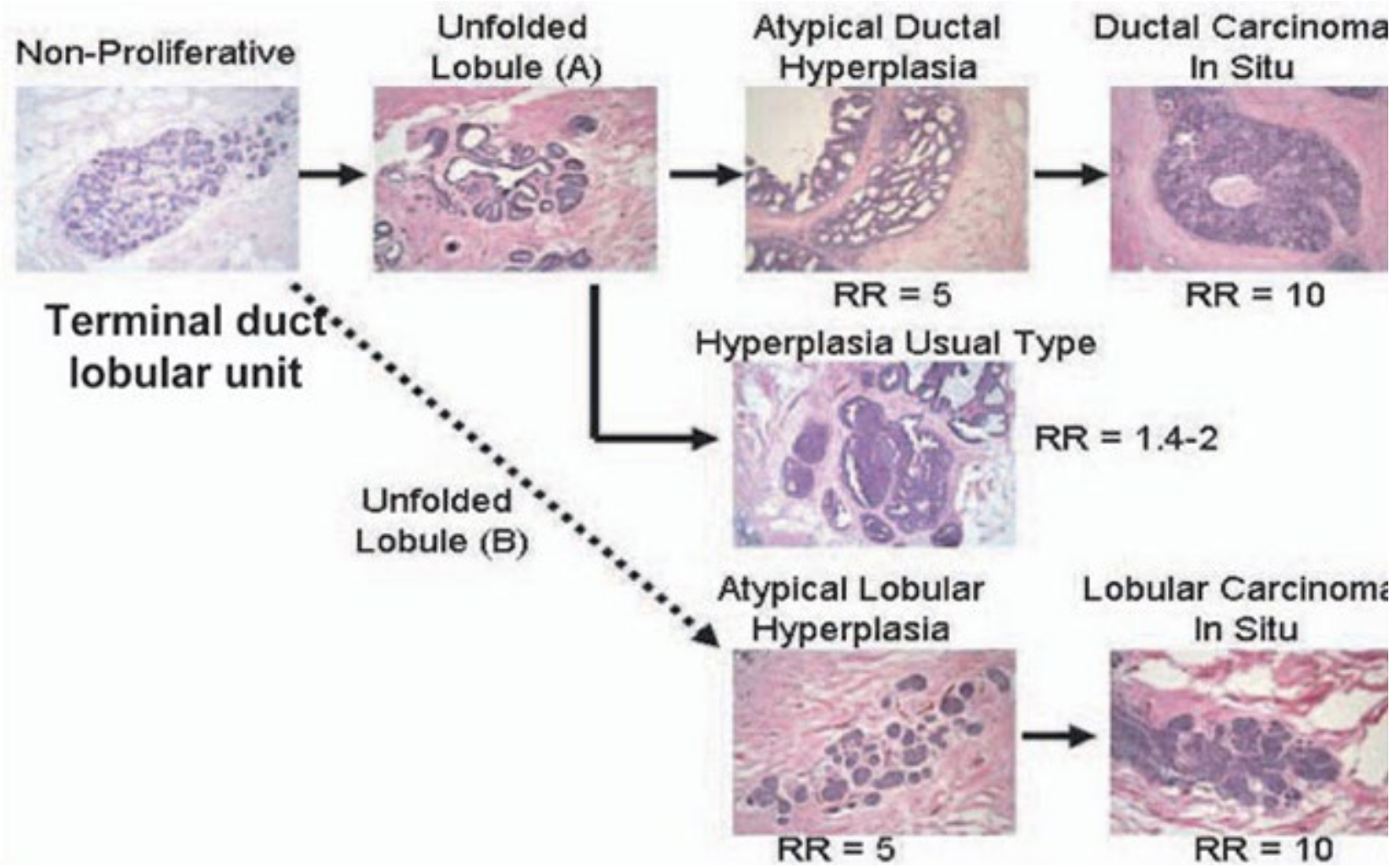
# Proliferative lesions & Intraepithelial Neoplasia



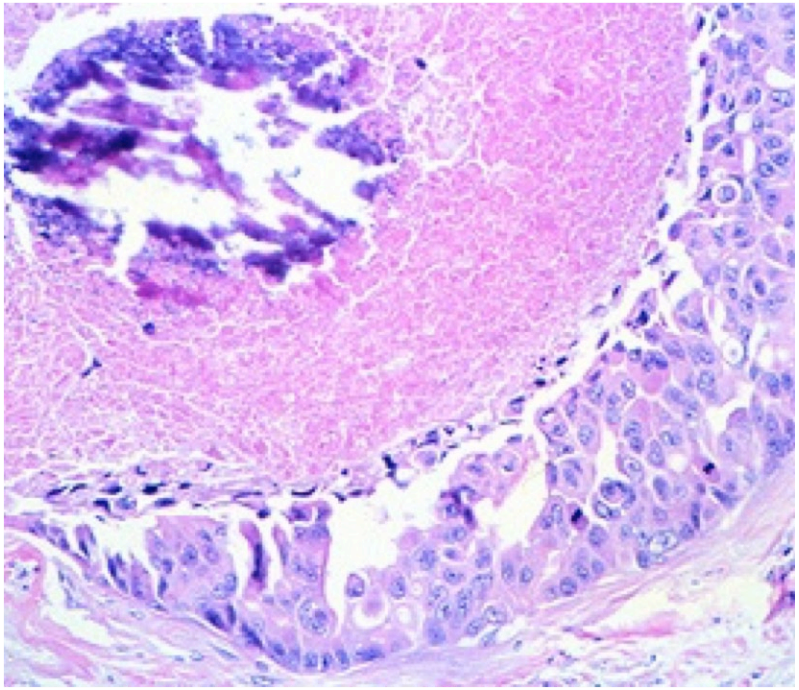

Fabian, *Endocr Relat Cancers* 2005 12:185-213

# Management of DCIS & Proliferative Breast Disease

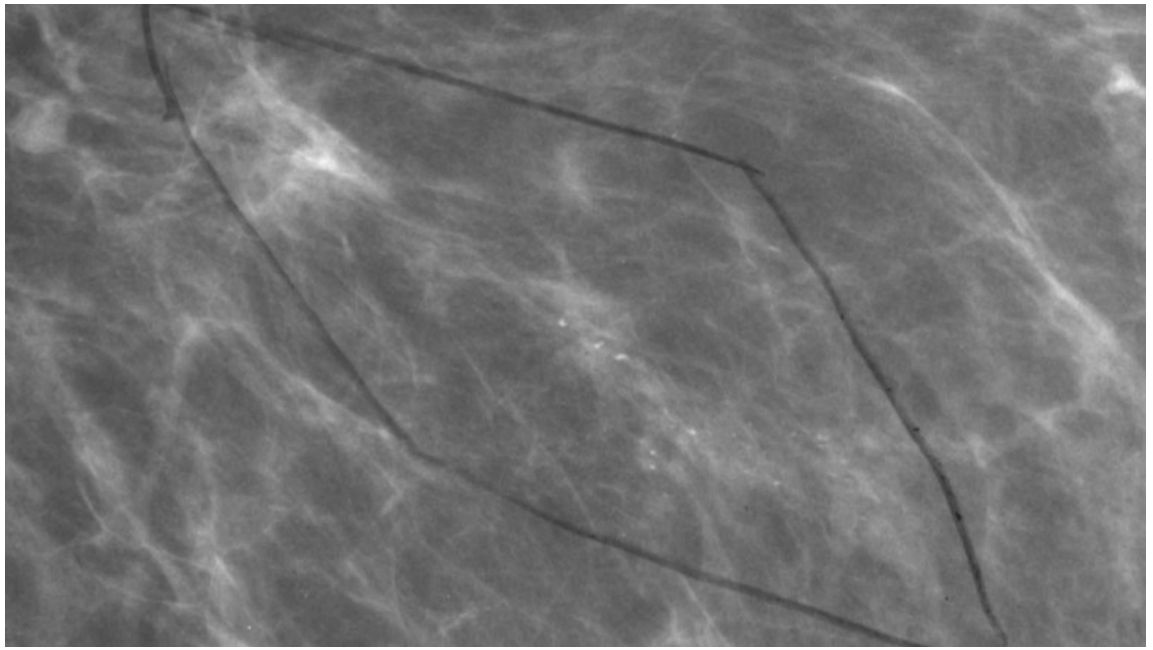
| | Risk for Invasive Ca | Upstaging | Surgery for Diagnosis/Tx | Treatment & Prevention |
|---|---|---|---|---|
| DCIS | Precursor | 10-30% to IC | Excision Clear margins (2mm) | Treatment |
| pLCIS or Florid LCIS | ?precursor | ~malignant | Excisional Bx/ clear margins | Treatment |
| LCIS (classic) | ↑Risk 10x | <5% | No if Imaging Concordance with Core Bx | RRM is not SOC Active Surveillance &Chemoprevention |
| ADH | ↑Risk 3-5x Bilaterally | 10-20% to DCIS or IC | Excisional Bx | Active Surveillance &Chemoprevention |
| ALH | ↑Risk 3-5x Bilaterally | <3% | No if Imaging Concordance with Core Bx | Active Surveillance &Chemoprevention |

# Non-invasive Breast Cancer: *DCIS*

- *Ductal carcinoma in situ* (DCIS) is a proliferation of malignant cells of the ducts not breaching basement membrane
- 50-75% is ER+ or PR+
- 1970 = 5.8/100k, 2004 = 32.5/100k
- 25% of new breast cancers
- 60K new cases each year
- Precursor lesion for invasive breast cancer
- Equal in risk to IBC for genetic mutations
- Seen in BRCA mutation carriers
- Increases risk of IBC 2 fold



# Diagnosis of *DCIS*



90%  with DCIS have suspicious microcalcifications on mammography
DCIS accounts for 80% of all breast cancers with calcifications

# Treatment of *DCIS:* Surgery

- Surgery either mastectomy or lumpectomy/BCT
  - Same cancer outcomes
  - For mastectomy, failure rate 1-2%
- Surgical Margins, 2 mm now standard
  - lower rates of IBTR
  - decrease re-excision rates
  - improve cosmetic outcomes
  - decrease health care costs.
- Contraindications to breast conserving therapy
  - Persistent positive margins
  - Multi-centric disease
  - Prior breast irradiation
- Sentinel node biopsy
  - for mastectomy
  - features in needle biopsy concerning for invasive disease

Morrow M et al., *Pract Radiat Oncol.* 2016 Sep-Oct;6(5):287-95. doi: 10.1016/j.prro.2016.06.011. Epub 2016 Jun 24.

# Treatment of *DCIS*: Benefit of Radiation

- Evaluated in 3 trials: NSABP B-17, EORTC 10853, UK trial
- In NSABP B-17, patients with *DCIS* were randomized to lumpectomy or lumpectomy + breast radiation
  - With 12 years follow up, radiation after lumpectomy was decreased in ipsilateral breast tumor recurrence by **50%**
  - Approximately 50% of recurrences are invasive
  - **No benefit in overall survival**
- Need for radiation in all patients with *DCIS* after lumpectomy is controversial

Fisher B, *et al. Semin Oncol* 2001;**28**:400. Julien JP, *et al. Lancet* 2000;**355**:528. Fisher ER, *et al. Cancer* 1999;**86**:429. Bijker N, *et al. JCO* 2006;**24**:3381. Houghton J, *et al. Lancet* 2003;**362**:95.

# Treatment of *DCIS*: BCS without Radiation

## Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study

*Lawrence J. Solin, Robert Gray, Lorie L. Hughes, William C. Wood, Mary Ann Lowen, Sunil S. Badve, Frederick L. Baehner, James N. Ingle, Edith A. Perez, Abram Recht, Joseph A. Sparano, and Nancy E. Davidson*

