

Therapy for Non-Invasive Breast Cancer & Prevention

Rachel Yung, MD
Assistant Professor, UWSOM
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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

Major Risk Factors

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

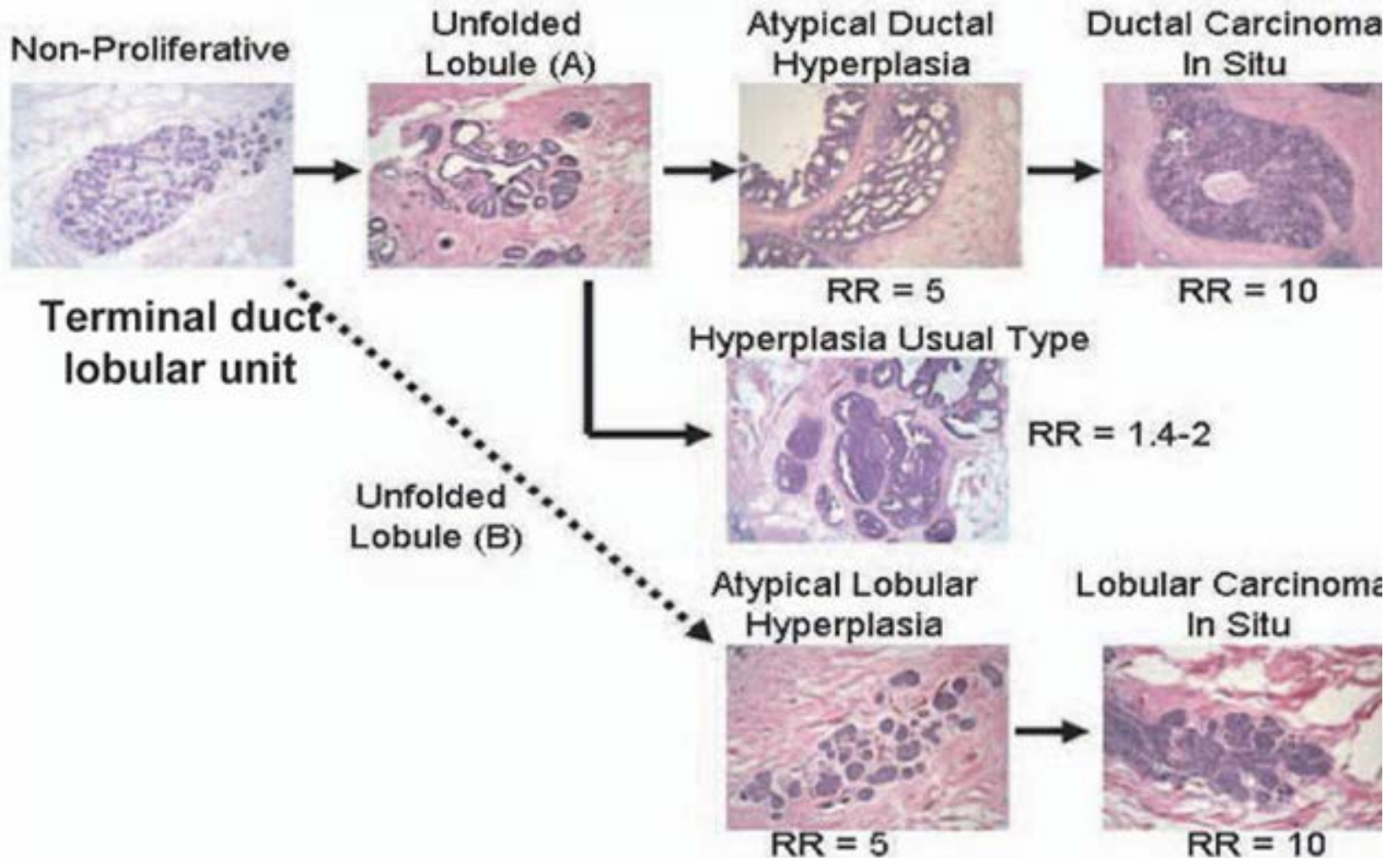
Modifiable Factors with Increased Risk

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

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 (strenuous exercise \geq 4 hrs/week)	Average RR reduction is 30% to 40%. The effect may be greatest for premenopausal women of normal or low body weight.

Proliferative lesions & Intraepithelial Neoplasia

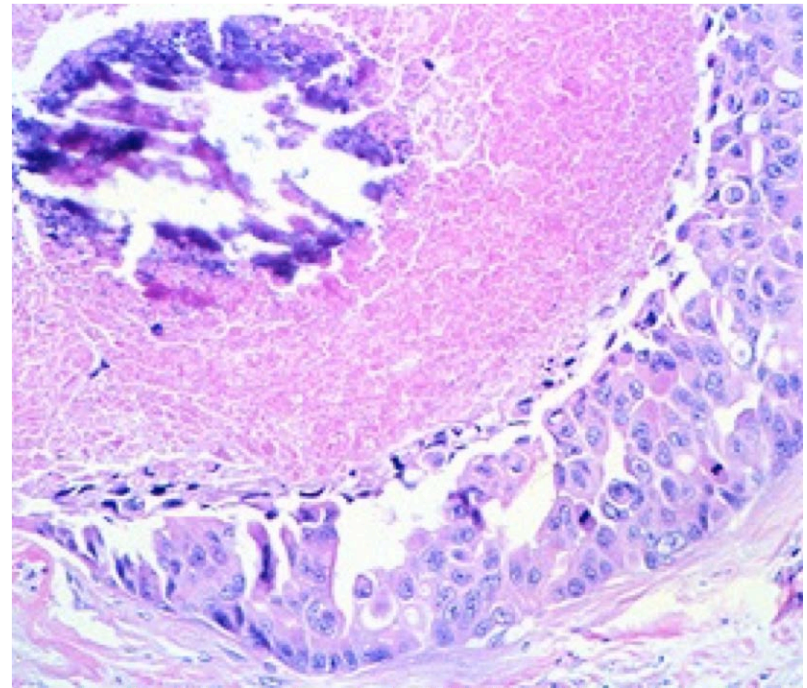


Management of DCIS & Proliferative Breast Disease

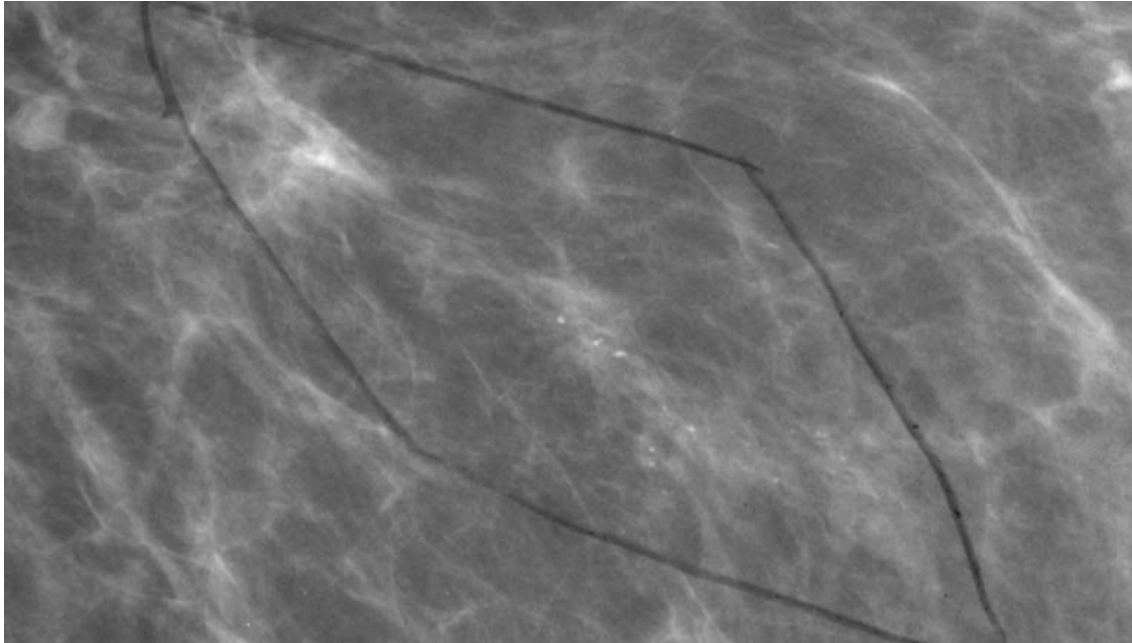
	Risk for Invasive Ca	Upstaging	Surgery for Diagnosis/Tx	Treatment & Prevention
DCIS	Precursor	10-30% to IBC	Excision Clear margins (2mm)	Treatment
pLCIS	?precursor	~malignant	Excisional Bx/ clear margins	Treatment
LCIS	Risk	<5%	Concordance with Core Bx	Chemoprevention
ADH	Risk	>20% to DCIS	Excisional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

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
 - For mastectomy, failure rate 1-2% with 97-98% DFS
- 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 done for mastectomy or features in needle biopsy concerning for risk of invasive disease

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

Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sznik, MSc; Ping Sun, PhD

Rethinking the Standard for Ductal Carcinoma In Situ Treatment

Laura Esserman, MD, MBA; Christina Yau, PhD

Original Investigation

Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ: A Population-Based Cohort Study

Yasuaki Sagara, MD; Melissa Anne Mallory, MD; Stephanie Wong, MD; Fatih Aydogan, MD; Stephen DeSantis, BS; William T. Barry, PhD; Mehra Golshan, MD

Invited Commentary

No Surgery for Low-Grade Ductal Carcinoma In Situ?

Julie A. Margenthaler, MD; Aislinn Vaughan, MD

Narod SA, et al. *JAMA Oncology* Published online August 20, 2015. Esserman L and Yau C. *JAMA Oncology* Published online August 20, 2015. Sagara Y et al., *JAMA Surgery* 2015;150(8):739-745. Margenthaler JA and Vaughan A. *JAMA Surgery* 2015;150.

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

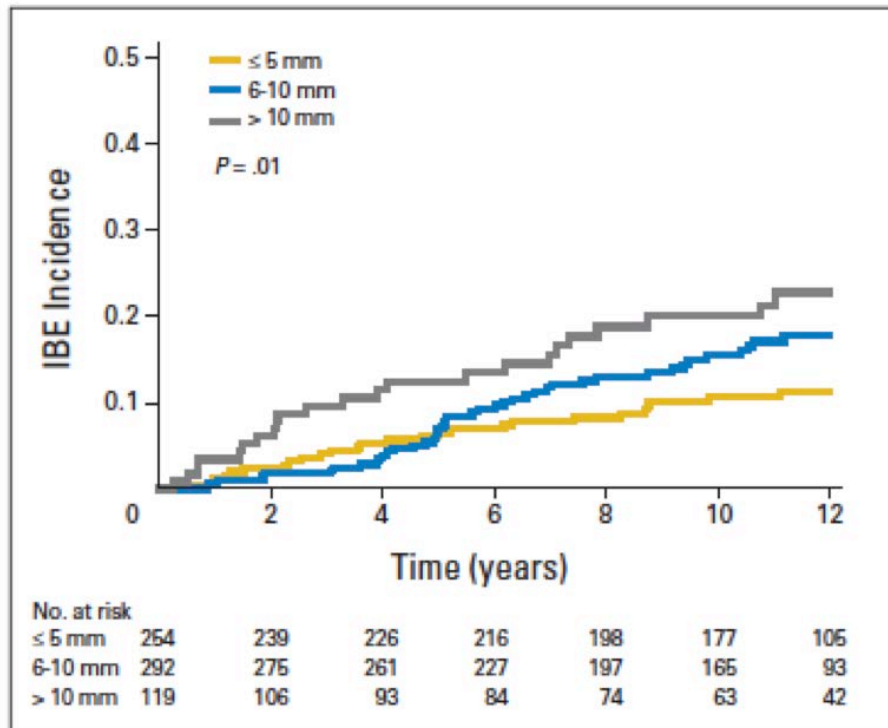


Fig 2 Ipsilateral breast events (IBEs) according to tumor size. The numbers at risk are given beneath the x-axis.

- 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

Points	Age (years)	Size (mm)	Histology	Score
0	61+	< 16	Low grade	0
1	40-60	16-40	Intermediate grade	
2	< 40	41+	High grade	6

A large blue downward-pointing arrow is positioned to the right of the table, indicating a decrease in score from 0 to 6.

DCIS s/p BCS SEER analysis: Radiation or not

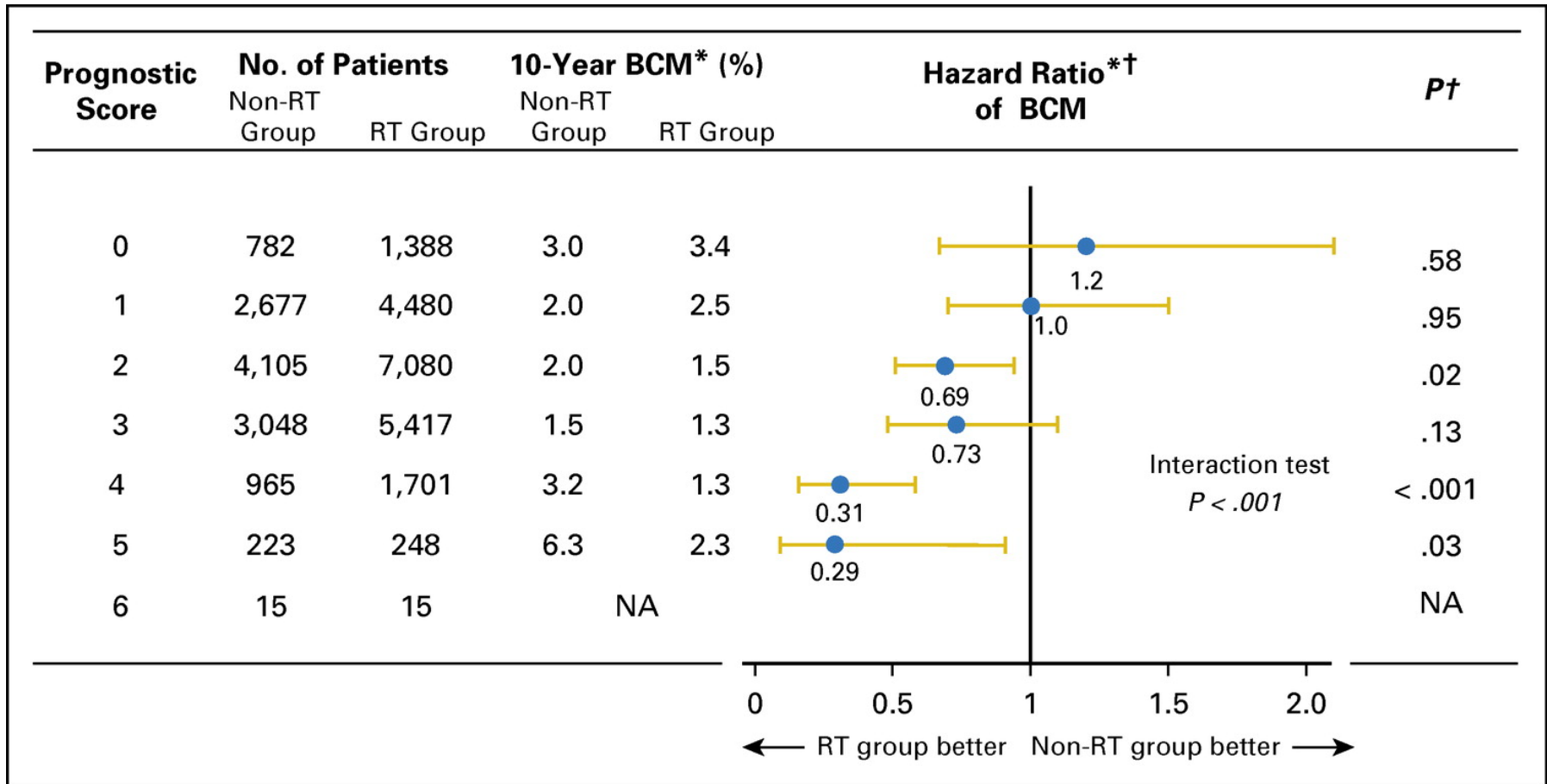
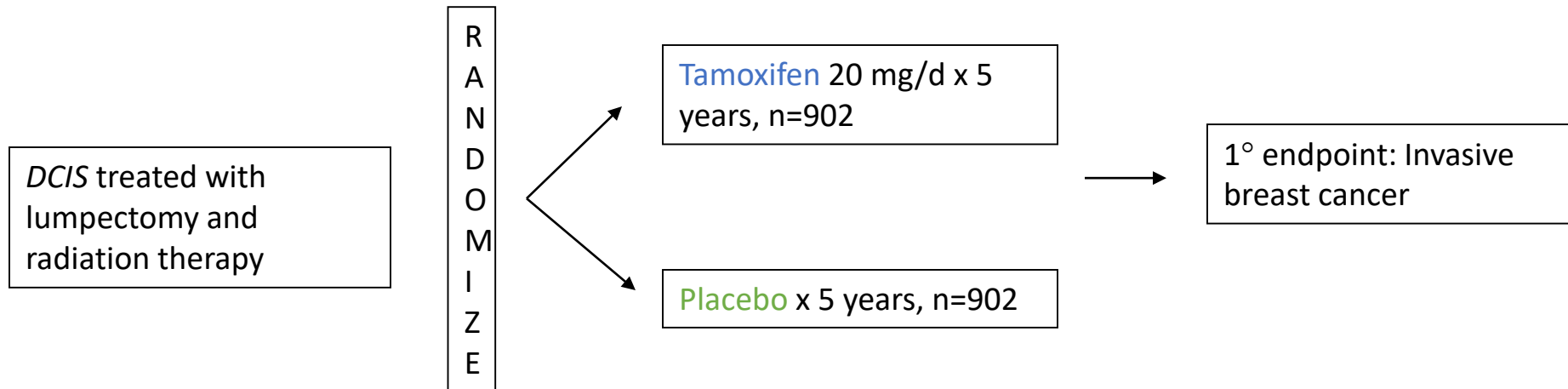


Fig 2. Hazard ratio comparing breast cancer mortality (BCM) between radiotherapy (RT) group and non-RT group according to prognostic score. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital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

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)

Treatment of *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

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)

Treatment of DCIS: Tamoxifen

Meta-Analysis of B-24 and UK/ANZ DCIS

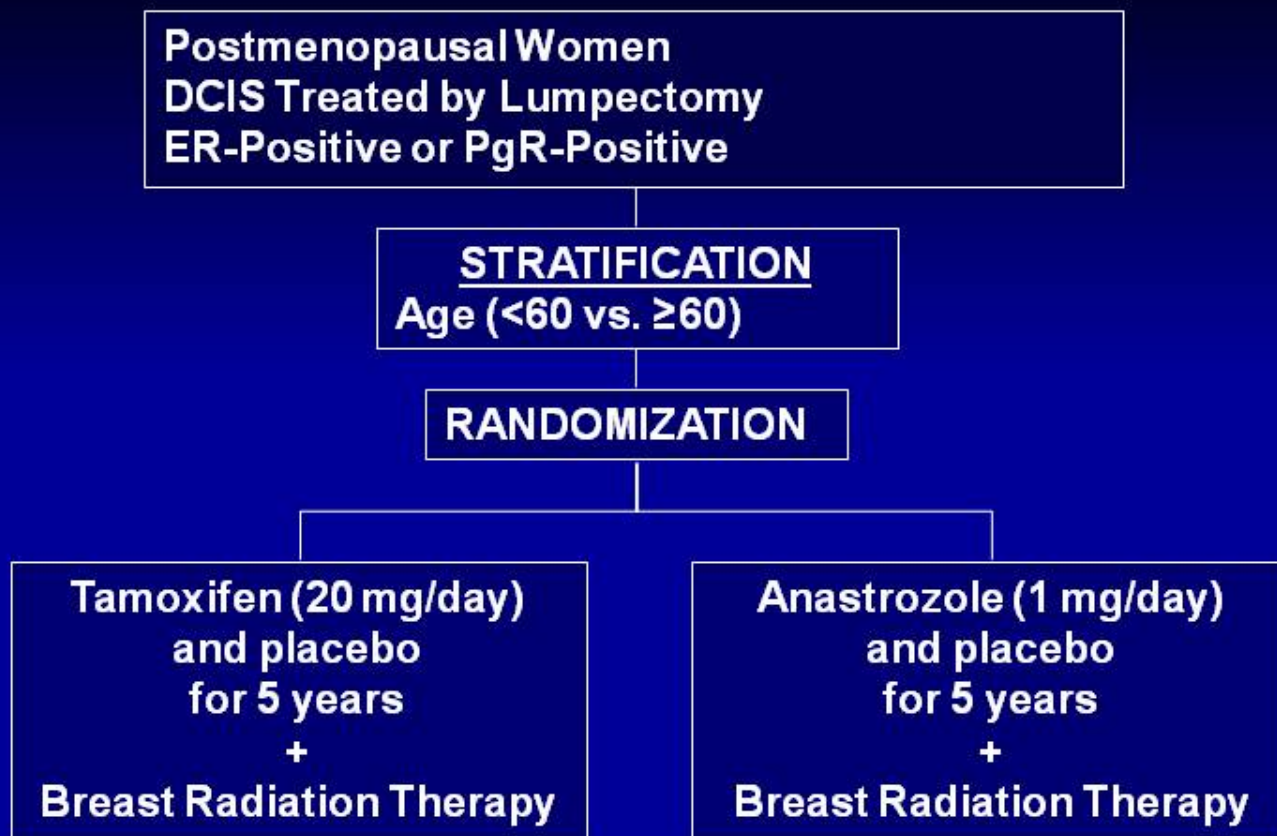
	DCIS (HR)	IBC (HR)
Ipsilateral side	0.75 (0.61-0.92)	0.79 (0.61-1.01)
Contralateral side	0.50 (0.28-0.87)	0.57 (0.39-0.83)

Included 3375 women

No OS benefit HR = 1.11 (0.89-1.39)