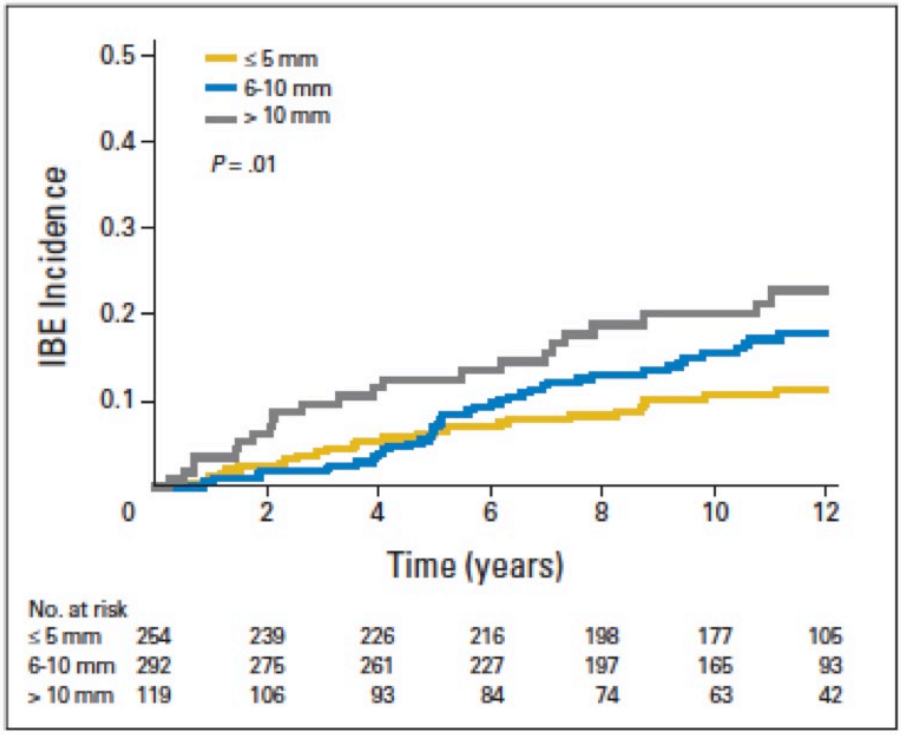
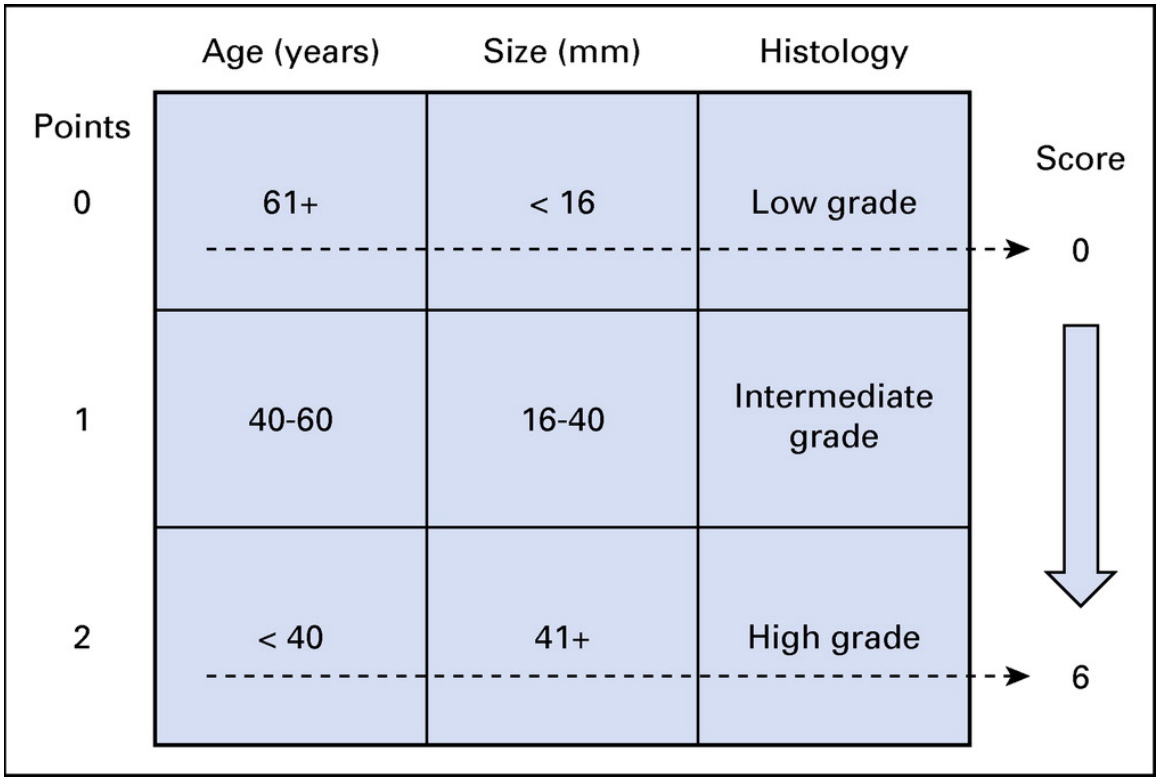



**Fig 2.** Ipsilateral breast events (IBEs) according to tumor size. The numbers at risk are given beneath the *x*-axis.

- Prospective trial of women with DCIS selected for lumpectomy without radiation in 2 cohorts
  1) low-int grade <2.5 cm
  2) high grade ≤ 1 cm
- Tamoxifen used in 30% of patients
- 12 yr rate of IBE 14.4% for cohort 1 and 24.6% for cohort 2
- Study cohort and tumor size associated with developing IBE

# DCIS s/p BCS SEER analysis: Radiation or not

- 32,177 women with DCIS from 1988-2007




Published in: Yasuaki Sagara; Rachel A. Freedman; Ines Vaz-Luis; Melissa Anne Mallory; Stephanie M. Wong; Fatih Aydogan; Stephen DeSantis; William T. Barry; Mehra Golshan; *Journal of Clinical Oncology* **2016,** 34, 1190-1196.
DOI: 10.1200/JCO.2015.65.1869

# DCIS s/p BCS SEER analysis: Radiation or not

| Prognostic Score | No. of Patients | | 10-Year BCM* (%) | | Hazard Ratio*† of BCM | P† |
|---|---|---|---|---|---|---|
| | Non-RT Group | RT Group | Non-RT Group | RT Group | | |
| 0 | 782 | 1,388 | 3.0 | 3.4 | 1.2 | .58 |
| 1 | 2,677 | 4,480 | 2.0 | 2.5 | 1.0 | .95 |
| 2 | 4,105 | 7,080 | 2.0 | 1.5 | 0.69 | .02 |
| 3 | 3,048 | 5,417 | 1.5 | 1.3 | 0.73 | .13 |
| 4 | 965 | 1,701 | 3.2 | 1.3 | 0.31 | < .001 |
| 5 | 223 | 248 | 6.3 | 2.3 | 0.29 | .03 |
| 6 | 15 | 15 | NA | | | NA |

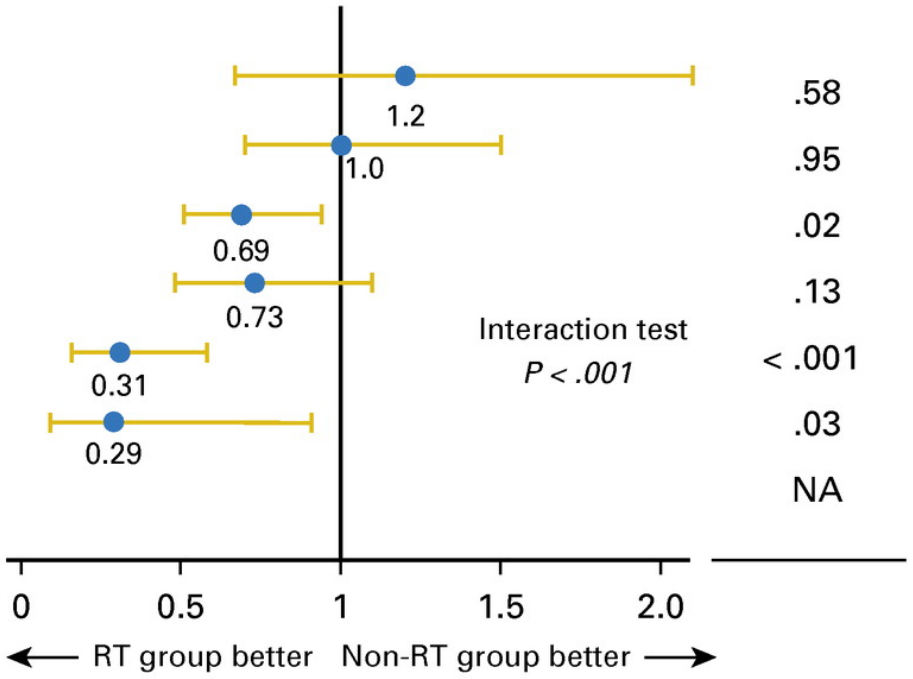



*Fig 2. Hazard ratio comparing breast cancer mortality (BCM) between radiotherapy (RT) group and non-RT group according to prognostic score. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status. NA, not applicable.*

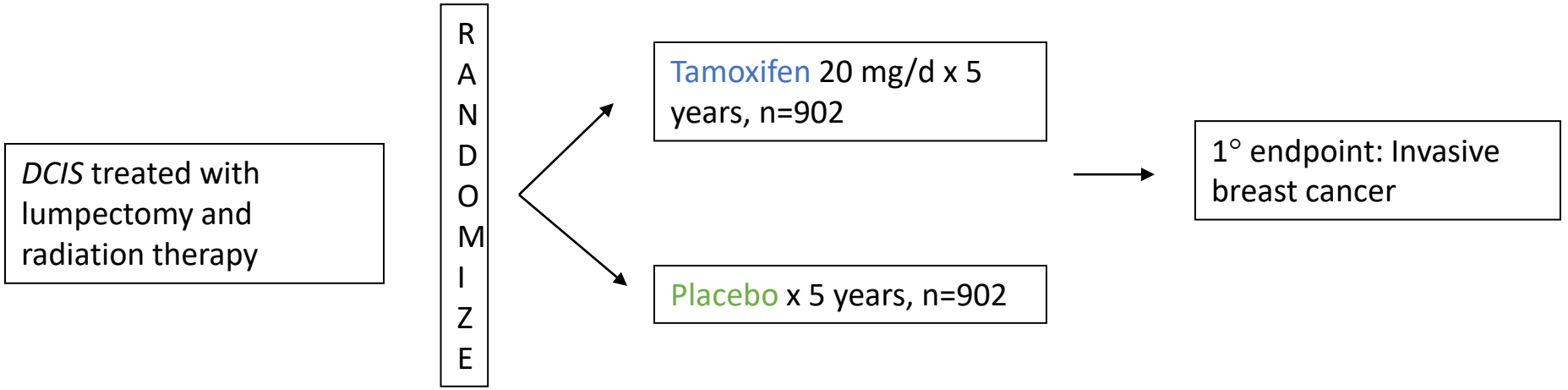
Published in: Yasuaki Sagara; Rachel A. Freedman; Ines Vaz-Luis; Melissa Anne Mallory; Stephanie M. Wong; Fatih Aydogan; Stephen DeSantis; William T. Barry; Mehra Golshan; *Journal of Clinical Oncology* **2016,** 34, 1190-1196.
DOI: 10.1200/JCO.2015.65.1869

# Treatment of DCIS: Radiation

- Radiation is used for most DCIS

- Omission of Radiation in low-risk patients can be considered:
  - Low or Intermediate grade DCIS
  - <1.6-2.5 cm of disease
  - Older Age (>60)
  - 1cm margins (less data on this)

# Medical Treatment for *DCIS*: Tamoxifen NSABP B-24




- 1804 women randomized between May 1991 and April 1994
- Microscopic margin-positive *DCIS* or *LCIS* was allowed (16%)
- ER- disease was allowed
- Median follow up was 74 months

Fisher B *et al*. 1999 *Lancet* **353**:1993.

# NSABP B-24 results

| | Placebo (n=899) | Tamoxifen (n=899) | RR (95% CI) |
|---|---|---|---|
| Breast cancer (total) | 130 | 84 | 0.63 (0.47-0.83) |
| Invasive | 70 | 41 | 0.57 (0.38-0.85) |
| Non-invasive | 60 | 43 | 0.69 (0.46-1.04) |
| Contralateral breast cancer | 36 | 18 | 0.48 (0.26-0.87) |
| Breast cancer at regional or distant sites | 7 | 3 | 0.42 (0.07-1.82) |
| Endometrial cancer | 2 | 7 | 3.39 (0.64-33.42) |
| Deaths, NED | 11 | 10 | 0.88 (0.33-2.28) |

Fisher B *et al*. 1999 *Lancet* **353**:1993.

# Treatment of DCIS: Tamoxifen
# Meta-Analysis of B-24 and UK/ANZ DCIS

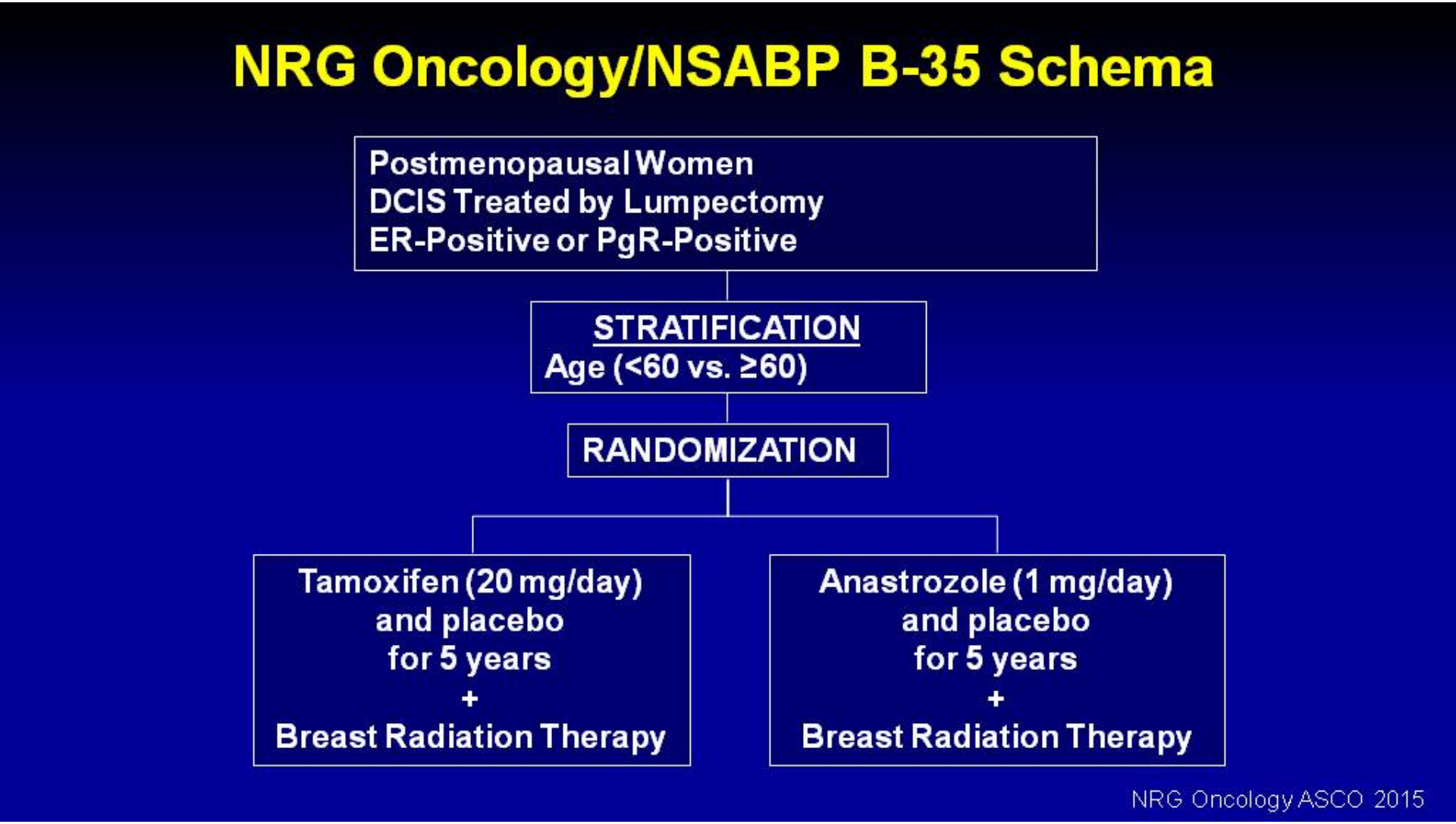
| | DCIS (HR) | IBC (HR) |
|---|---|---|
| Ipsilateral side | 0.75 (0.61-0.92) | 0.79 (0.61-1.01) |
| Contralateral side | 0.50 (0.28-0.87) | 0.57 (0.39-0.83) |