Treatment of *DCIS*: Tamoxifen vs AI

NRG Oncology/NSABP B-35 Schema



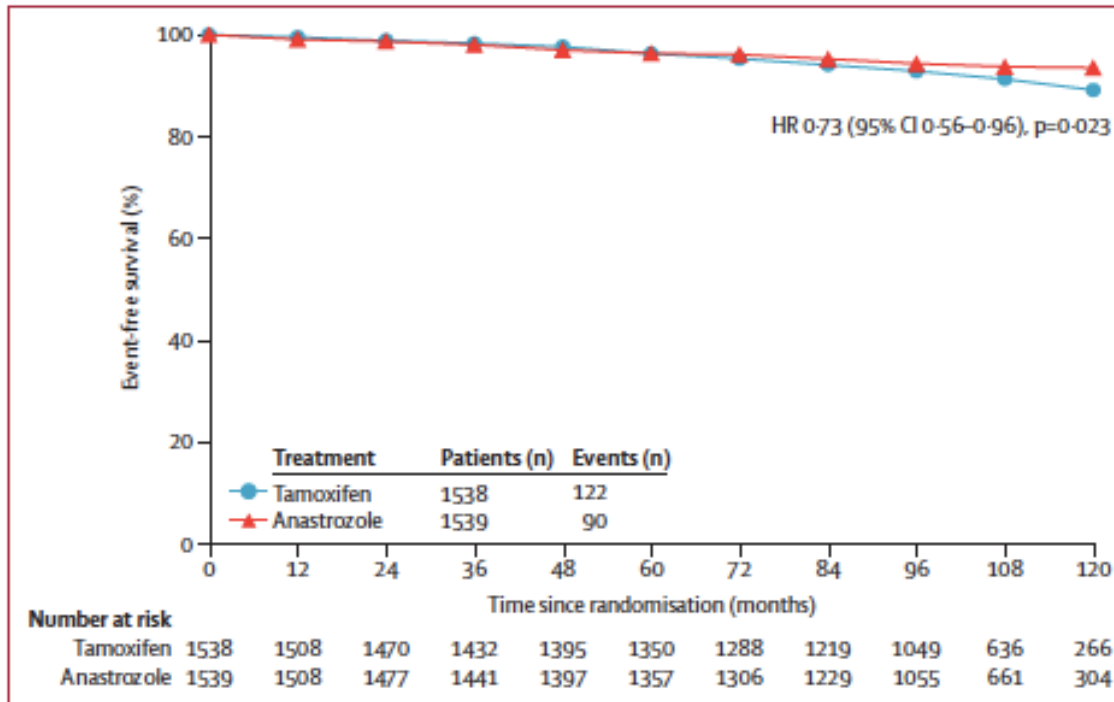
NRG Oncology ASCO 2015

3104 patients randomized between January 2003 and June 2006

Primary Endpoint: Breast Cancer-Free Interval (BCFI)

Median Follow up 9 years

NSABP B-35 Results

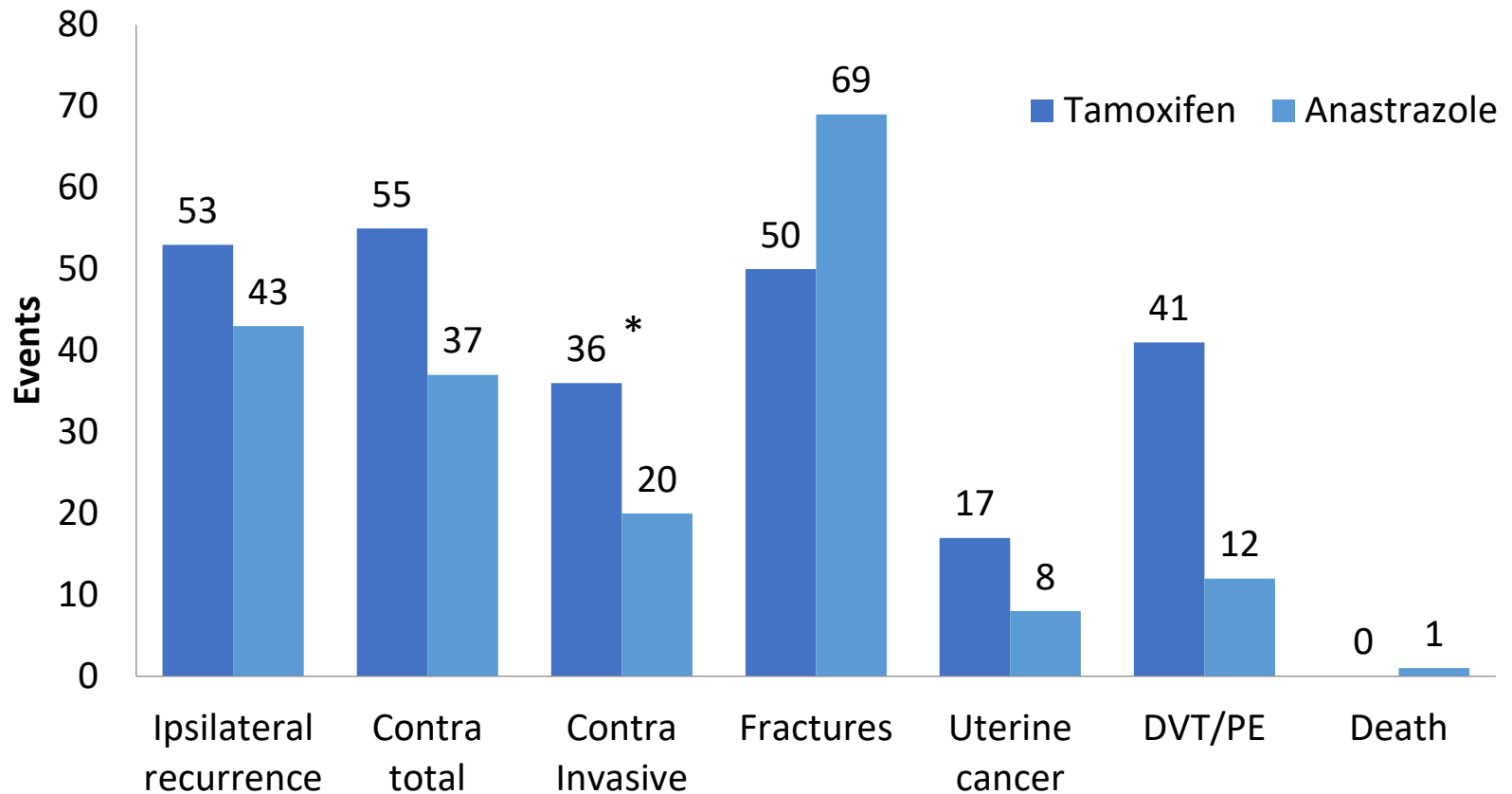


Breast Cancer Free Interval, B-35

	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

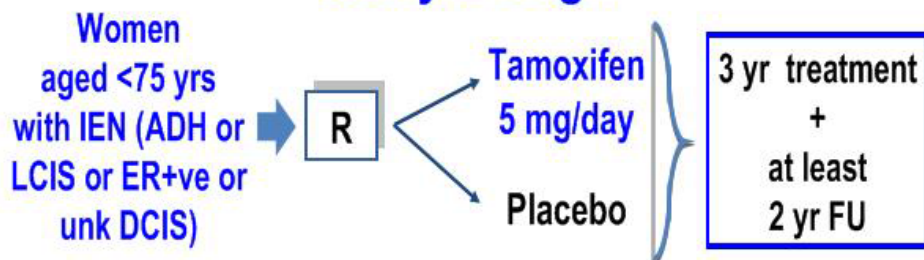
NSABP B-35 Results



Adapted from presentation by Richard Margolese at 2015 ASCO Annual Meeting

Randomized placebo controlled phase III trial of **low-dose tamoxifen** to prevent local and contralateral recurrence in breast intraepithelial neoplasia (JCO, 2019, DeCensi)

Study Design



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

Results: Low Dose Tamoxifen

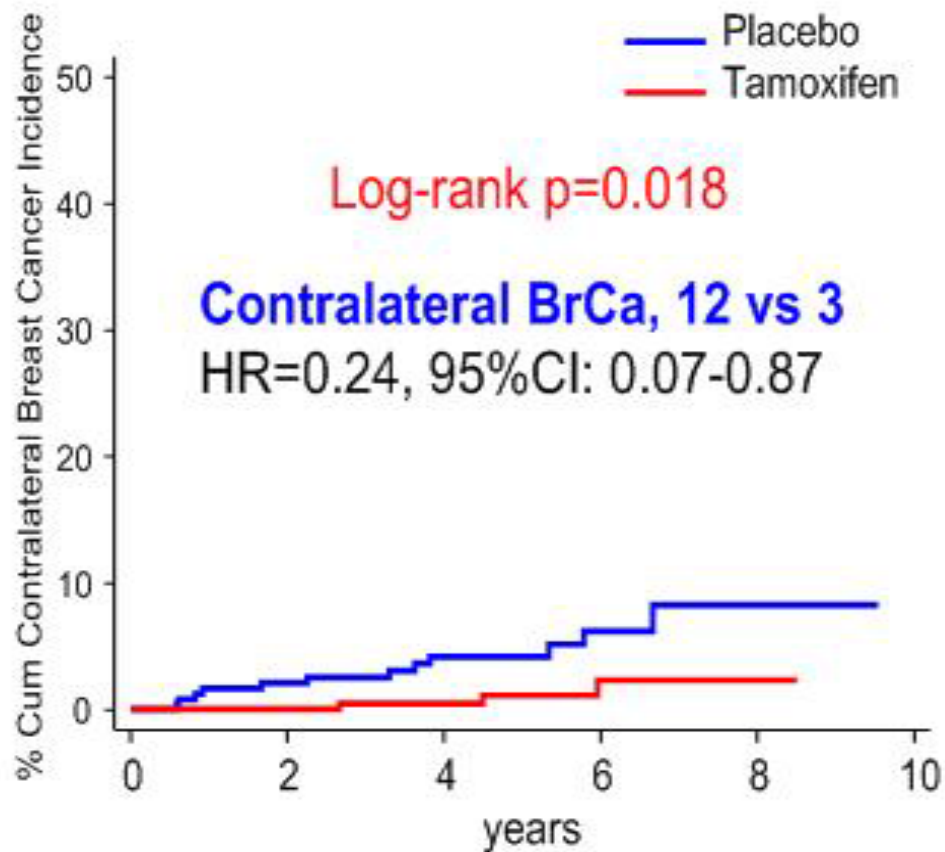
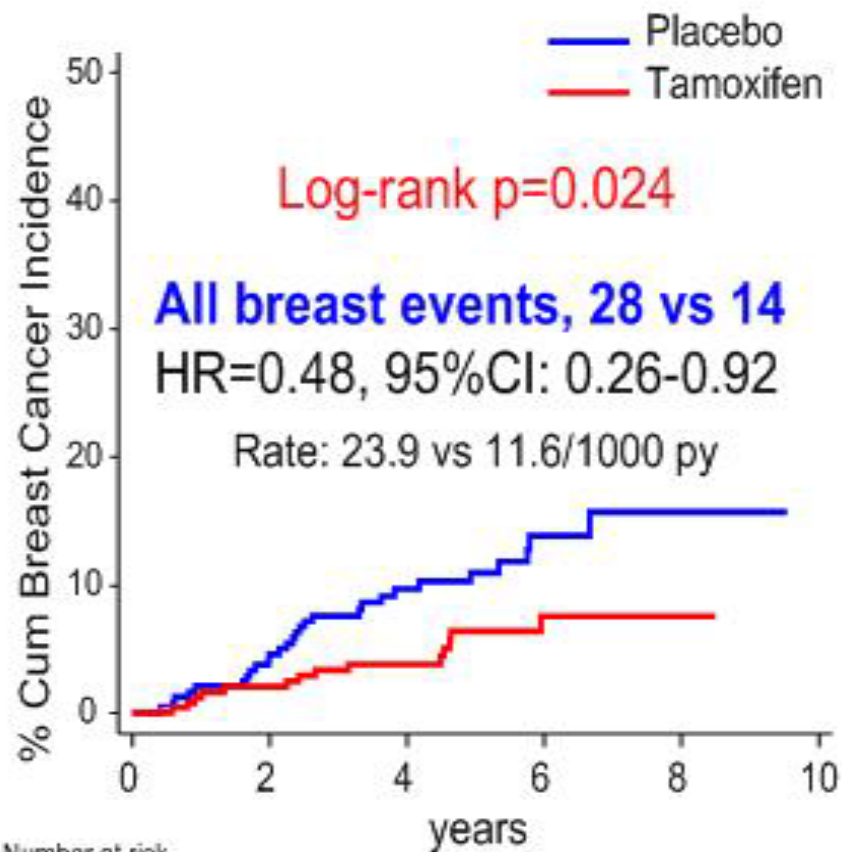


TABLE 3. Serious Adverse Events by Allocated Arm

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

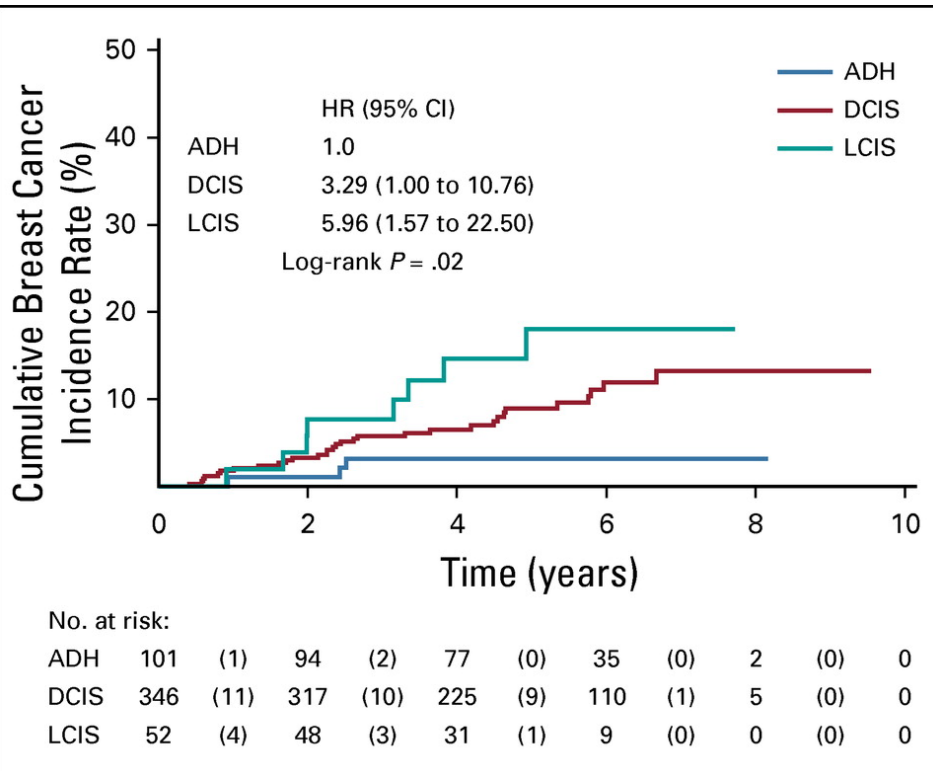
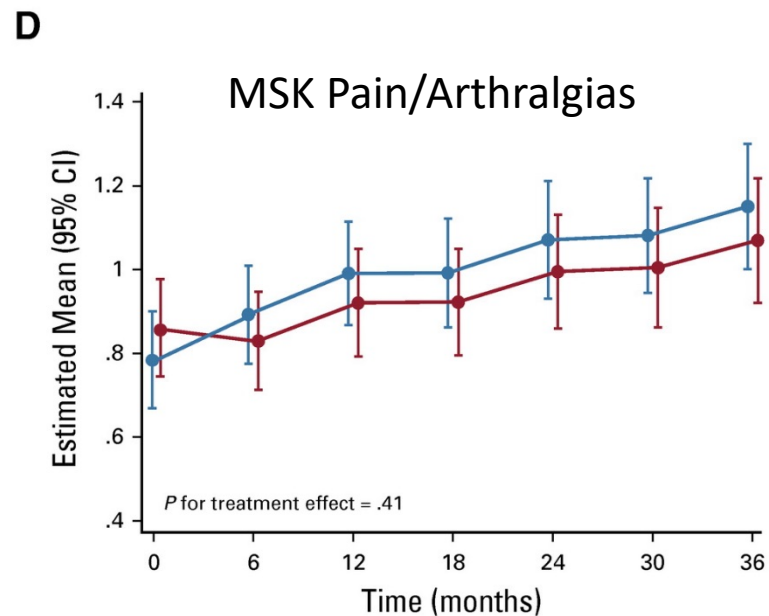
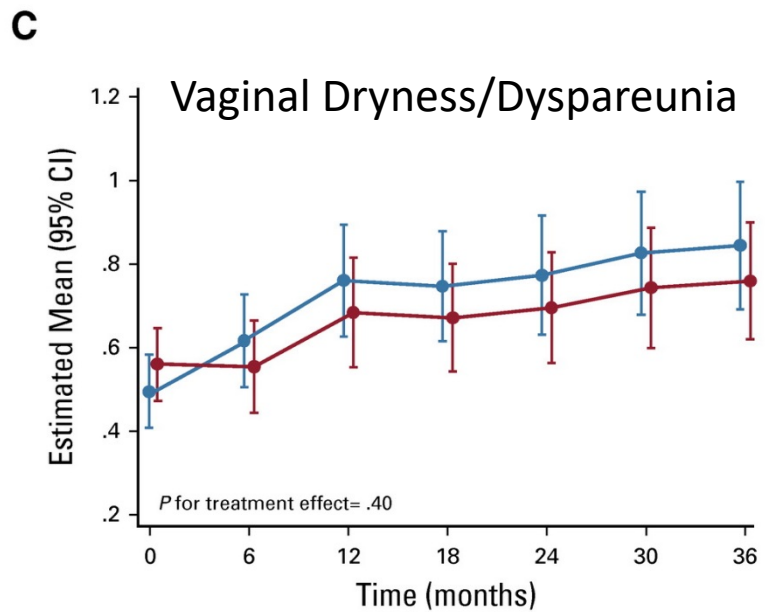
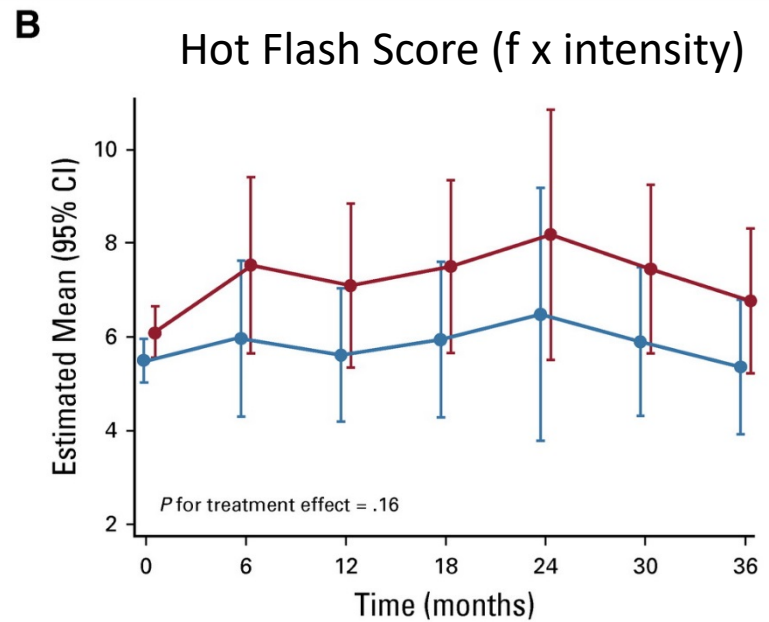
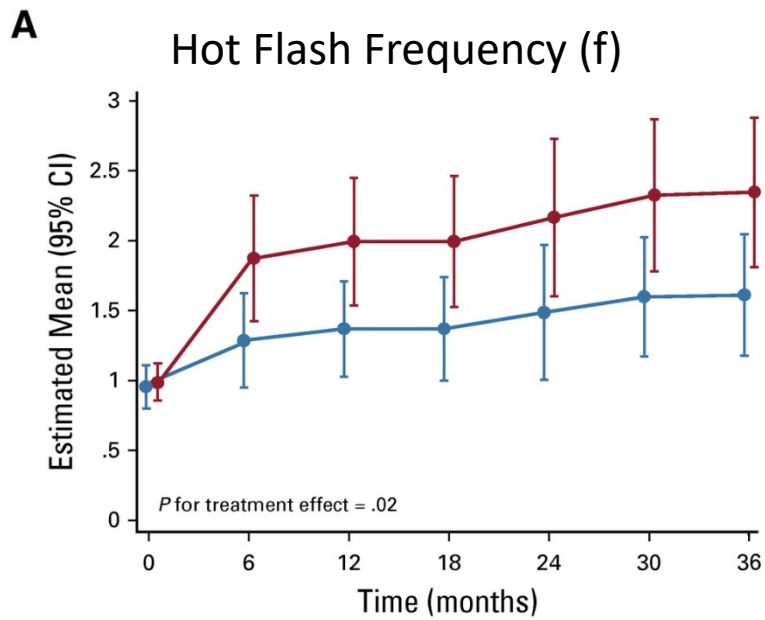


TABLE A1. Prespecified Subgroup Analyses

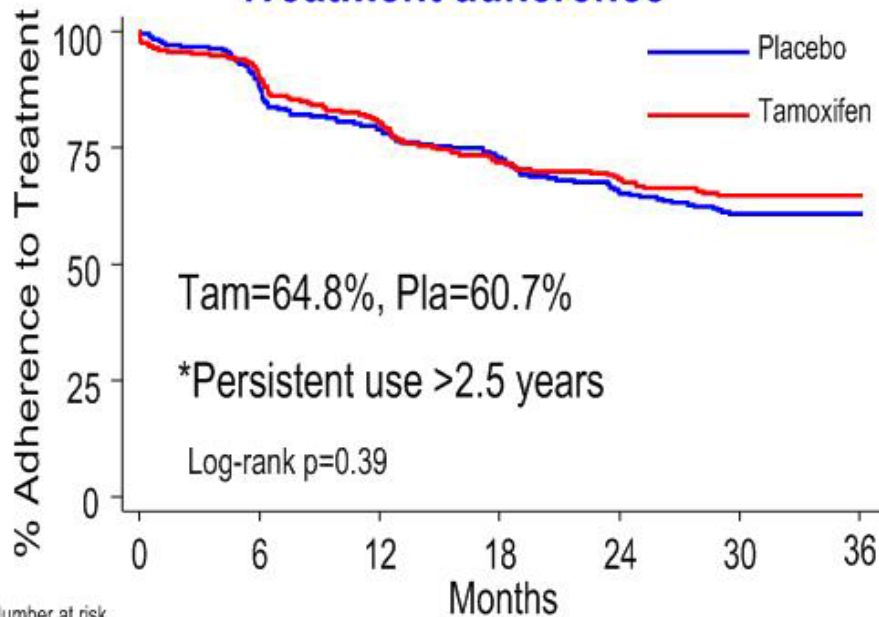
Subgroup	No. of Patients	P^*	HR (95% CI)
Diagnosis within 12 months since random assignment	458	.16	0.41 (0.20 to 0.82)
Diagnosis between 12 and 60 months	42		1.59 (0.27 to 9.53)
ADH + DCIS	447	.54	0.53 (0.26 to 1.08)
LCIS	52		0.31 (0.06 to 1.51)
ER positive	333	.84	0.51 (0.24 to 1.10)
ER unknown	166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



Treatment adherence*



Number at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Placebo	247	(29)	218	(23)	195	(15)	180	(18)	162	(12)	149	(0)	109
Tamoxifen	253	(25)	228	(24)	204	(22)	182	(9)	173	(9)	163	(0)	114

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

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)

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

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 Mastectomy
 - Contraindicated after Bilateral mastectomies

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
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LCIS	Risk	<5%	Concordance with Core Bx	Chemoprevention
ADH	Risk	>20% to DCIS	Excisional Biopsy	Chemoprevention
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Chemoprevention

Possible public health impact of chemoprevention

Question:

- What would effect be if tamoxifen was taken by all women meeting FDA criteria for prevention and also in all subset with anticipated net benefit (using Gail models)?