Included 3375 women

No OS benefit  HR = 1.11 (0.89-1.39)

Staley H, *et al*. 2012 *Cochrane* 23076938

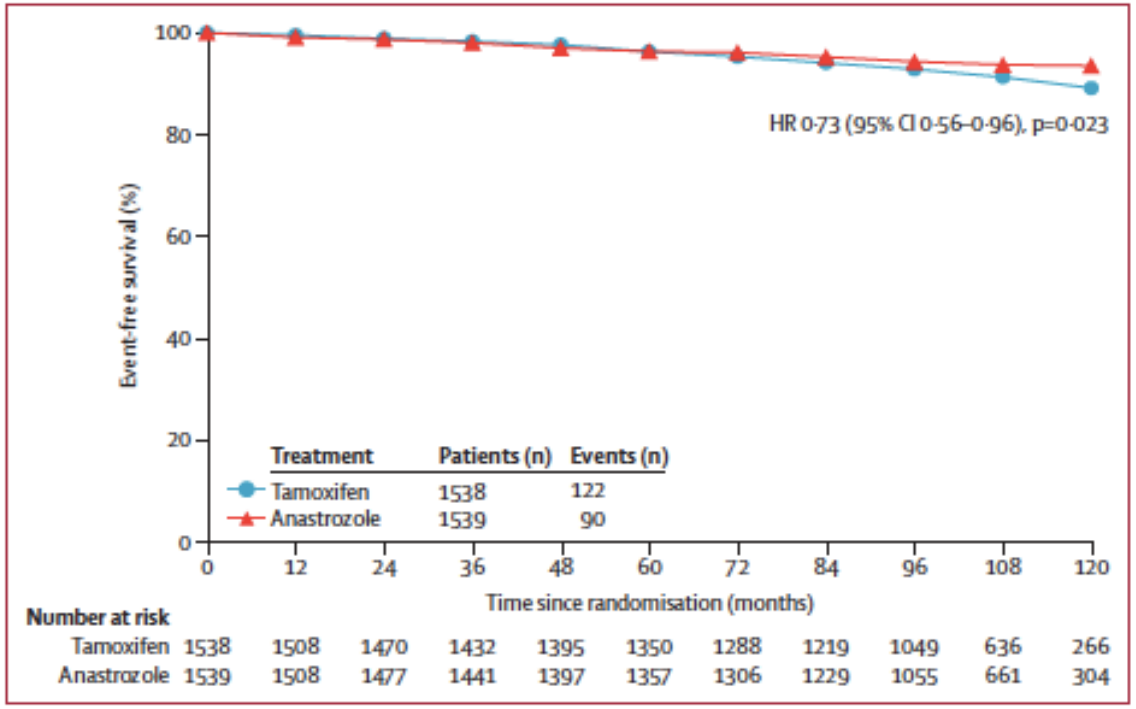
# Treatment of *DCIS*: Tamoxifen vs AI




3104 patients randomized between January 2003 and June 2006
Primary Endpoint: Breast Cancer-Free Interval (BCFI)
Median Follow up 9 years

Margolese RG et al., Lancet. 2016 Feb 27;387(10021):849-56. doi: 10.1016/S0140-6736(15)01168-X. Epub 2015 Dec 11.

# NSABP B-35 Results



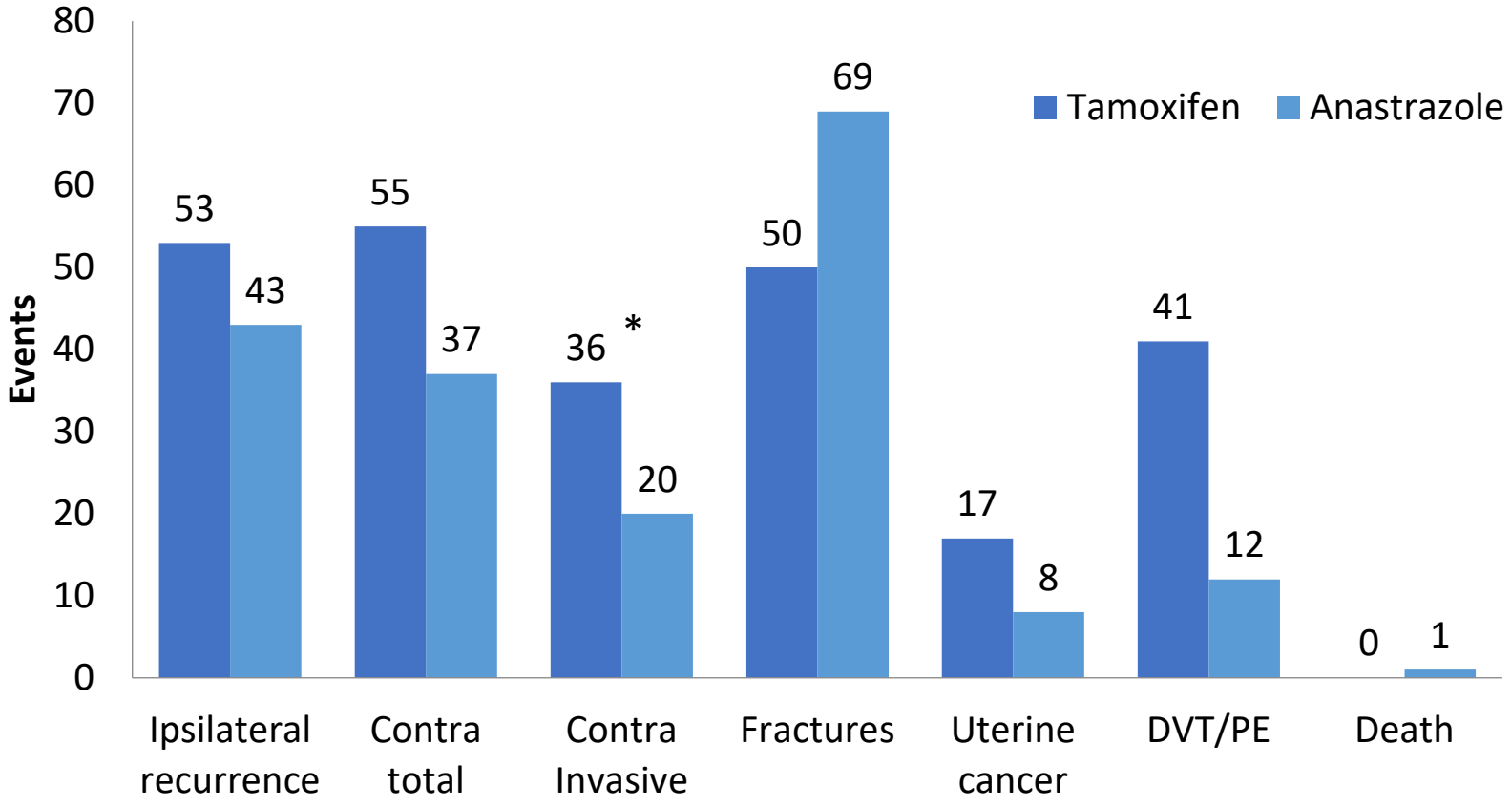

Breast Cancer Free Interval, B-35

| | Tamoxifen (n=1535) | Anastrozole (n=1535) |
|---|---|---|
| **Overall toxicity** | | |
| Grade 0/1 | 312 (20%) | 318 (21%) |
| Grade 2 | 771 (50%) | 771 (50%) |
| Grade 3 | 380 (25%) | 384 (25%) |
| Grade 4 | 59 (4%) | 50 (3%) |
| Grade 5 (death) | 13 (1%) | 12 (1%) |
| **Thromboembolic events** | | |
| Grade 0/1 (none/superficial thrombosis) | 1494 (97%) | 1522 (99%) |
| Grade 2 (deep-vein thrombosis) | 4 (<1%) | 1 (<1%) |
| Grade 3 (uncomplicated pulmonary embolism) | 20 (1%) | 8 (1%) |
| Grade 4 (life-threatening pulmonary embolism) | 17 (1%) | 3 (<1%) |
| Grade 5 (death) | 0 | 1 (<1%) |
| **Arthralgia** | | |
| Grade 0/1 (none/mild pain) | 1177 (77%) | 1031 (67%) |
| Grade 2 (moderate pain) | 302 (20%) | 427 (28%) |
| Grade 3 (severe pain) | 55 (4%) | 77 (5%) |
| Grade 4 (disabling) | 1 (<1%) | 0 |
| **Myalgia** | | |
| Grade 0/1 (none/mild pain) | 1367 (89%) | 1317 (86%) |
| Grade 2 (moderate pain) | 150 (10%) | 187 (12%) |
| Grade 3 (severe pain) | 18 (1%) | 30 (2%) |
| Grade 4 (disabling) | 0 | 1 (<1%) |

*Table 5:* **Adverse events by treatment group**

Margolese RG et al., Lancet. 2016 Feb 27;387(10021):849-56. doi: 10.1016/S0140-6736(15)01168-X. Epub 2015 Dec 11.

# NSABP B-35 Results



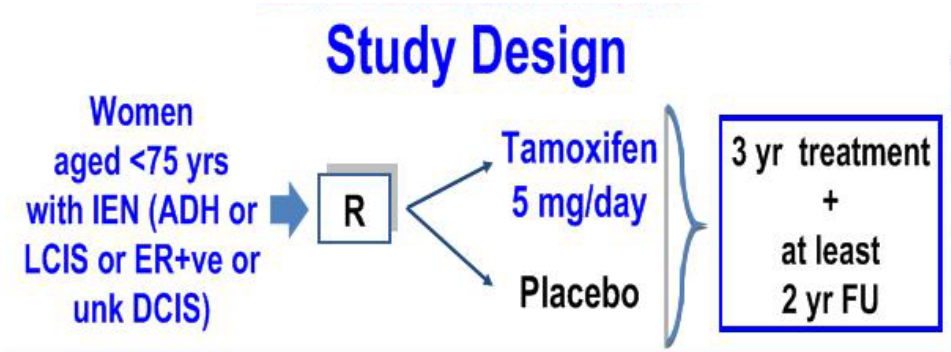

Adapted from presentation by Richard Margolese at 2015 ASCO Annual Meeting

# Conclusions, Implications B-35

- Anastrozole is more effective than Tamoxifen in reducing incidence of invasive breast cancer in patients with DCIS
- Expected side effects for Anastrozole and Tamoxifen seen
- Both Anastrozole and Tamoxifen are effective treatments for women with ER+ DCIS who desire adjuvant therapy

Margolese RG et al., Lancet. 2016 Feb 27;387(10021):849-56. doi: 10.1016/S0140-6736(15)01168-X. Epub 2015 Dec 11.

# Low-dose Tamoxifen for Breast Atypia and Intraepithelial Neoplasia




**Primary endpoint: Incidence of invasive breast cancer or DCIS**

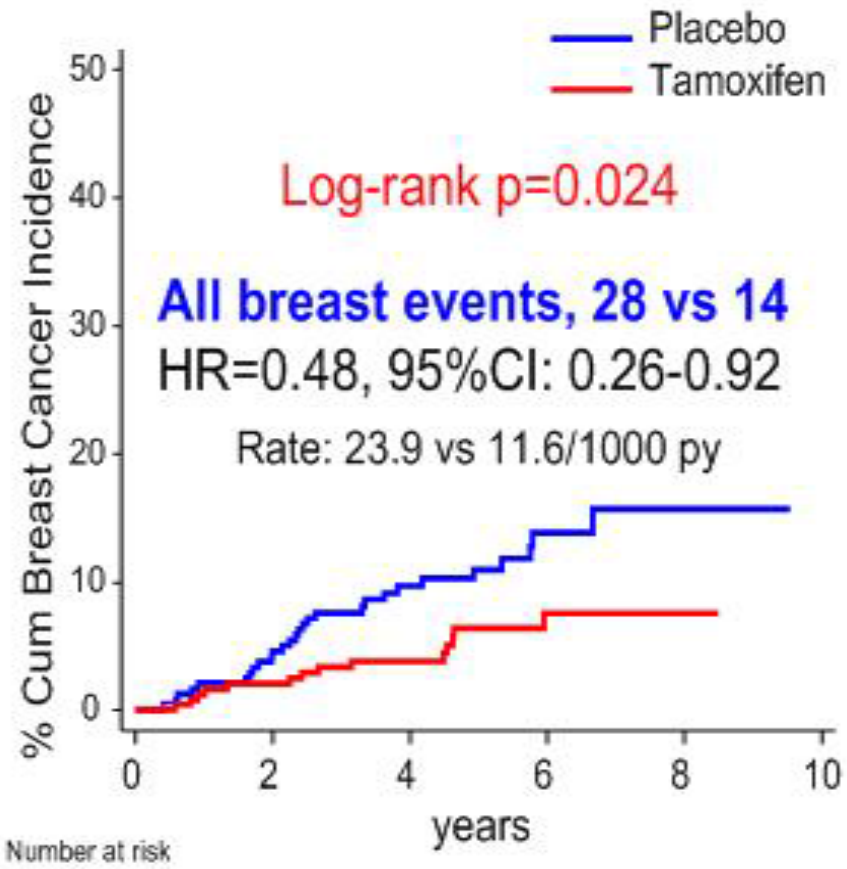
- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

**Main subject and tumor characteristics (n = 500)**

| | Tamoxifen N=253 | Placebo N=247 |
|---|---|---|
| Age, mean (SD) | 54 (9.6) | 54 (9.1) |
| Pre-menopausal, % | 46 | 44 |
| BMI, mean (SD) | 25.7 (4.8) | 25.3 (4.2) |
| ADH, % | 20 | 20 |
| LCIS, % | 11 | 10 |
| DCIS, % | 69 | 70 |
| ER/PR+ve/unknown, % | 66 / 34 | 67 / 33 |
| HER 2-neu 3+, % | 8 | 9 |
| Quadrantectomy/Mastectomy % | 84 / 16 | 82 / 18 |
| Radiotherapy, % | 43 | 43 |

JCO, 2019, DeCensi

# Results: Low Dose Tamoxifen



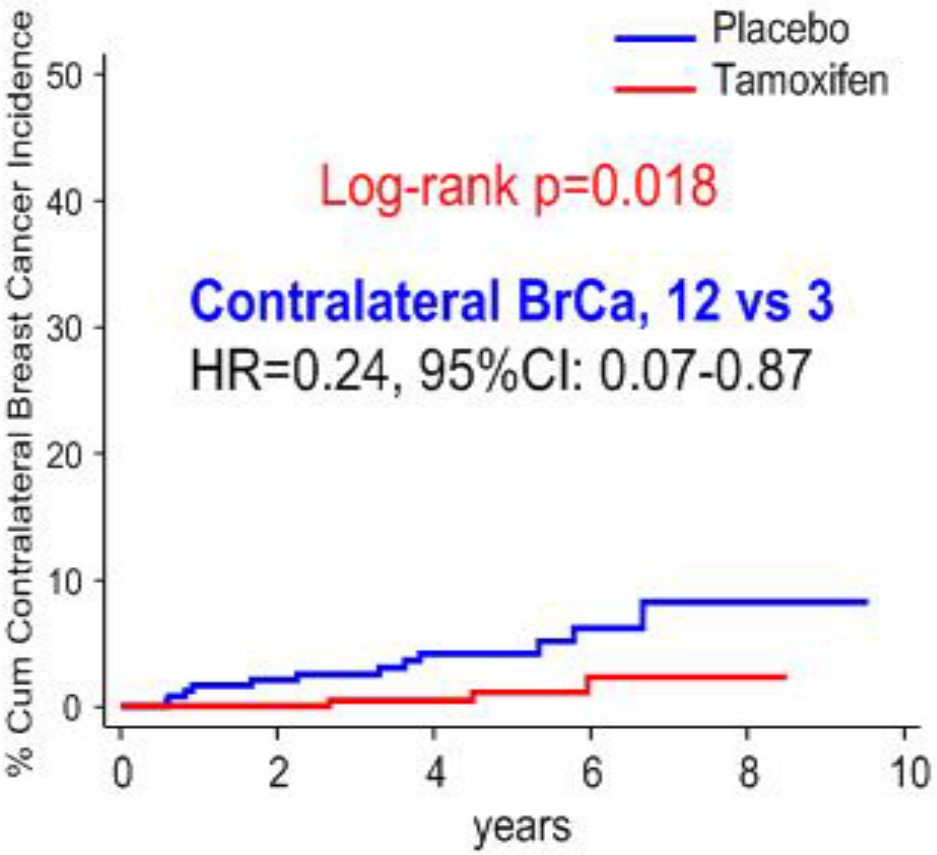



**TABLE 3.** Serious Adverse Events by Allocated Arm

| Adverse Event | Tamoxifen (n = 249) | Placebo (n = 246) |
|---|---|---|
| Endometrial cancer | 1 (0.4) | — |
| Deep vein thrombosis or pulmonary embolism | 1 (0.4) | 1 (0.4) |
| Other neoplasms | 4 (1.6) | 6 (2.4) |
| Coronary heart disease | 2 (0.8) | 2 (0.8) |
| Infection | 2 (0.8) | 2 (0.8) |
| Saphenous varices | 1 (0.4) | |
| Temporal angioma | — | 1 (0.4) |
| Tibial fracture | — | 1 (0.4) |
| Gallbladder stones | — | 1 (0.4) |
| Death | 1 (0.4) | 2 (0.8) |
| Total | 12 (4.8) | 16 (6.5) |

NOTE. Data are presented as No. (%). The safety analysis included all patients who received at least one dose of drug or placebo (495 patients).

# Risk and Results by Pathology

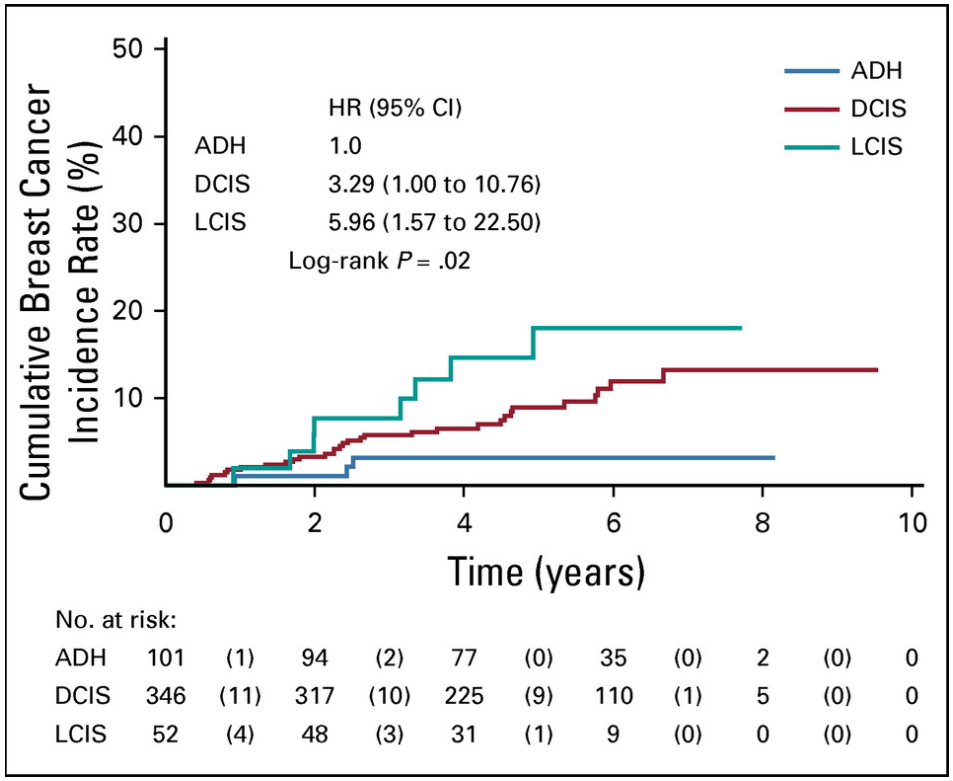
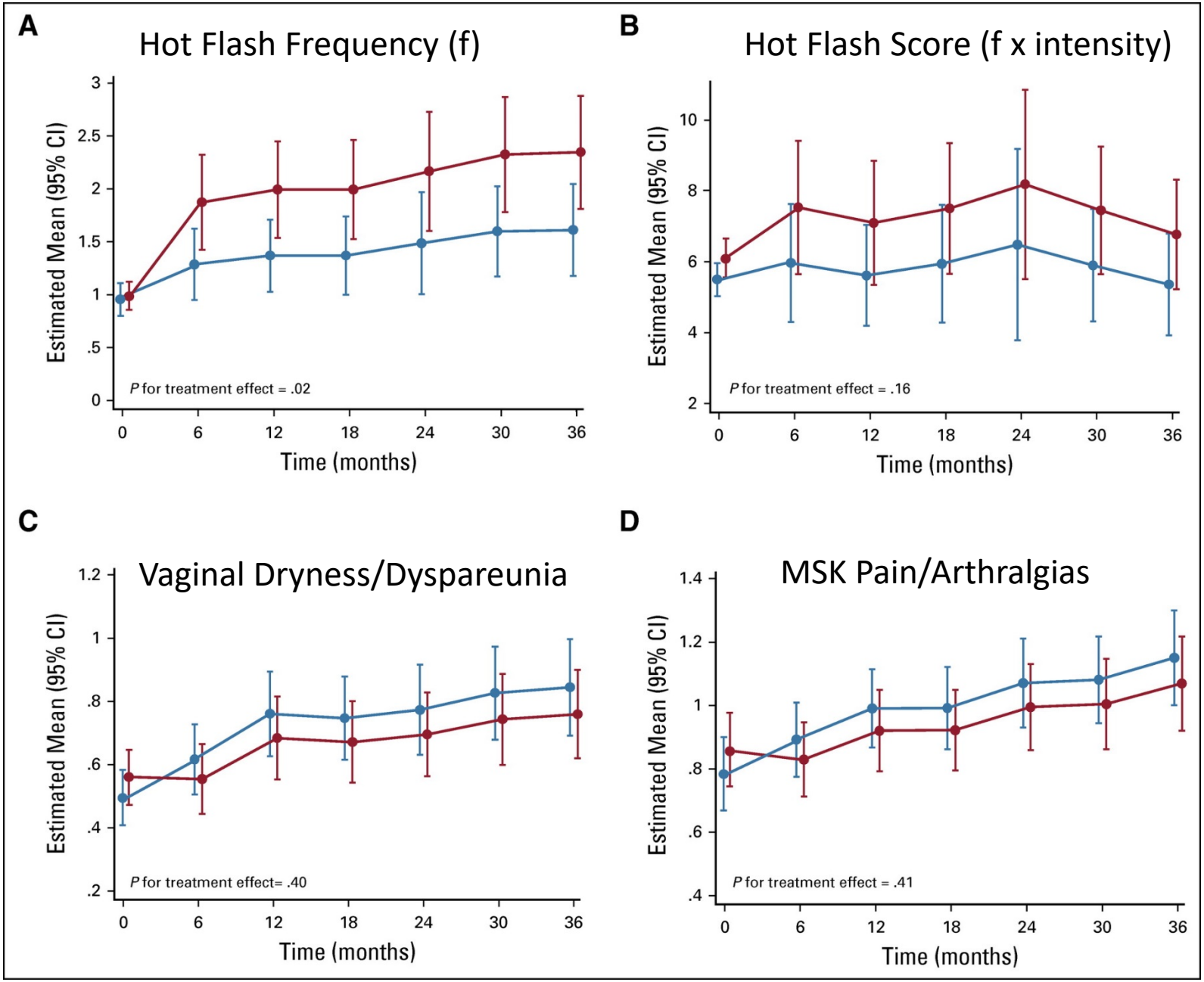



**TABLE A1.** Prespecified Subgroup Analyses

| Subgroup | No. of Patients | *P** | HR (95% CI) |
|---|---|---|---|
| Diagnosis within 12 months since random assignment | 458 | .16 | 0.41 (0.20 to 0.82) |
| Diagnosis between 12 and 60 months | 42 | | 1.59 (0.27 to 9.53) |
| ADH + DCIS | 447 | .54 | 0.53 (0.26 to 1.08) |
| LCIS | 52 | | 0.31 (0.06 to 1.51) |
| ER positive | 333 | .84 | 0.51 (0.24 to 1.10) |
| ER unknown | 166 | | 0.45 (0.14 to 1.49) |

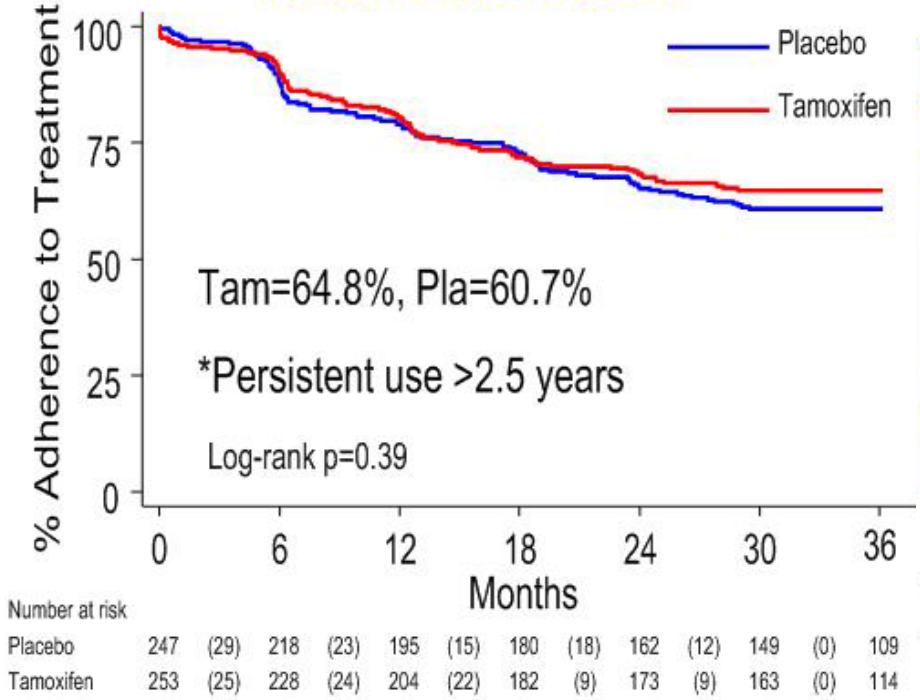
Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hazard ratio; LCIS, lobular carcinoma in situ.

*For interaction with treatment arm.