Methods:

- Used data from the year 2000 NHIS to determine both proportion eligible and proportion with favorable risk benefit—5% of women aged 35-79.
- Matching this to age composition of US population with census data estimated

Results:

- 2,431,911 white women would be GOOD candidates for tamoxifen
- Expected breast cancer incidence at 5 years ~58,148 without tamoxifen
- 28,492 cases prevented with tamoxifen.

Cost of Survivorship

- Cost of local therapy: 15.5K (in 1998\$)
(Barlow, JNCI 2001)

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 - 52% of these with moderate/severe pain

(Gartner, JAMA, 2009)

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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)
- Risk of death: 89.7% 5 year survival
(<https://seer.cancer.gov/statfacts/html/breast.html>)

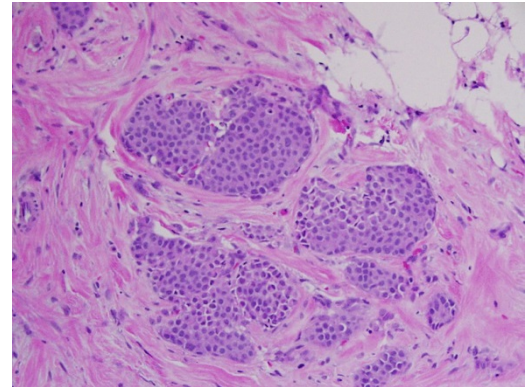
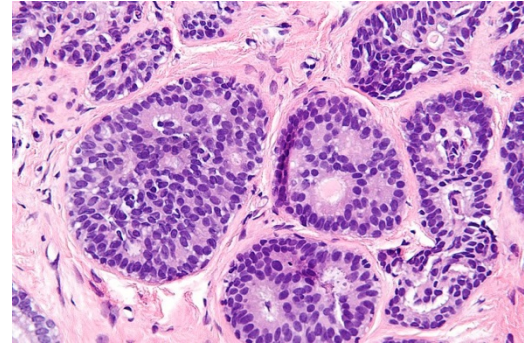
Who should we consider chemoprevention in?

ASCO/NCCN guidelines:

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

Gaps in our recommendations?

- Consider in BRCA2 mutation carriers
- Not strong/specific recommendations for less penetrant mutations
- No data in those with chest RT < 30 (ongoing trials)



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/>

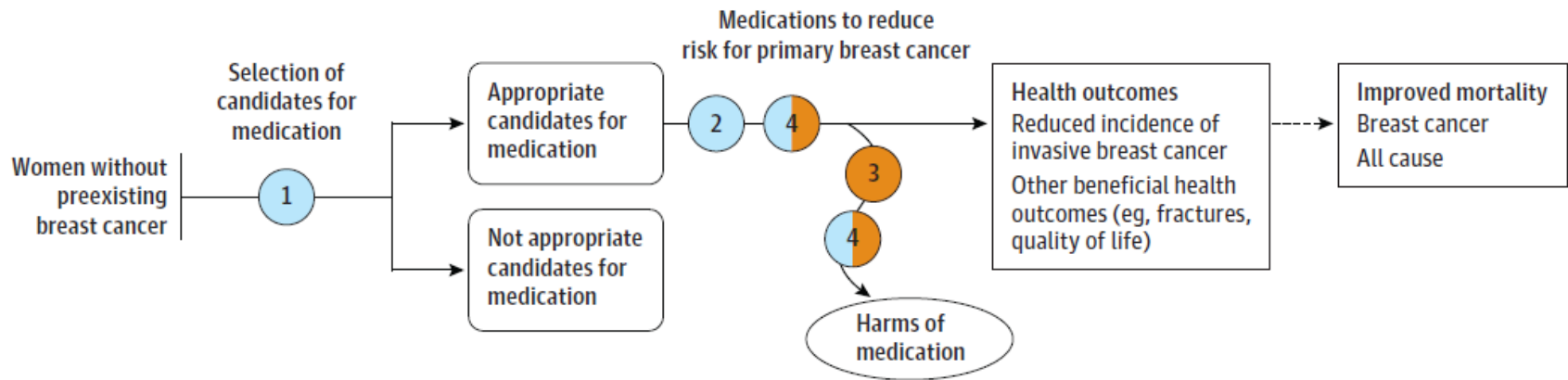
Tyrer-Cuzick, IBIS Breast Cancer Risk Evaluation Tool

- 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>

USPSTF schema

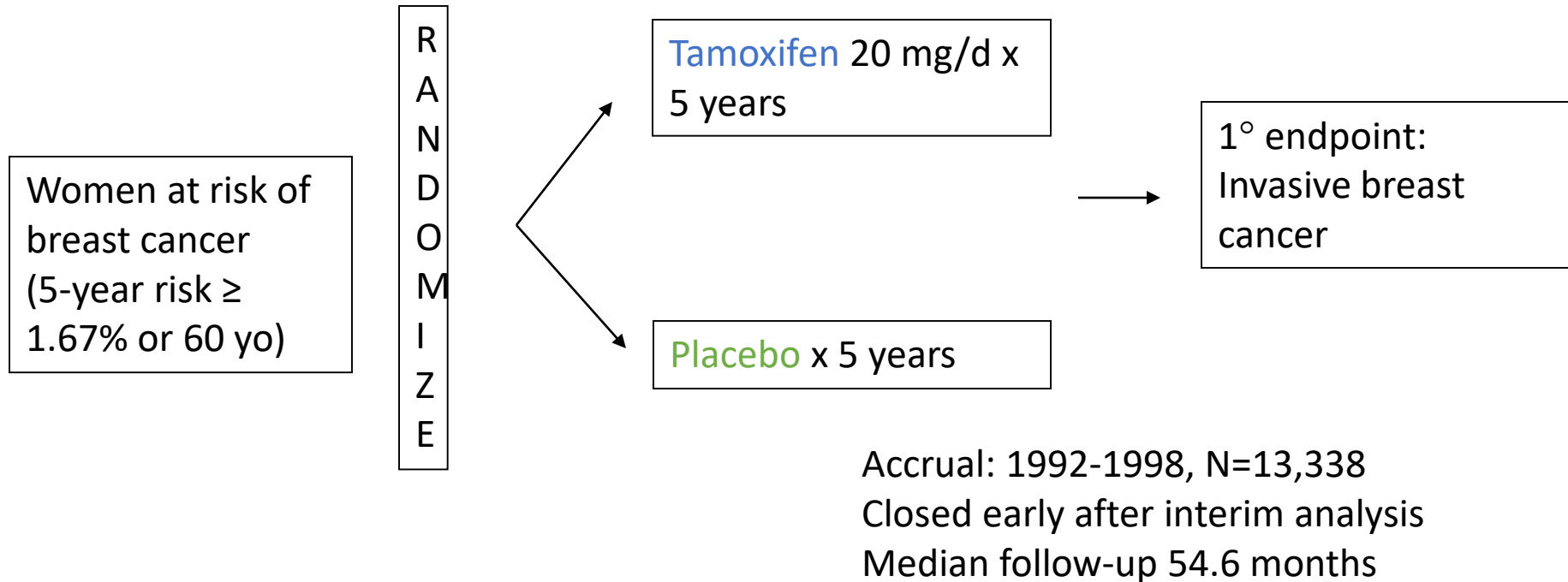


USPSTF recommendations and guidelines updated in 2019

The Chemoprevention Trials

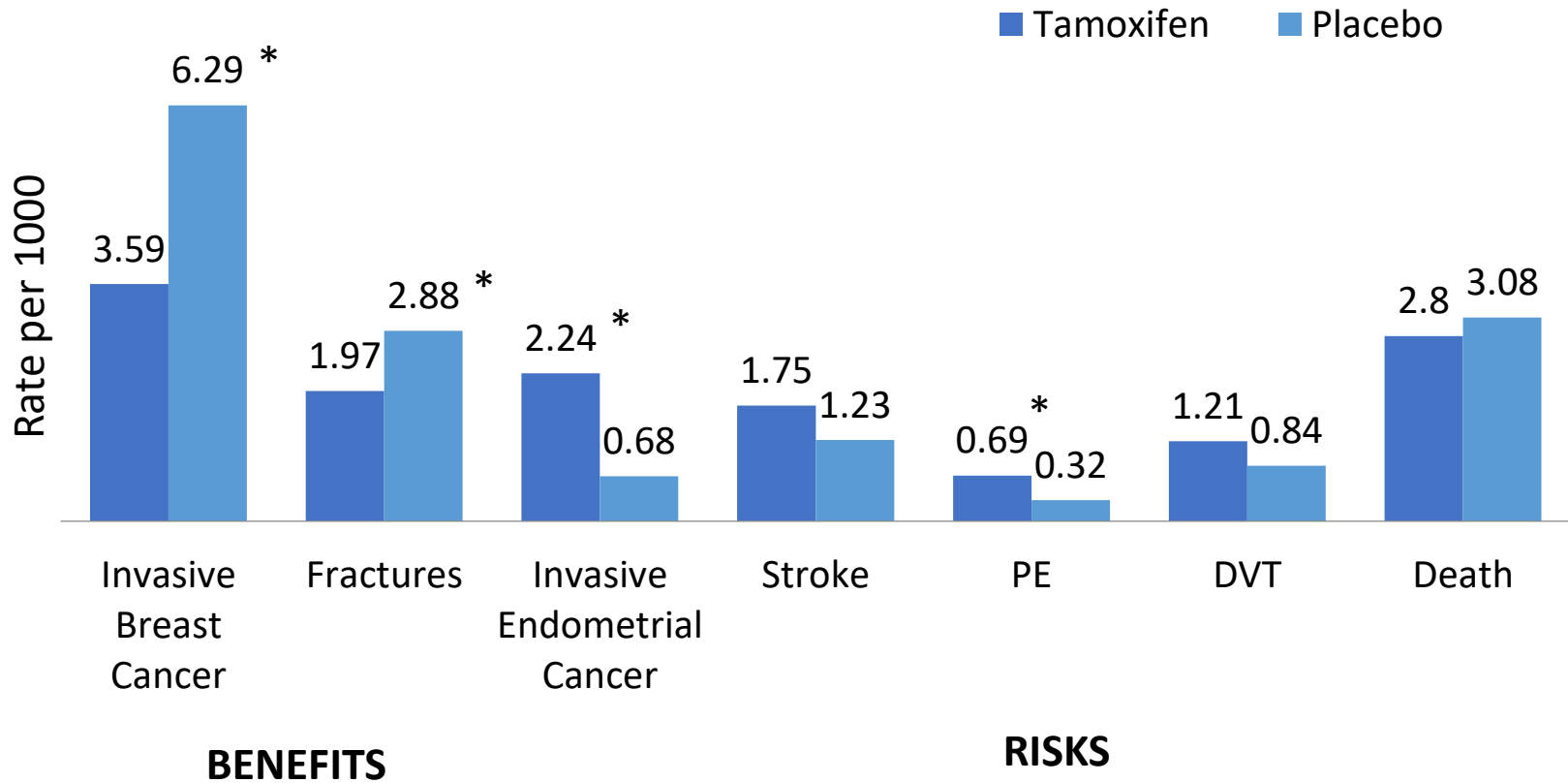
Trial	Agent	Year	N	RR/HR	notes
STAR	Ral vs Tam	2006	19747	1.24 (1.05-1.47)	Postmen, No LCIS (50% prior TAH)
IBIS-I	Tam vs placebo	2007	7154	0.74 (0.58-0.94)	
NSABP P-1	Tam vs placebo	2005	13388	0.57 (0.46-0.70)	Pre and post
Royal Marsden	Tam vs placebo	2007	2471	0.78 (0.58-1.04)	
Italian Tamoxifen	Tam 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)