A
Hot Flash Frequency (f)
Estimated Mean (95% CI)
P for treatment effect = .02
Time (months)
B
Hot Flash Score (f x intensity)
Estimated Mean (95% CI)
P for treatment effect = .16
Time (months)
C
Vaginal Dryness/Dyspareunia
Estimated Mean (95% CI)
P for treatment effect= .40
Time (months)
D
MSK Pain/Arthralgias
Estimated Mean (95% CI)
P for treatment effect = .41
Time (months)

# Adherence and Impact

## Treatment adherence*




## Estimate of treatment impact at 5 years

| | |
|---|---|
| Number needed to treat* | 22 (95% CI, 20-27) |
| Number needed to harm** | 218 (95% CI, 193-265) |
| Likelihood of benefit | 10 (218/22) |

*5 year cumulative incidence of breast events: 6.4% on T and 11.0% on P
**5 year cumulative incidence of SAE: 0.87% on T and 0.41% on P

# Low Dose Tamoxifen Summary:

5mg Tamoxifen/day for 3 years with 5 years of follow up

- ↓50% risk of a breast cancer (DCIS/IC)
- ↓75% risk of a contralateral breast cancer
- No difference in DVT or Endometrial cancers with placebo
- Hot Flashes worse than placebo, but compliance was good

But how does this compare to standard of care?

- 500 patients (compared to >3000 in 5 years at 20mg)

➢Good back up option for those not tolerant to 20mg of Tamoxifen

➢Good upfront option for hesitant patients

# Summary of Treatment for DCIS

- Surgical resection (2mm margin)
  - Mastectomy
  - BCS
  - SLNB indicated in mastectomy
- Radiation
  - Most get radiation
  - Omission possible for low-risk patients
- Endocrine therapy (only indicated for ER+ disease)
  - Treatment for BCT with Tamoxifen or AI
  - Consideration Chemoprevention for Unilateral Mastectomy
  - Contraindicated after Bilateral Mastecomies

# Management of DCIS & Proliferative Breast Disease

| | Risk for Invasive Ca | Upstaging | Surgery for Diagnosis/Tx | Treatment & Prevention |
|---|---|---|---|---|
| DCIS | Precursor | 10-30% to IBC | Excision Clear margins (2mm) | Treatment |
| pLCIS | ?precursor | ~malignant | Excisional Bx/ clear margins | Treatment |
| LCIS | Risk | <5% | Concordance with Core Bx | Chemoprevention |
| ADH | Risk | >20% to DCIS | Excisional Biopsy | Chemoprevention |
| ALH | Risk | <5% | Concordance with Core Bx | Chemoprevention |

# Chemoprevention

# Cost of Survivorship

- Cost of local therapy: 15.5K (in 1998$)

  (Barlow, JNCI 2001)

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- Side effects: Pain after local therapy
  - 47% of Danish patients with some pain
  - 52% of these with moderate/severe pain

  (Gartner, JAMA, 2009)

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  (Barlow, JNCI 2001)

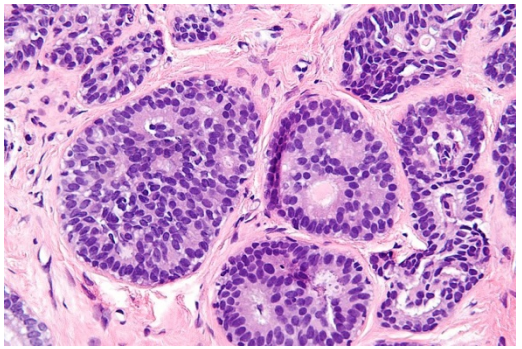
- Side effects: Pain after local therapy
  - 47% of Danish patients with some pain
  - 52% of these with moderate/severe pain

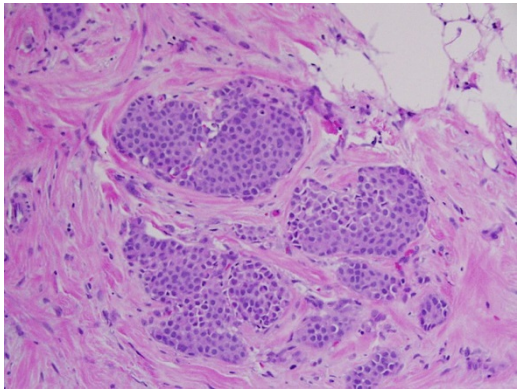
  (Gartner, JAMA, 2009)

- Risk of death: 89.7% 5 year survival

  (https://seer.cancer.gov/statfacts/html/breast.html)

# Who should we consider chemoprevention in?





ASCO/NCCN guidelines:

- Age >35 with life expectancy of 10yrs
  - **h/o Atypical Hyperplasia, LCIS**
  - ≥ 1.7 Gail model
  - >20% Lifetime risk
  - Prior chest RT < 30

Gaps in our recommendations?

- Consider in BRCA2 mutation carriers
- Not strong/specific recommendations for less penetrant mutations

# Breast Cancer Risk Assessment Models

## Gail Model

- Derived from a prospective study of women undergoing mammographic screening
- Incorporates family history (1st degree), benign breast disease, age of menarche, age of first pregnancy, and race
- http://www.cancer.gov/bcrisktool/

## Tyrer-Cuzick, IBIS Breast Cancer Risk Evaluation Tool

- Incorporates 1st and 2nd degree relatives, reproductive factors, BMI, atypical hyperplasia, LCIS
- http://www.ems-trials.org/riskevaluator/

## Breast Cancer Surveillance Consortium Risk Calculator

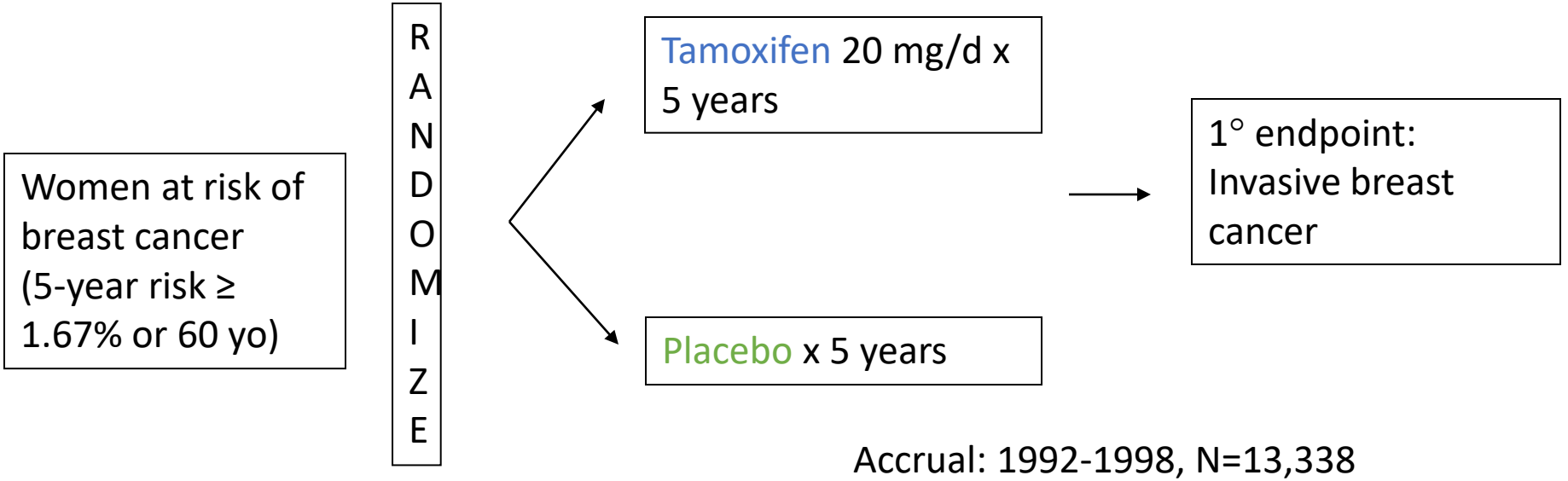
- Estimates 5 year and 10 year breast cancer risk based on age, race/ethnicity, family history of breast cancer, history of breast biopsy, and BI-RADS breast density
- https://tools.bcsc-scc.org/BC5yearRisk/intro.htm

Gail MH *et al*. 1989 *J Natl Cancer Inst* **81**:1879. Tyrer, Statist. Med. 2004; **23**:1111–1130. Tice JA *et al., J Clin Oncol* 2015, published online August 17, 2015.

# The Chemoprevention Trials

| Trial | Agent | Year | N | RR/HR | notes |
|---|---|---|---|---|---|
| STAR | Ral vs Tam | 2006 | 19747 | **1.24 (1.05-1.47)** | Postmen, No LCIS (50% prior TAH) |
| IBIS-I | Tam vs placebo | 2007 | 7154 | 0.74 (0.58-0.94) | |
| NSABP P-1 | Tam vs placebo | 2005 | 13388 | 0.57 (0.46-0.70) | Pre and post |
| Royal Marsden | Tam vs placebo | 2007 | 2471 | 0.78 (0.58-1.04) | |
| Italian Tamoxifen | Tam vs placebo | 2007 | 5408 | 0.80 (0.56-1.15) | |
| **USPSTF meta** | **Tamoxifen** | 2013 | | **0.70 (0.59-0.82)** | |
| MORE/CORE | Ral vs placebo | 2004 | 5129, 2576 (2:1) | 0.34 (0.22-0.50) | |
| RUTH | Ral vs placebo | 2006 | 10101 | 0.56 (0.27-0.71) | |
| **USPSTF meta** | **Raloxifene** | 2013 | | **0.44 (0.27-0.71)** | |
| IBIS-II | Anastrozole vs placebo | 2014 | 3864 | 0.47 (0.32-0.68) | 40-70 yo (postmen) Avg Tyrer-Cuzick 7.7% |
| MAP-3 | Exemestane vs placebo | 2011 | 4050 | 0.35 (0.18-0.70) | Avg age 62.5, 35+ Avg Gail 2.3% |

# Tamoxifen Breast Cancer Prevention Trial (NSABP P-1)

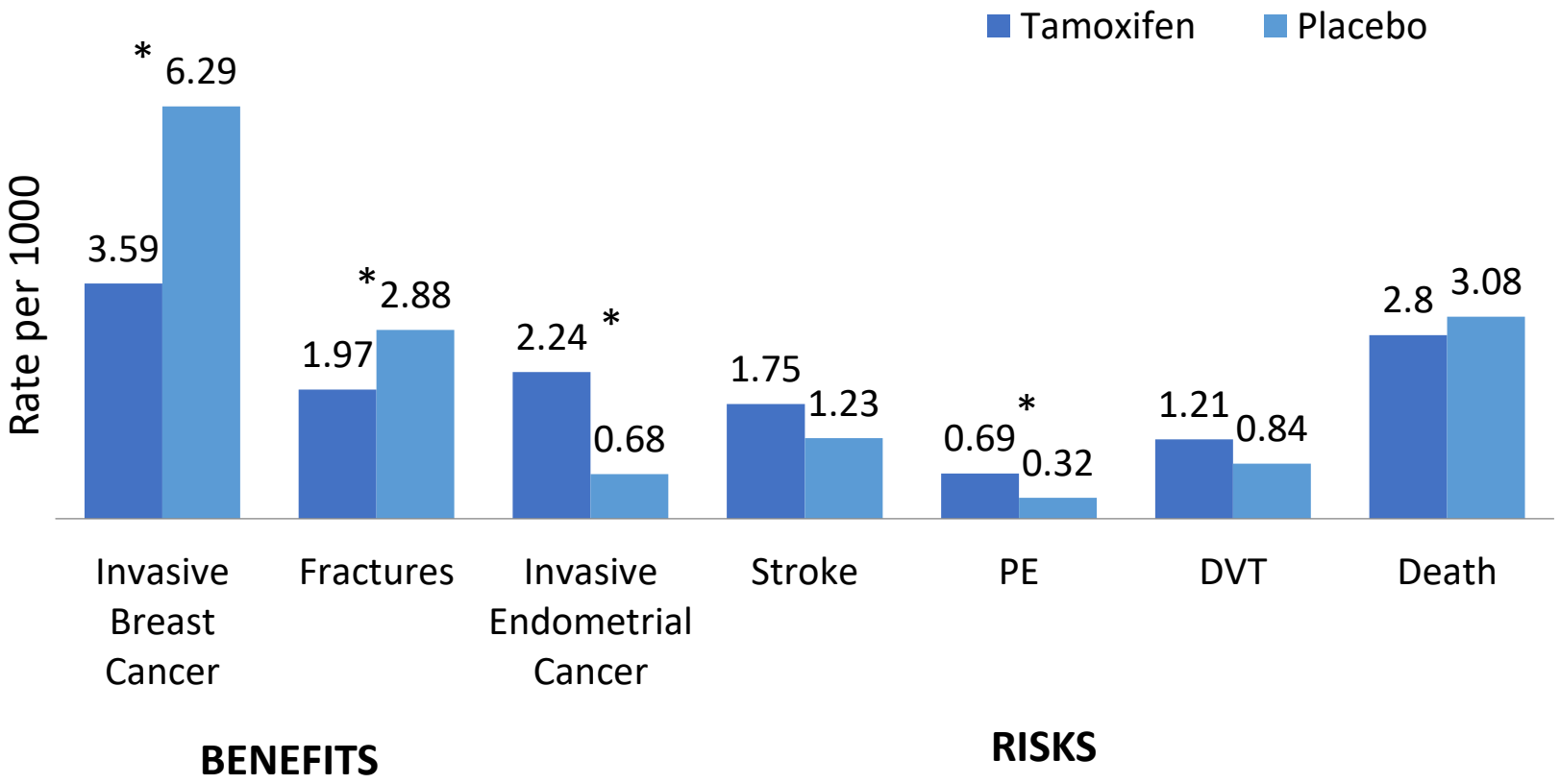



Accrual: 1992-1998, N=13,338
Closed early after interim analysis
Median follow-up 54.6 months

Analysis showed a 49% reduction in incidence of invasive breast cancer in participants treated with tamoxifen