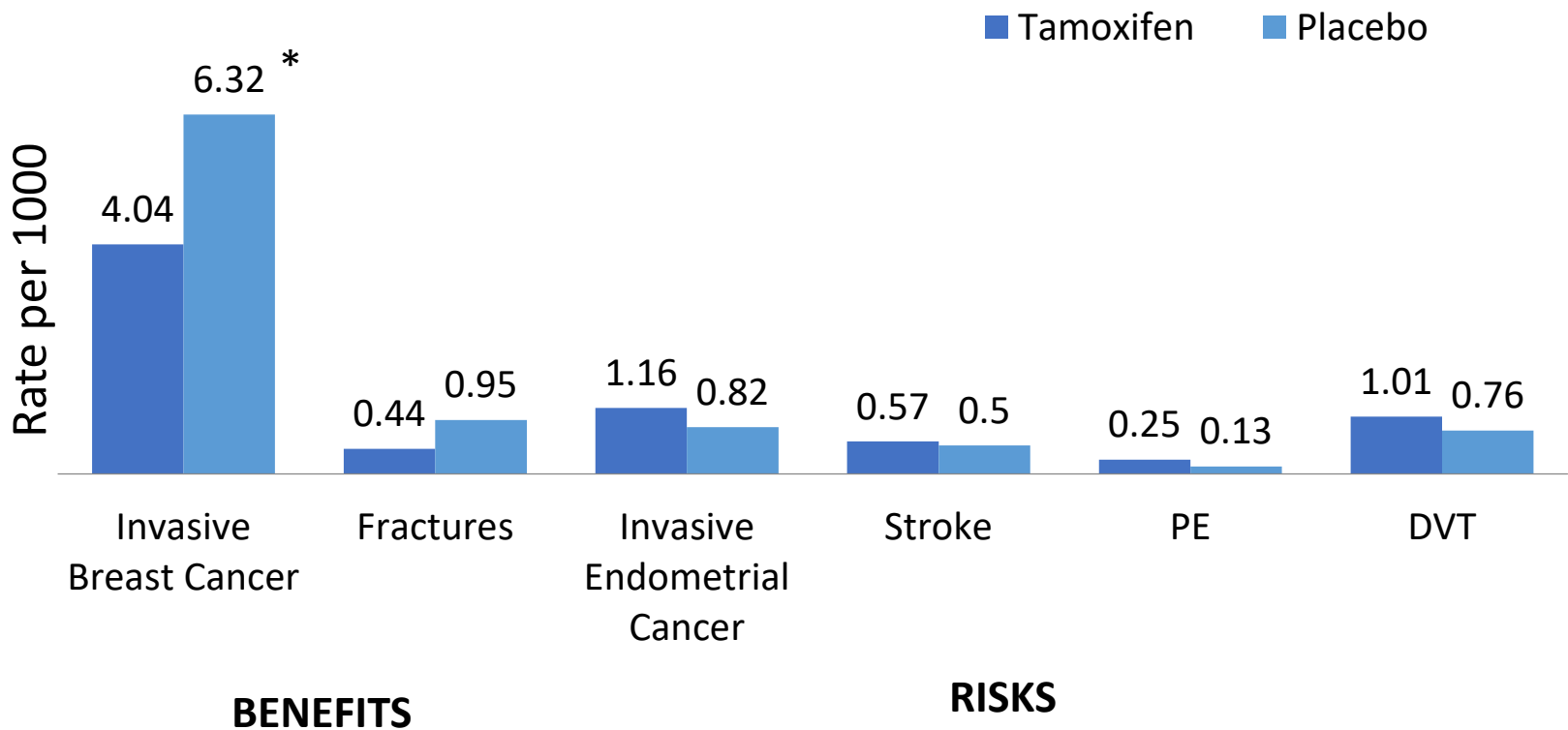


Analysis showed a 49% reduction in incidence of invasive breast cancer in participants treated with tamoxifen

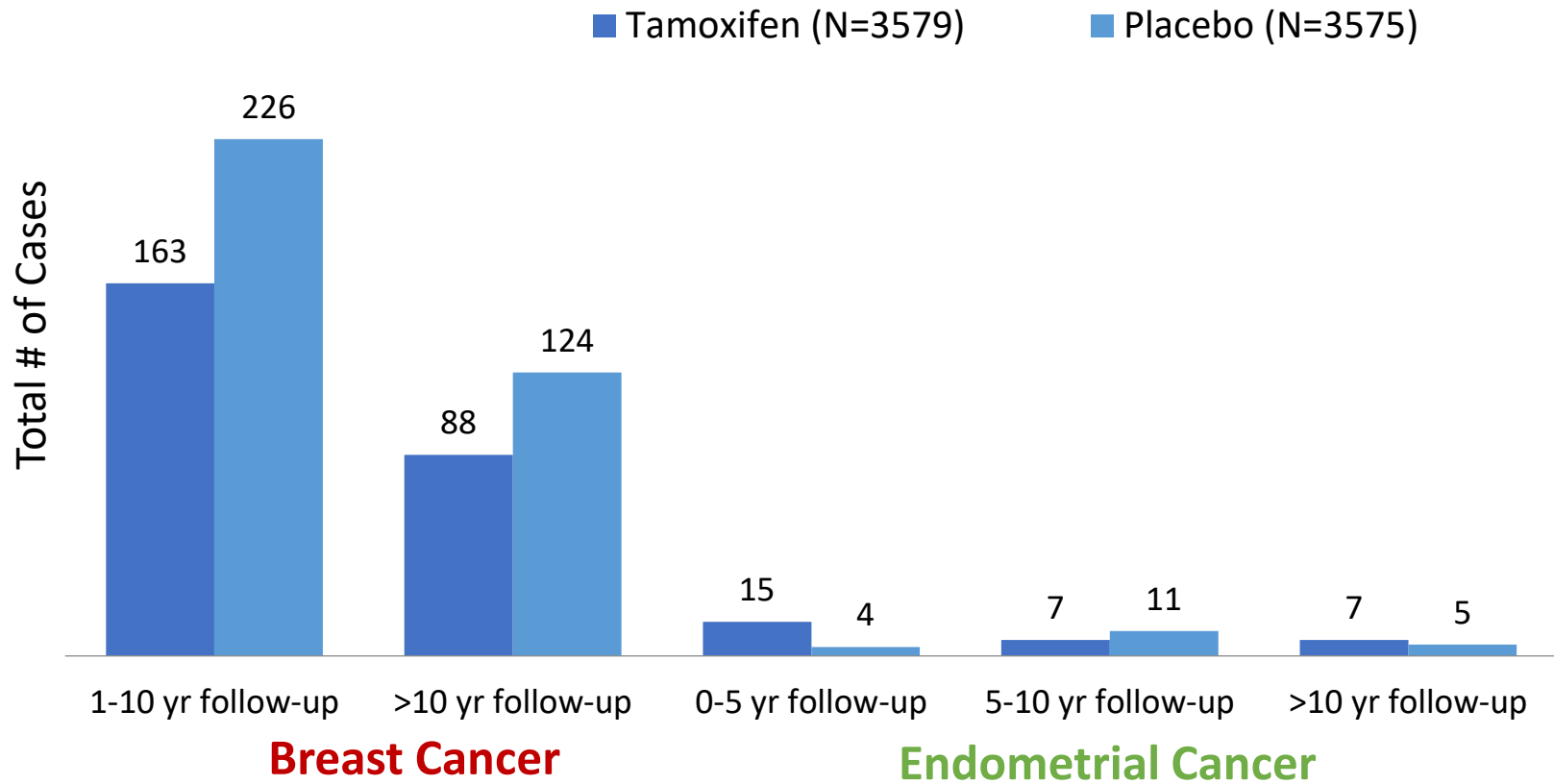
NSABP P-1, All High-Risk Women



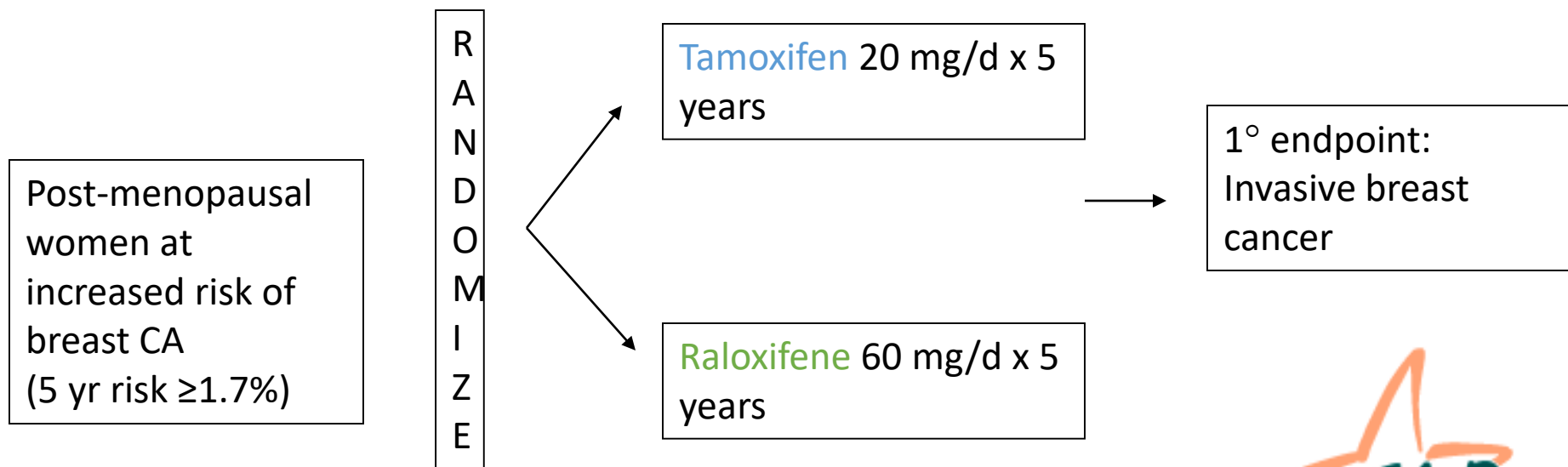
NSABP P-1 Women <50



IBIS-I Long-Term Follow-Up with Tamoxifen



STAR Trial (NSABP P-2)