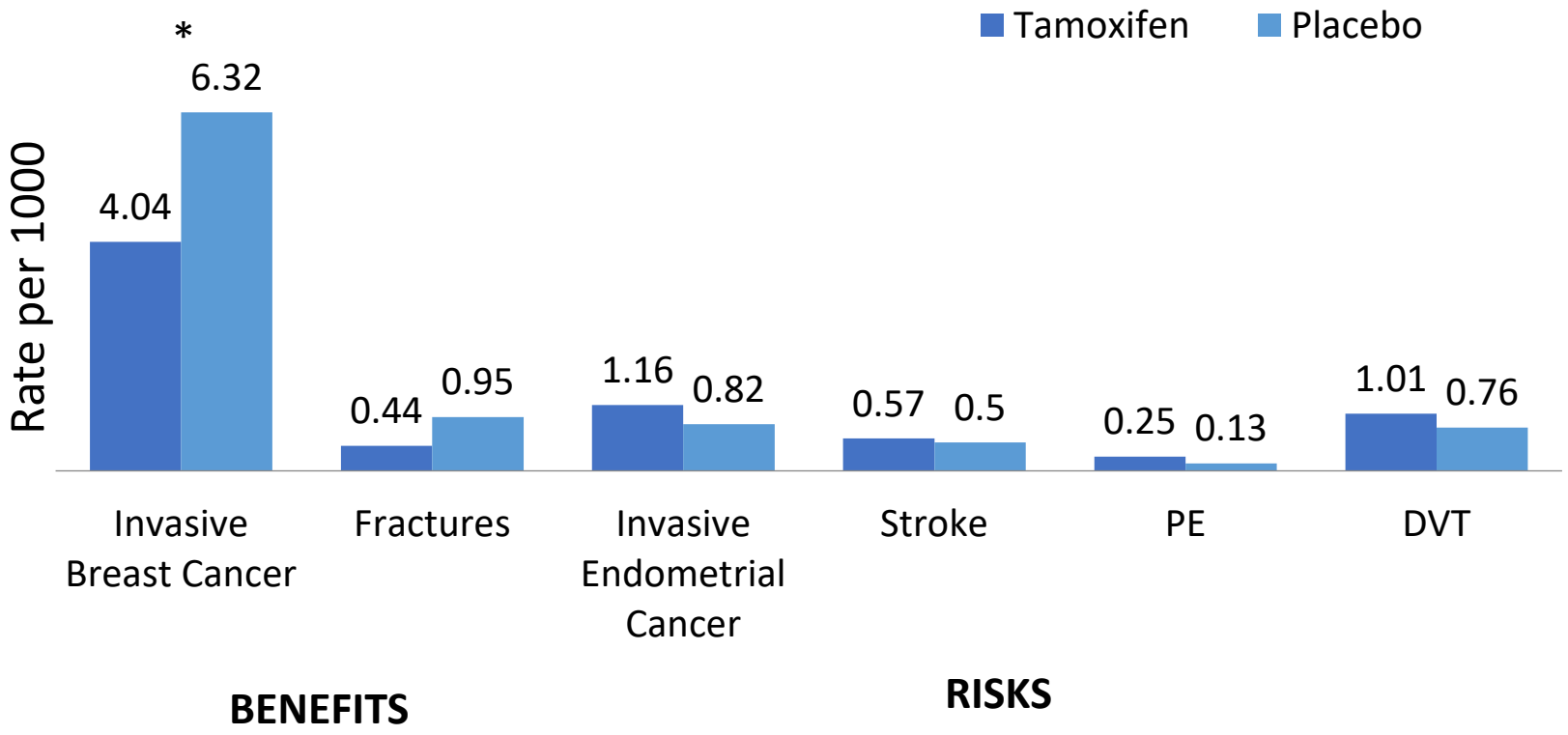
Fisher B *et al*. 1998 *J Natl Cancer Inst* **90**:1371.

# Tamoxifen Risks and Benefits:
# **All High-Risk Women** (NSABP P-1)



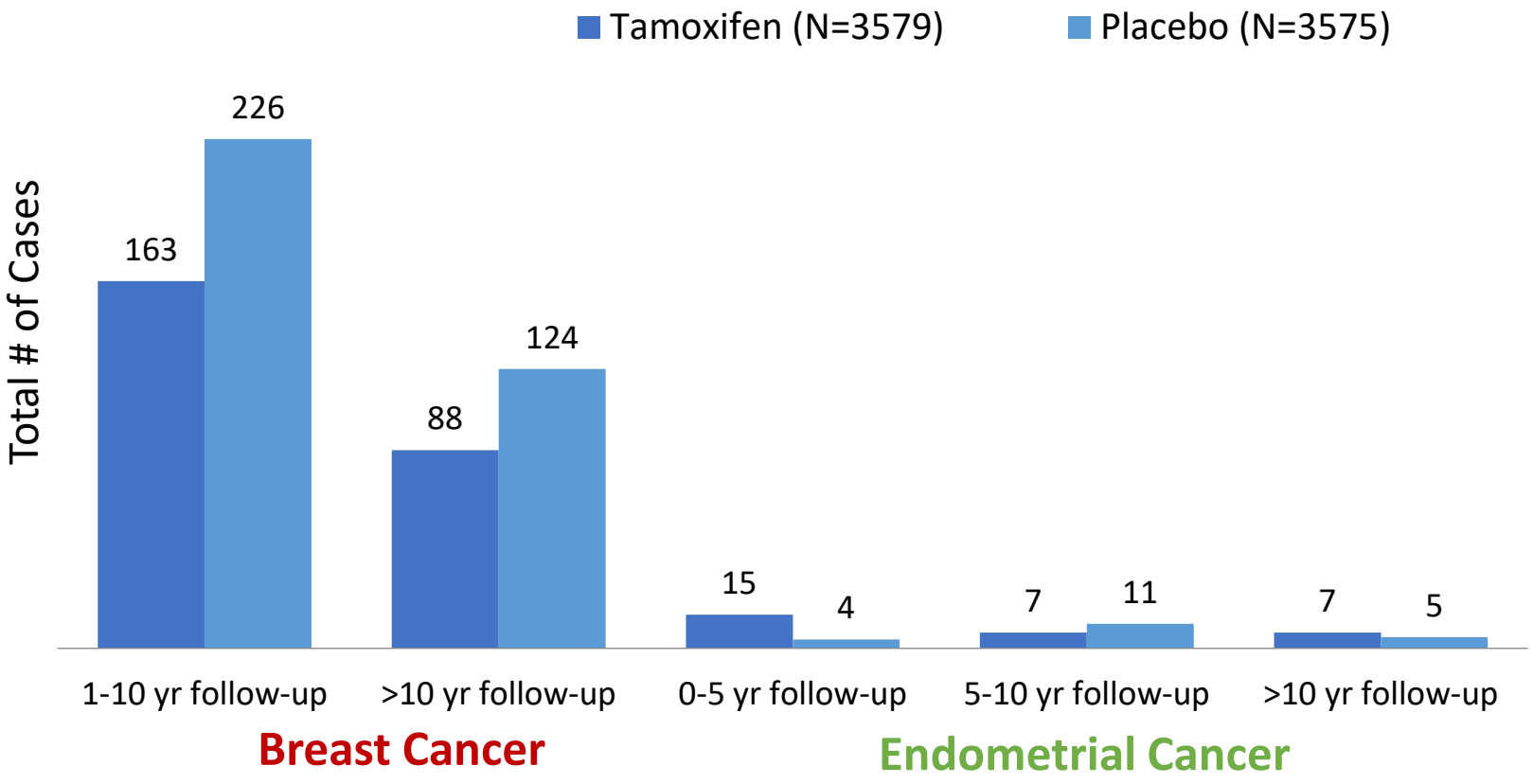

Fisher B *et al. Journal of the National Cancer Institute*, Vol. 97, No. 22, November 16, 2005

# Tamoxifen Risks and Benefits: **Women <50** (NSABP P-1)



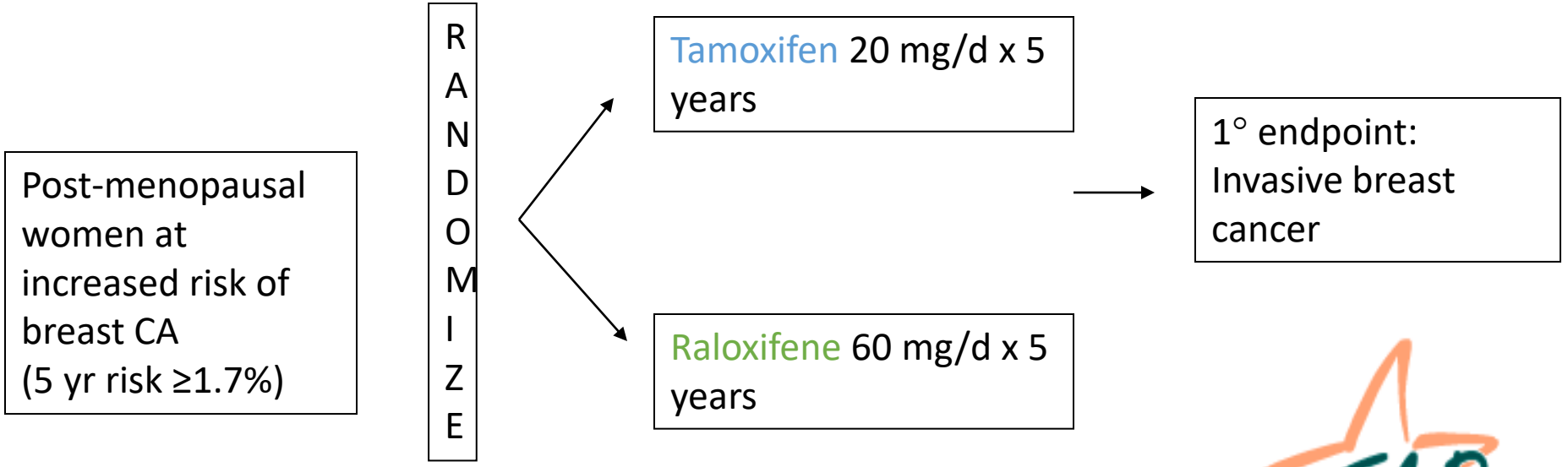

Fisher B *et al., Journal of the National Cancer Institute*, Vol. 97, No. 22, November 16, 2005

# Tamoxifen Risks and Benefits: **Long-Term** Follow-Up with Tamoxifen (IBIS-I)




Cuzick J *et al., Lancet Oncol*. 2015 Jan;16(1):67-75. doi: 10.1016/S1470-2045(14)71171-4. Epub 2014 Dec 11.

# Tamoxifen vs Raloxifene: STAR Trial (NSABP P-2)

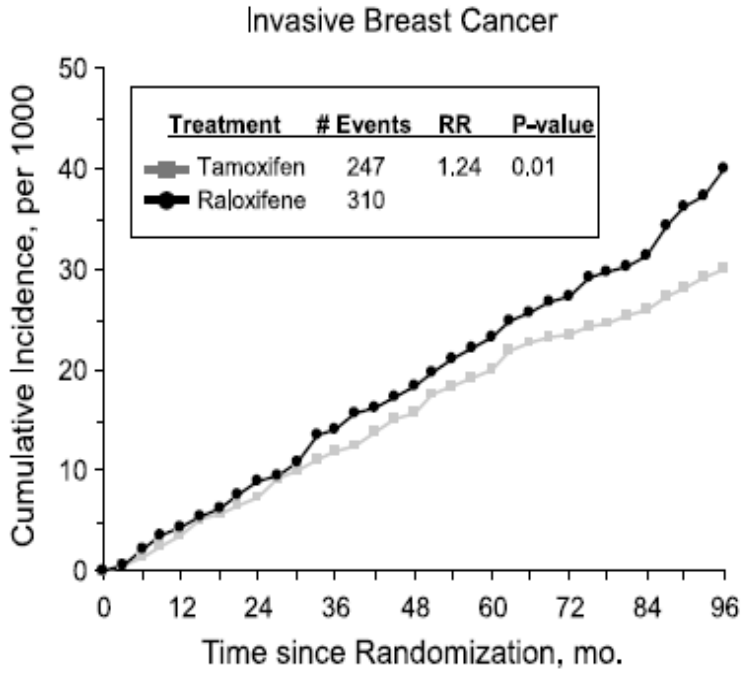


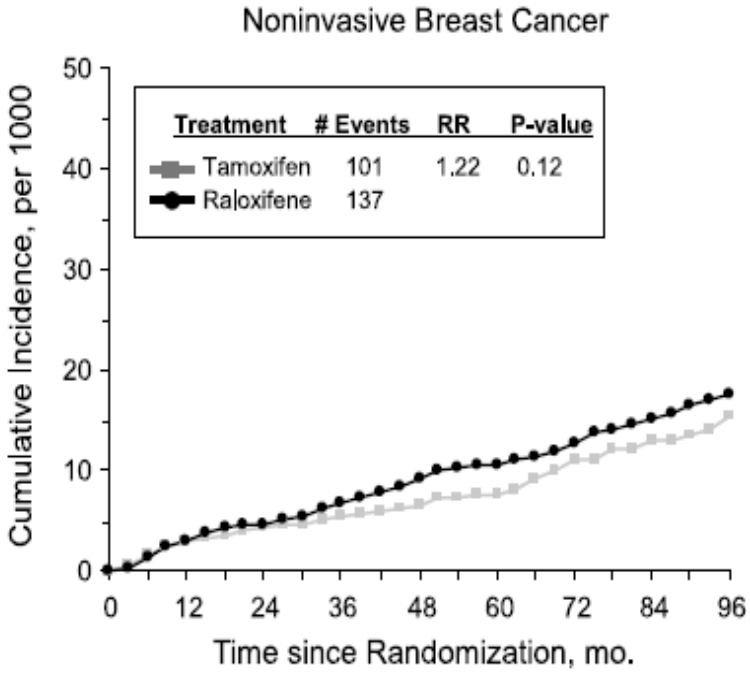

- Accrued 19,471 patients between July 1999-Nov 2004
- Mean age participants at randomization 58.5 years
- 93% of participants were white
- Mean predicted 5-year risk of IBC was 4.03%

STAR
Study of Tamoxifen And Raloxifene

Vogel VG *et al*. 2006 *JAMA* **295**:2727. Vogel VG *et al. Cancer Prev Res (Phila)* **3**:696-706, 2010.

# STAR Long Term Update 2010: Tamoxifen is more effective



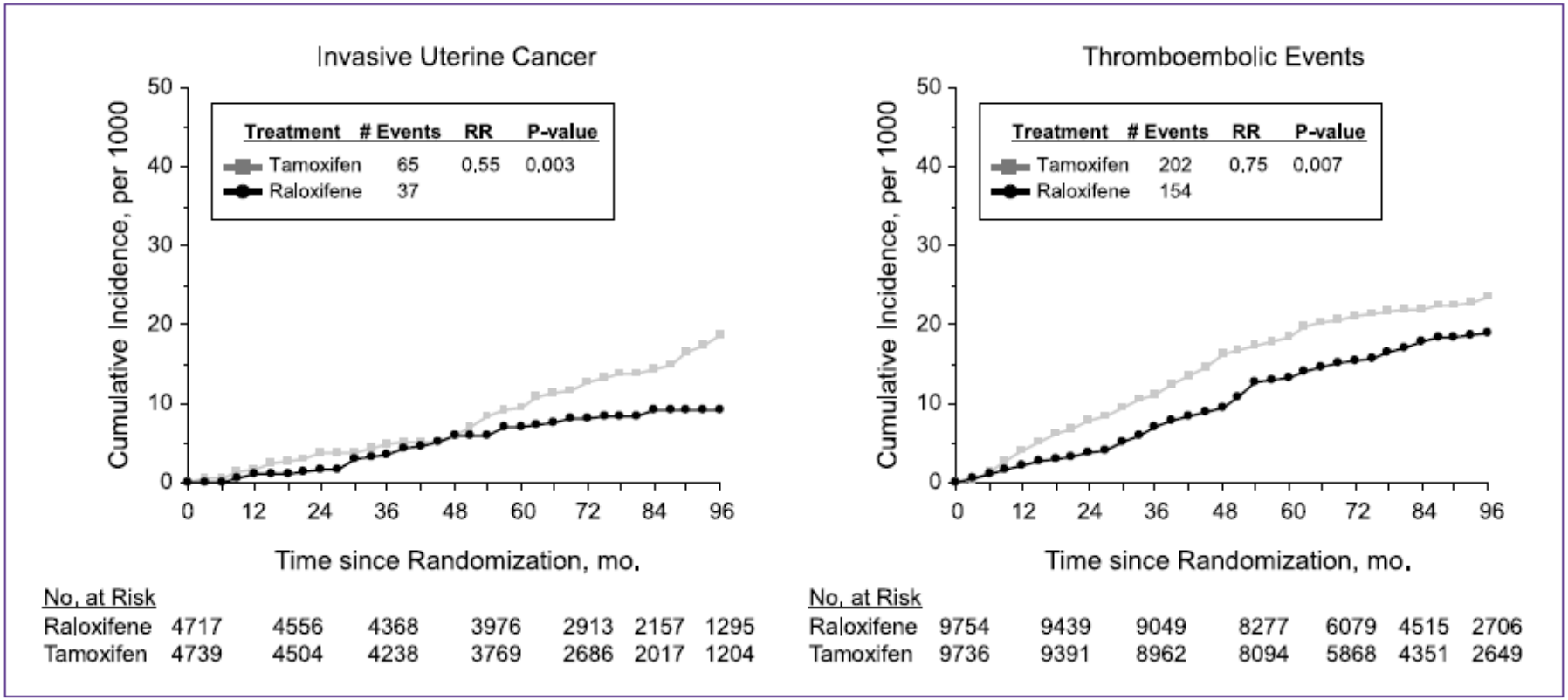




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Raloxifene | 9754 | 9398 | 8973 | 8196 | 5999 | 4453 | 2650 |
| Tamoxifen | 9736 | 9387 | 8939 | 8059 | 5833 | 4326 | 2621 |

| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Raloxifene | 9754 | 9365 | 8925 | 8125 | 5938 | 4405 | 2616 |
| Tamoxifen | 9736 | 9359 | 8901 | 8019 | 5793 | 4290 | 2593 |

Vogel et al *Cancer Prevention Research* 3(6) 696-706 2010

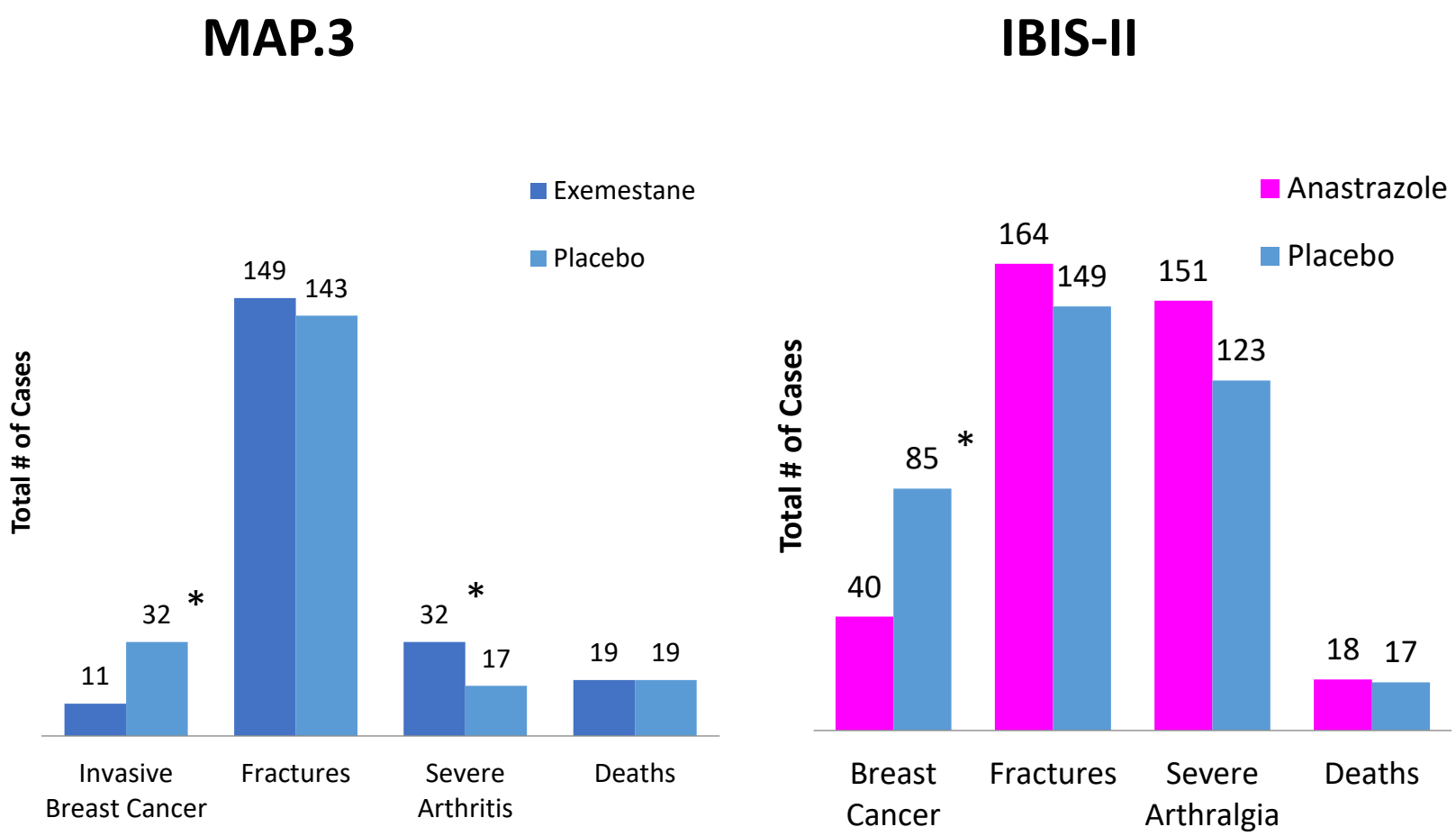
# …and more toxic




*Hysterectomy for benign disease was double in Tamoxifen group, RR = 0.45 (0.37-0.54)

Vogel et al *Cancer Prevention Research* 3(6) 696-706 2010

# Risks and Benefits of AIs

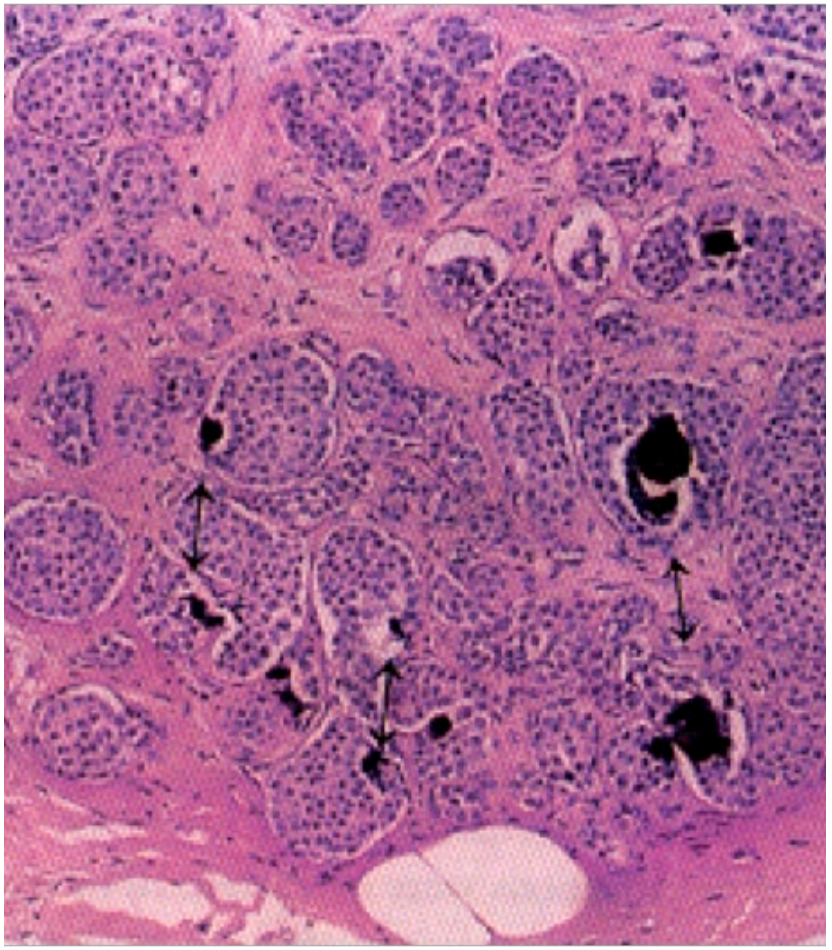



No Direct comparison of AI to Tamoxifen for prevention, but extrapolation from treatment data for Breast cancer is often used.

Goss PE, Ingle JN, Ales-Martinez JE, *et al. NEJM* 2011;364(25):2381-91. Cuzick J *et al., Lancet* 2014;383:1041-48.

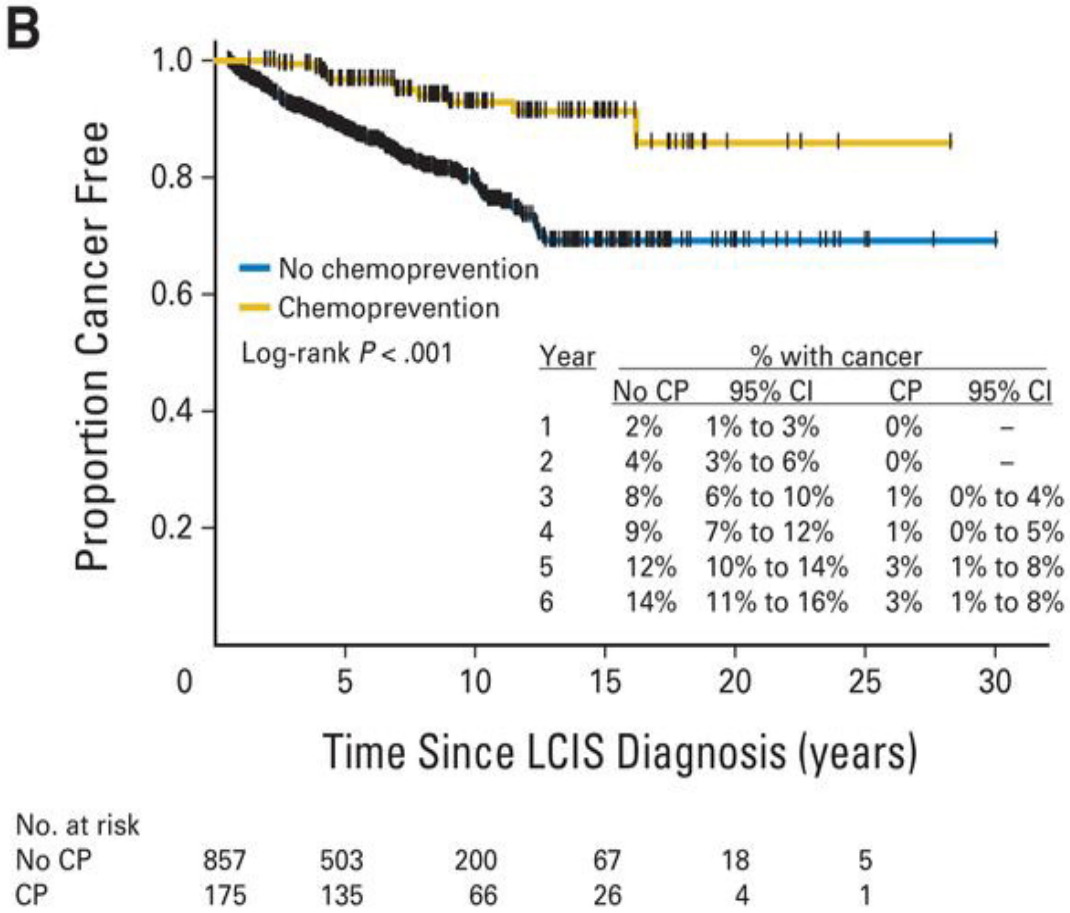
# *LCIS:* Proliferative Breast Disease

- Risk factor not a direct precursor lesion for invasive carcinoma
- Restaged by AJCC
  - NOT a Cancer
- 7-11 Fold increase of Cancer
  - Increases risk of IDC, ILC, Mixed IC and DCIS
- Usually incidental finding on Bx
- Mean age 44-46
- 80-90% in premenopausal
- Strongly ER+ typically
- Increased incidence in HRT users



# LCIS: Longitudinal Experience and Breast Cancer Risk

- 29-year study
- 1060 patients
- LCIS at MSKCC
- Without chemoprevention
  - Incidence 2% per year
  - Cumulative 26% at 15 yr
- Chemoprevention reduced incidence of breast cancer
  - 7% vs. 21% at 10 yrs
  - HR 0.27




King TA, *et al.* *J Clin Oncol* 2015;33.