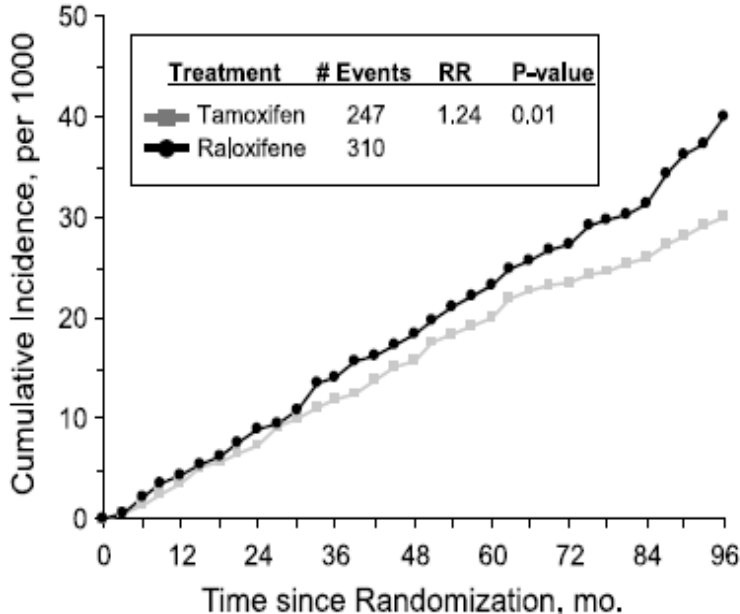


- Accrued 19,471 patients between July 1999-Nov 2004
- Mean age participants at randomization 58.5 years
- 93% of participants were white
- Mean predicted 5-year risk of IBC was 4.03%

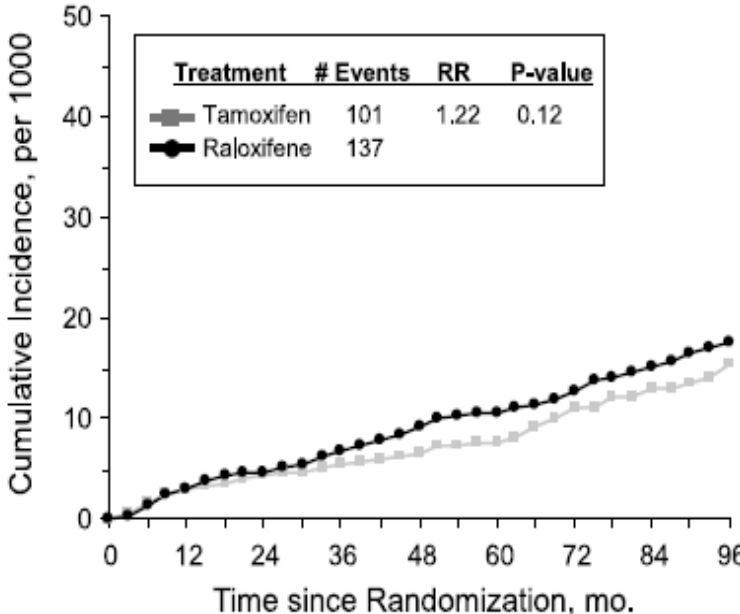


STAR Update 2010: Tamoxifen is more effective

Invasive Breast Cancer



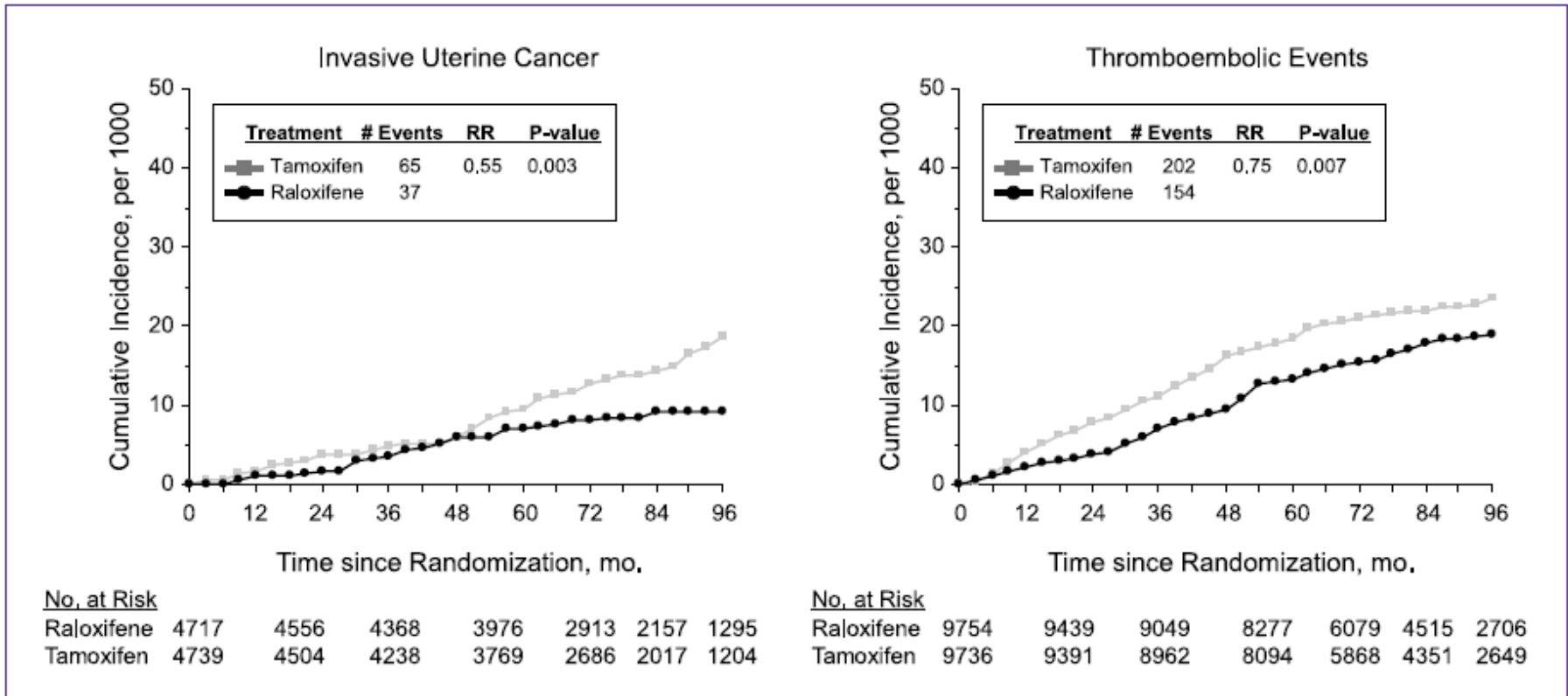
Noninvasive Breast Cancer



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

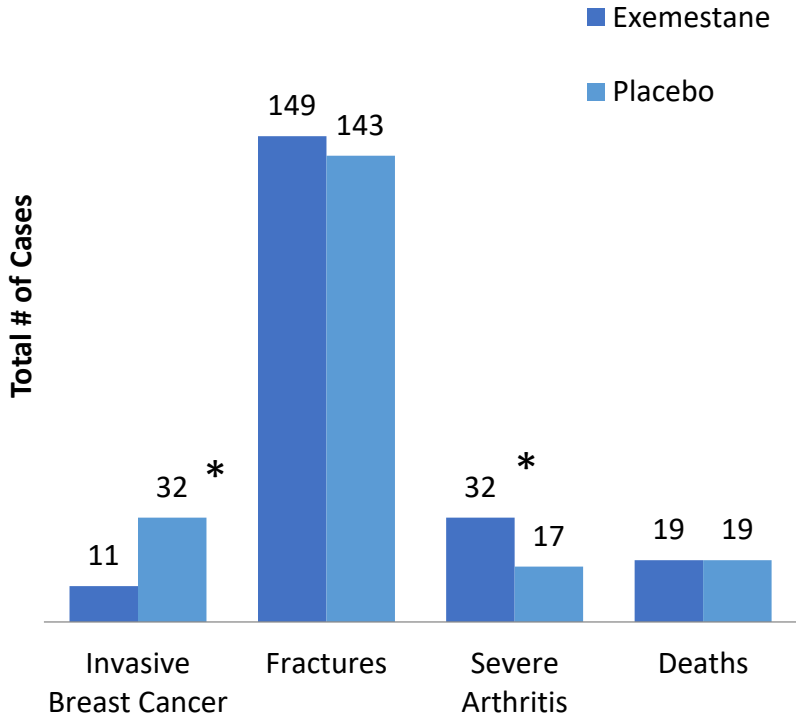
...and more toxic



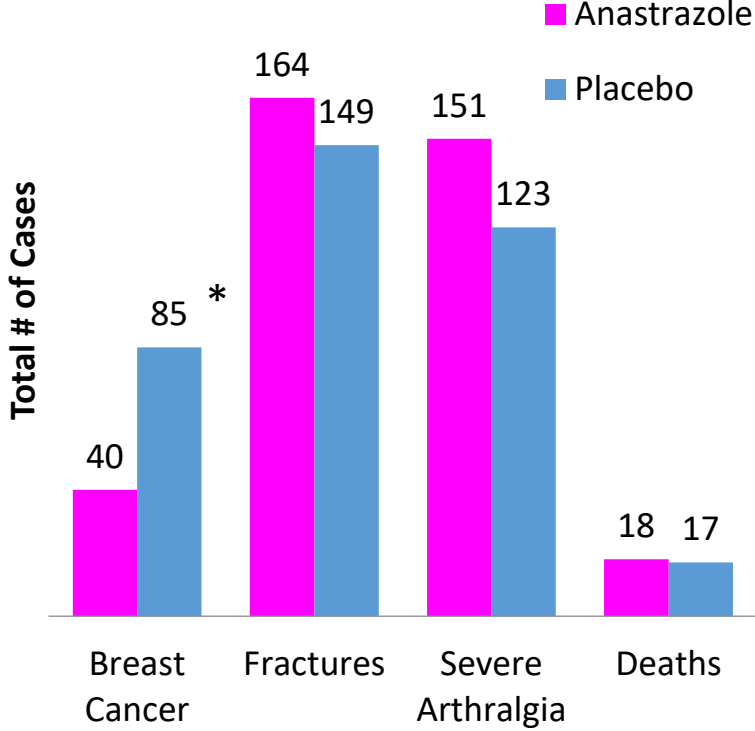
*Hysterectomy for benign disease was double in Tamoxifen group, RR = 0.45 (0.37-0.54)

Risks and Benefits of AIs

MAP.3



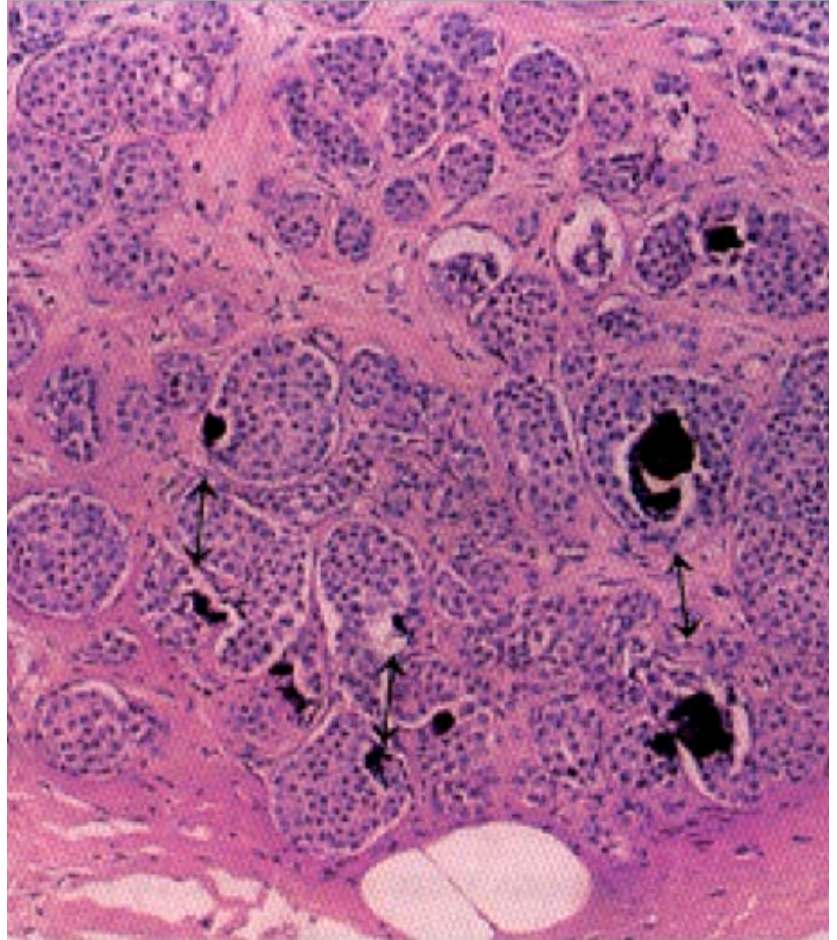
IBIS-II



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

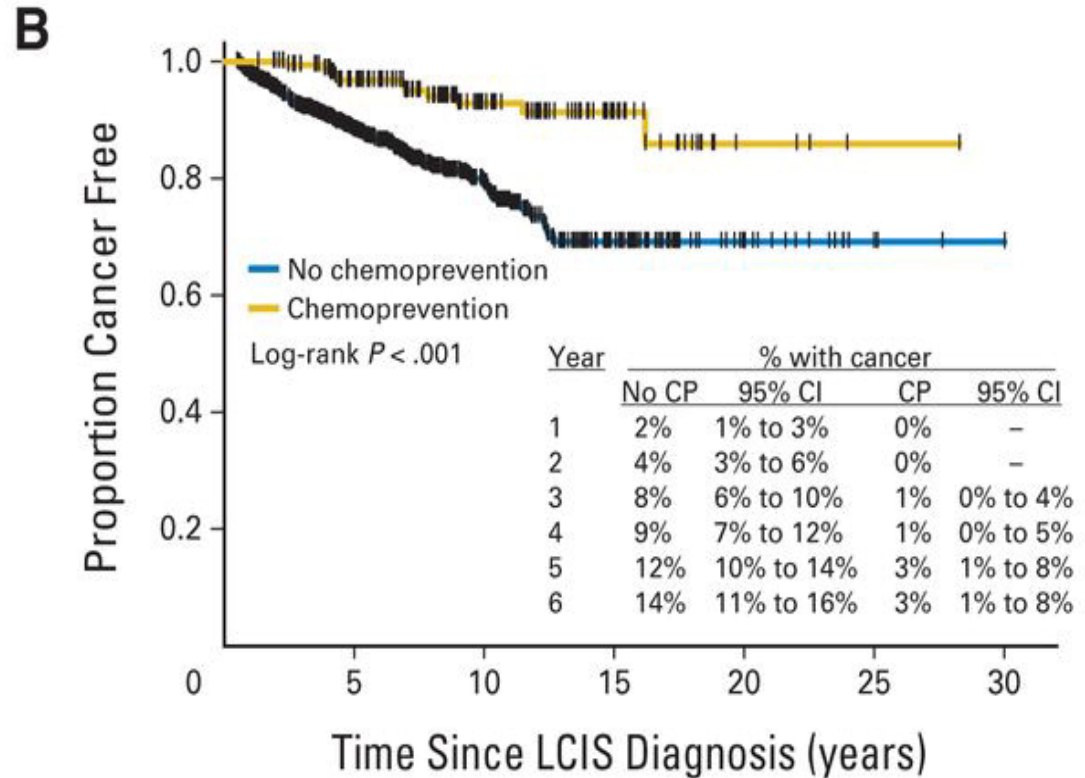
LCIS: Proliferative Breast Disease

- 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
- Incidence 2% per year
- Cumulative 26% at 15 yrs
- Chemoprevention reduced incidence of breast cancer
 - 7% vs. 21% at 10 yrs
 - HR 0.27



No. at risk	0	5	10	15	20	25	30
No CP	857	503	200	67	18	5	
CP	175	135	66	26	4	1	

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 what was told was 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

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%)

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

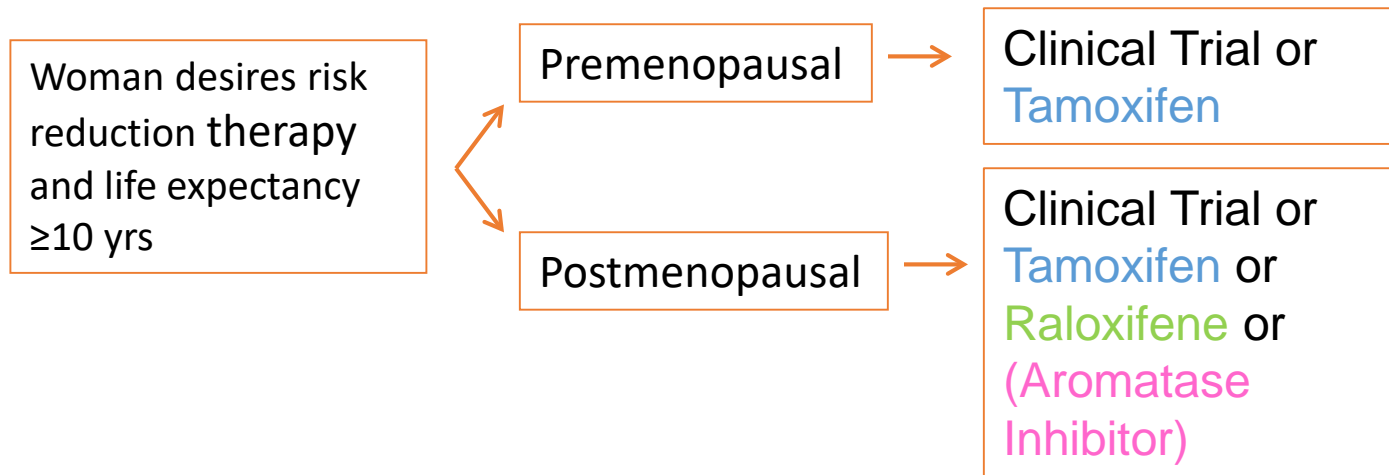
Adherence

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

Options for Chemoprevention for Breast Cancer (Including proliferative breast disease)



Who should get chemoprevention?

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

More strongly encourage (Ideal candidates)

- Tamoxifen
 - Premenopausal (40-50) women with high risk (risk reduction of ~50%)
 - Postmenopausal women <60 with high risk of cancer and low risk of SAE
- Raloxifene
 - Postmenopausal women at above average risk with osteopenia who are considering medication for either (risk reduction of ~38%)
- AI
 - Postmenopausal women who are unable to take Tamoxifen or Raloxifene or who have had DCIS and BCT (risk reduction of ~50-60%).

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

Obesity - Nurses Health Study

- Initially enrolled 121,700 married women RN's ages 30-55 in 1976 and has been collecting survey data on health status since.
- Identified a subset of 87,000+ pre/postmenopausal women at entry(95% followup) without prior history of cancer
- Identified a smaller subset of women who joined the study when premenopausal and have since become menopausal (49,514)
 - Assessed effect of postmenopausal weight gain exclusively in this group.

Weight gain substudy in 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)
<i>P</i> for trend		<.001	<.001		.001
<i>P</i> for weight loss trend¶		.02	.02		.02

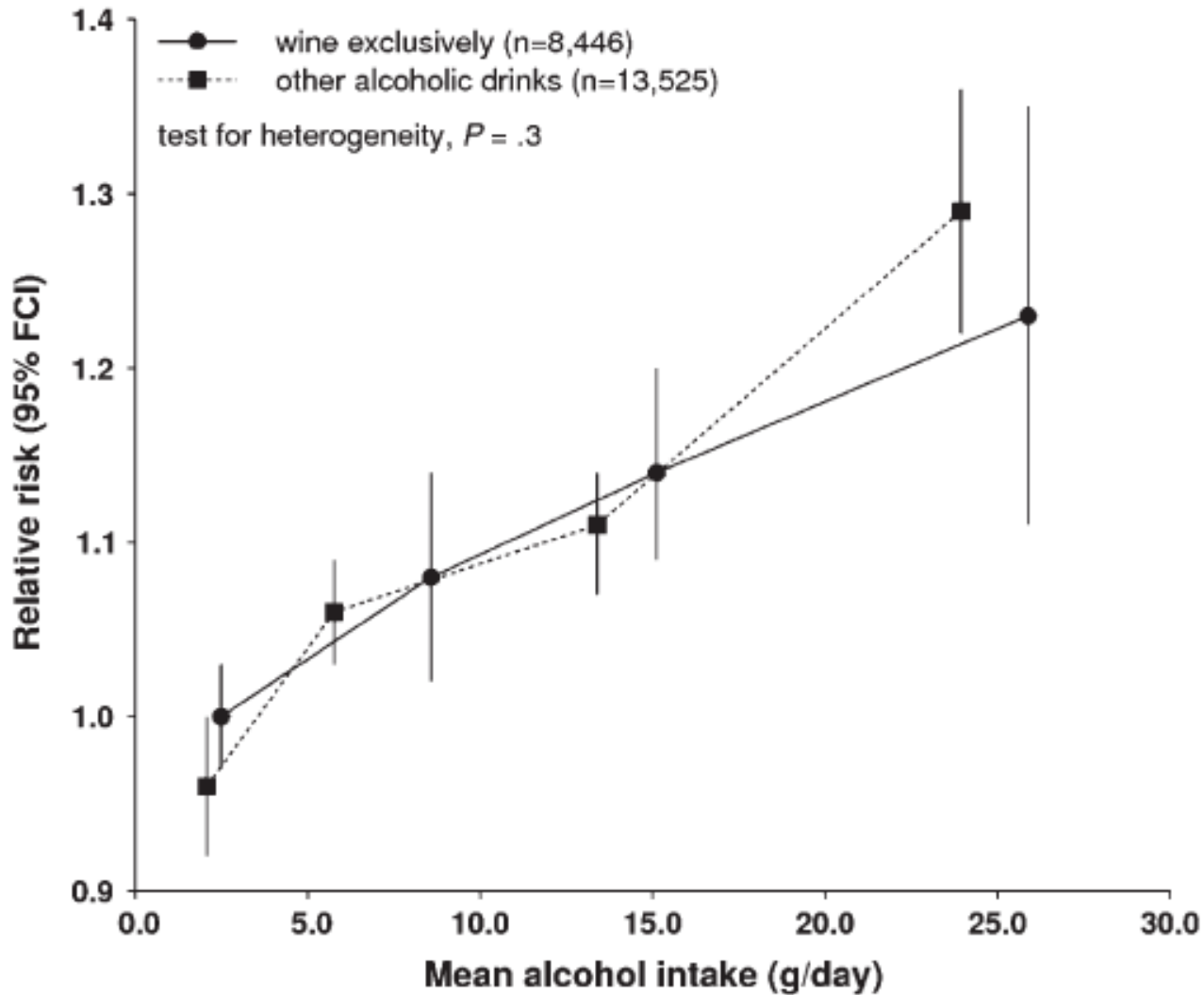
Obesity and Breast Cancer

- Study shows not only that BMI corresponds to breast cancer risk, but also (limited by observational nature of study) *shows the MODIFYING BMI* can both positively and negatively influence breast cancer risk.

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 ≥ 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%

Take home points

- 1) DCIS requires surgery to a clear 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 risk factor for developing Breast Cancer and surgical removal is not required, but chemoprevention should be considered.
- 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.

Breast and Ovarian
Cancer Prevention Program



The Women's Center



Women's Wellness Clinic



The Women's Center



Thanks!