What’s the reality?
Who is getting it and actually taking it?

# Shared decision making-Patient perspective

Life experiences

"they said, "Oh, but this is like a 50 percent reduction." Well, all I know is my sister said what bad side effects she had and she attributed it a lot to tamoxifen."

STAR decliner, 52 years old, Gail score 3.94

"What happened is I come from an extraordinarily long line of breast cancer victims. I say "victims" because they haven't all been survivors, unfortunately."

STAR participant, 48 years old, Gail score 4.17

Understanding the risk/benefits

"Well, I might not get breast cancer but I might get uterine cancer. What good is that?" And actually breast cancer I think is a lot easier to detect a lot of times, especially when you're getting mammogram on a regular basis, as I am."

STAR decliner, 58 years old, Gail score 5.34

"I looked at the risks of taking tamoxifen, I looked at what my own known personal risk of developing the disease is, and I also looked at what the consequences of not doing anything would be, and the benefits—possible benefits—of participation, for me, so far outweighed any detrimental possible effects of possibly taking tamoxifen"

STAR participant, 48 years old, Gail score 4.7

Holmberg, *Med Decis Making*, 2015

# Shared decision making-Provider stats

350 PCP (FM, IM, Gyn) survey

- 27% prescribed Tam last 12 month
- Prescribers more likely to
  - have family member with breast cancer (20 vs 9%)
  - Believe that the benefits outweigh risks (63% vs 39%)
  - Easy to determine who is eligible (28 vs 11%)
  - Colleagues that are prescribing it (33% vs 17%)

Armstrong, *Arch Internal Med*, 2006

# Shared decision making-Results

12+ studies evaluating decision guides, process

Range of Chemoprevention uptake 0.9%-56%

Higher rates of chemoprevention:

- In person discussion
- Oncology/High Risk specialty clinics
- Opportunity for clinical trials
- Higher risk of breast cancer

Nelson, *Ann Inter Med*, 2013

# Adherence

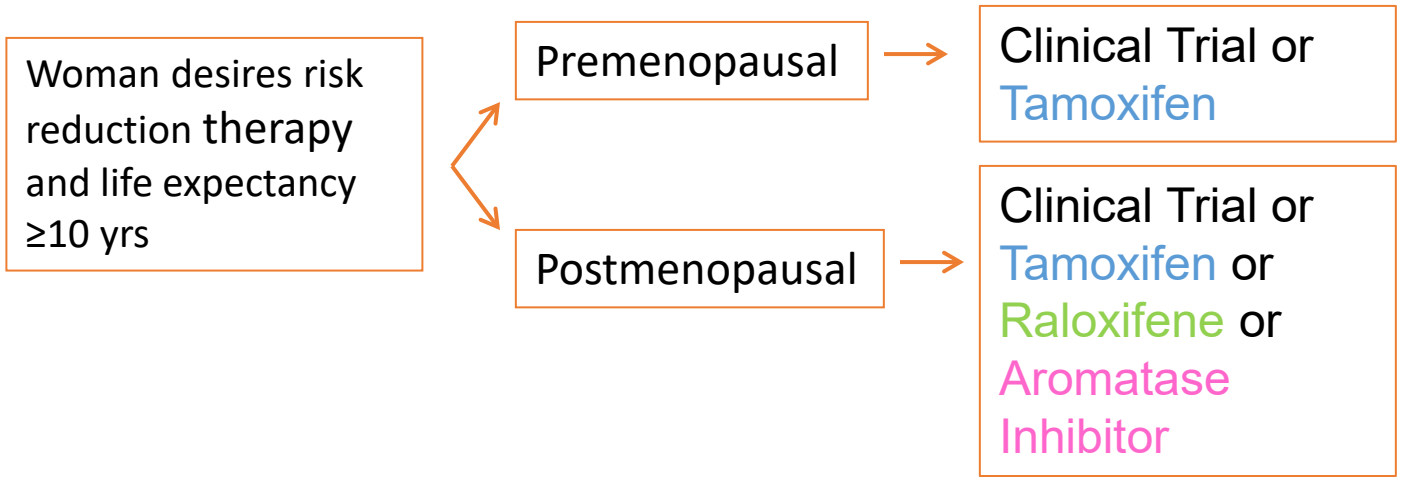
Difference in Adherence between arms in Placebo trials is 1-8%

Difference in STAR was 72% (Raloxifene) vs 68% (Tamoxifen)

Similar rates to adherence in breast cancer treatment studies

Nelson, *Ann Inter Med*, 2013

# Summary: Options for Chemoprevention for Breast Cancer (Including proliferative breast disease)




Adapted from NCCN Guidelines Version 1.2016.

# Who should get chemoprevention?

## Ideal candidates

Tamoxifen

- Premenopausal (40-50) women with high risk
- Postmenopausal women <60 with high risk of cancer and low risk of SAE

Raloxifene

- Postmenopausal women >average risk with osteopenia

Aromatase Inhibitor

- Postmenopausal women at highest risk with low risk of SAE (or Tam/Raloxifene is contraindicated.

## Offer/Consider

- motivated women with above average risk (Risk models)
- BRCA2 mutation carriers who are considering screening rather than risk reducing surgery, or significantly delayed risk reducing surgery

## Remember

- Shared decision making is important
- Consider medications for the best fit

# Can we change risk with lifestyle modifications?

How do we treat the whole woman?

# Modifiable Factors with Increased Risk

| Factor | Relative risk (RR) or Effect |
|---|---|
| Combined Hormone Therapy | ~26% increase |
| Ionizing radiation to chest < 30 | 5 to 20 |
| Obesity (>82 kg vs. <59 kg) | 2.85 |
| Alcohol intake (4 drinks/day vs. non-drinkers) | 1.32 |
| Parity (Nulliparous vs. parous) | 2 |

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

# Modifying Weight changes BC Risk (NHS)

**Table 2.** Relative Risk of Postmenopausal Breast Cancer According to Weight Change Since Age 18 Years

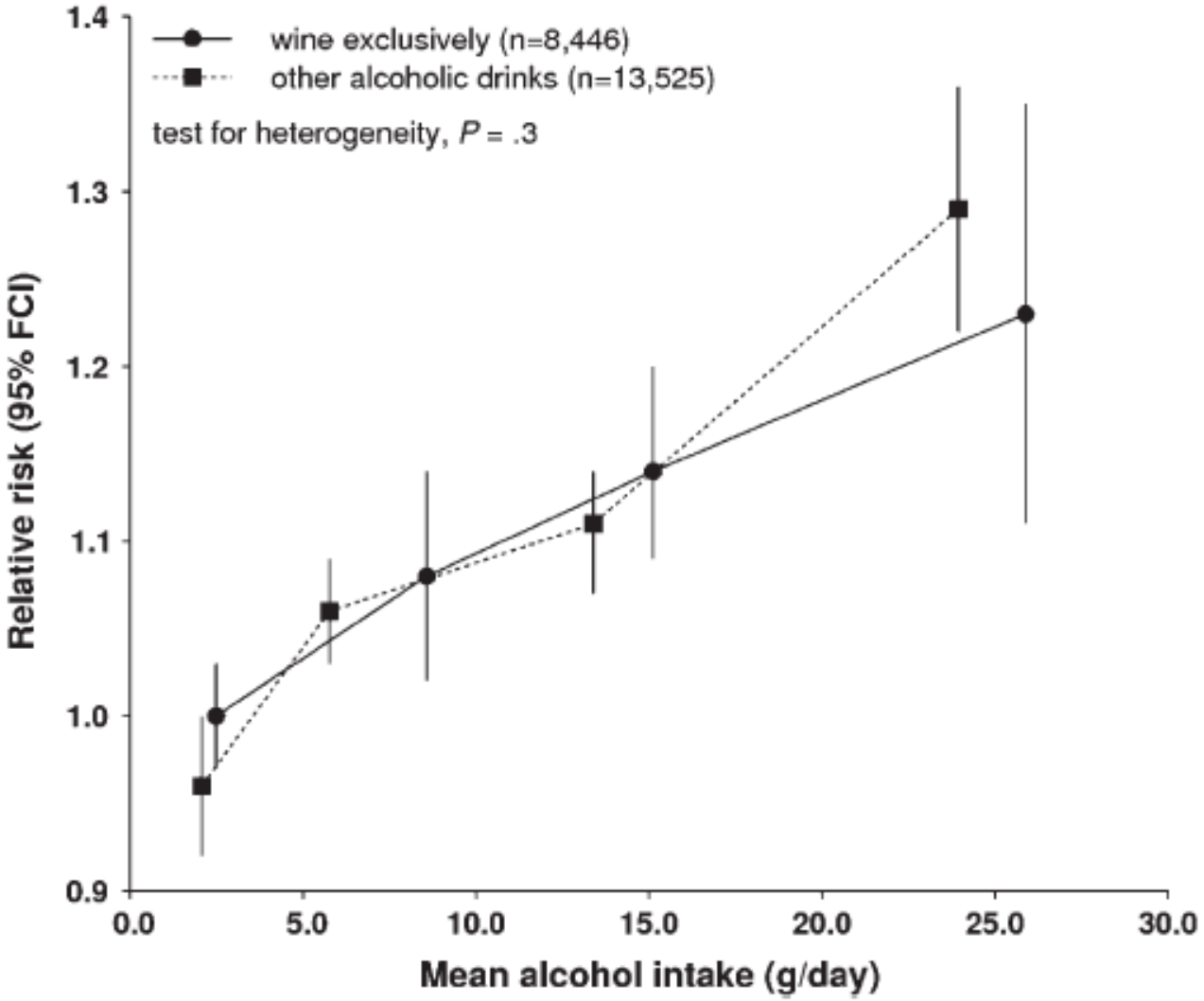
| Weight Change Since Age 18 y, kg | Simple Update* | | | Stable Change† | |
|---|---|---|---|---|---|
| | No. of Cases | Age-Adjusted RR | MV-Adjusted RR (95% CI)‡ | No. of Cases§ | MV-Adjusted RR (95% CI)‡ |
| Overall | | | | | |
| Loss | | | | | |
| ≥10.0 | 53 | 0.72 | 0.84 (0.62-1.13) | 48 | 0.80 (0.58-1.11) |
| 5.0-9.9 | 99 | 0.88 | 0.94 (0.75-1.18) | 84 | 0.90 (0.69-1.17) |
| 2.0-4.9 | 152 | 0.97 | 1.00 (0.82-1.21) | 109 | 1.05 (0.83-1.33) |
| Loss or gain <2.0 | 317 | 1.00 | 1.00 | 190 | 1.00 |
| Gain | | | | | |
| 2.0-4.9 | 420 | 1.12 | 1.10 (0.95-1.28) | 315 | 1.08 (0.90-1.29) |
| 5.0-9.9 | 798 | 1.17 | 1.15 (1.01-1.31) | 749 | 1.13 (0.96-1.33) |
| 10.0-19.9 | 1357 | 1.16 | 1.15 (1.01-1.30) | 1320 | 1.13 (0.97-1.32) |
| 20.0-24.9 | 429 | 1.18 | 1.21 (1.05-1.40) | 411 | 1.17 (0.99-1.40) |
| ≥25.0 | 768 | 1.36 | 1.45 (1.27-1.66) | 749 | 1.43 (1.22-1.68) |
| *P* for trend‖ | | <.001 | <.001 | | .001 |
| *P* for weight loss trend¶ | | .02 | .02 | | .02 |

Elliason et al. *JAMA* 2006; 296:193-201

# Alcohol and risk of breast cancer: Million Women Study

- Study of 1,280,296 women who completed a survey on demographics and lifestyle aspects upon presentation to UK breast cancer screening clinics between 1996 and 2001
- Cohort followed prospectively for development of variety of cancers, including breast cancer, via the NHS registry
- Alcohol intake categorized as 0, 2 or less, 3-6, 7-14 or $\geq$ 15 drinks per week
- Women resurveyed at three years
- Median Follow up 7.2 years.

# Million Women Study Results




For every 10g/d alcohol consumed, relative risk for breast cancer was increased by 12%

# Overall Take Home Points

1) DCIS requires surgery to a clear/2mm margin (BCT or mastectomy for local therapy) and treatment with Tamoxifen or AI should be considered for ER+ DCIS s/p BCT

2) LCIS is a significant risk factor for developing Breast Cancer and surgical removal is not required, but chemoprevention should be considered/recommended.

3) Women at above average risk should be offered chemoprevention
   - Extrapolated Effectiveness: AI > Tam > Raloxifene
   - Side effects: Raloxifene > Tamoxifen > AI

4) Survivorship has costs

5) Counsel on lifestyle choices: Exercise, Weight, and alcohol.

# Thanks!

UNIVERSITY of WASHINGTON