Fred Hutch Cancer Center

Therapy for Non-Invasive Breast Cancer & Prevention

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Disclosures

Research funding from Pfizer

Objectives

1) Review Breast Cancer Stats and Risk Factors

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

3) Evaluate who should we consider for medical risk reduction.

4) Compare and contrast SERMs and Aromatase Inhibitors.

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

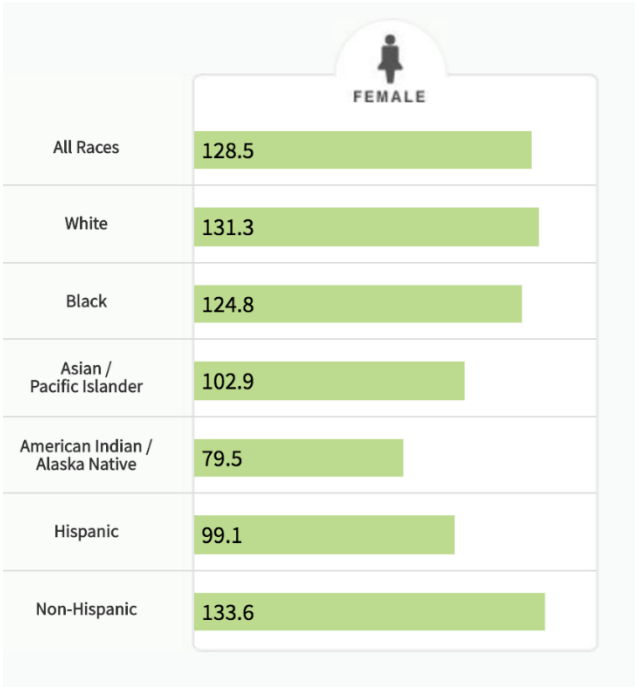
Epidemiology: Breast Cancer Incidence and Mortality

- Most common cancer in women
- 29% of all new cancers
- 2nd leading cause of cancer death in US
- 287,850 cases diagnosed
- 51,400 cases of DCIS dx
- 43,250 died of breast cancer

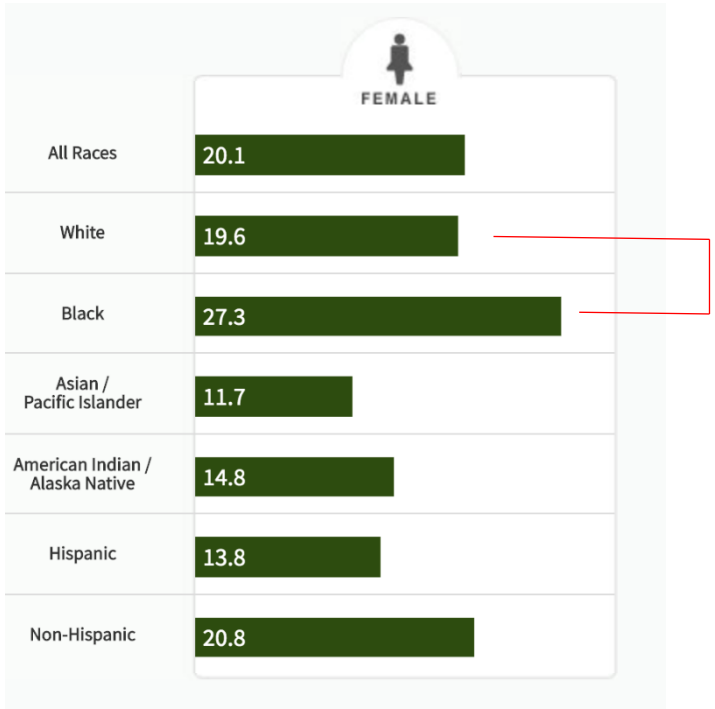
SEER 2022 https://seer.cancer.gov/statfacts/html/breast.html, https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.htm

Breast Cancer Disparities

Incidence



Mortality

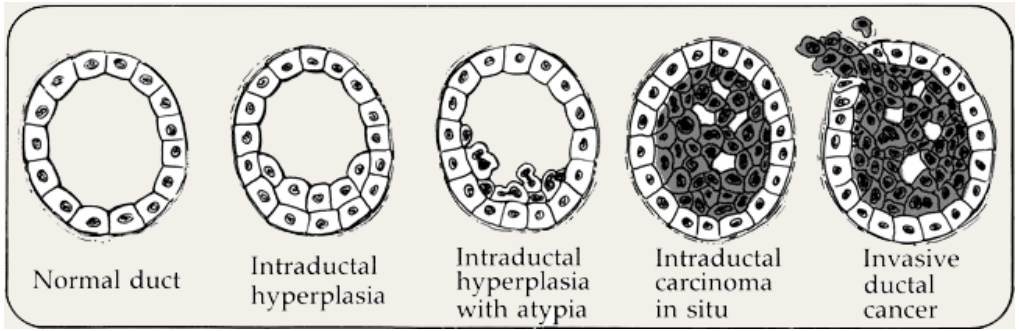


40% Higher Mortality

SEER 2020 – cases per 100,000

Categories of Risk Factors for Breast Cancer

- Sex, Age
- Genetics
- Reproductive/Hormonal history
- Family history
- Breast history (pathology, density, radiation exposure)
- Lifestyle factors
  - BMI/Exercise
  - Alcohol
  - Sleep patterns
- Race, Height



Is Breast Cancer Preventable?

Cause is multifactorial

- Genetics
- Estrogen Exposure
- Environmental factors
- Behavioral factors
  - Tobacco use
  - Obesity
  - Poor nutrition
  - Alcohol
  - Physical activity

Modifiable risk factors

- Ionizing Radiation
- Tobacco use
- Nulliparity or 1st birth > age 30
- Breastfeeding
- Alcohol consumption
- Sedentary lifestyle
- Postmenopausal obesity
- Chemoprevention

ASCO University, “Cancer Screening and Prevention: Breast Cancer”, 2016.

Risk Factors

Factor	Relative risk (RR)
Female sex	100
Age (30 vs. 70)	10
Intraepithelial neoplasia (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	10 to 20
Ionizing radiation to chest < 30	5 to 20
Breast density (Ext den vs scattered)	2.2

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017. Height: 10997541

Breast density

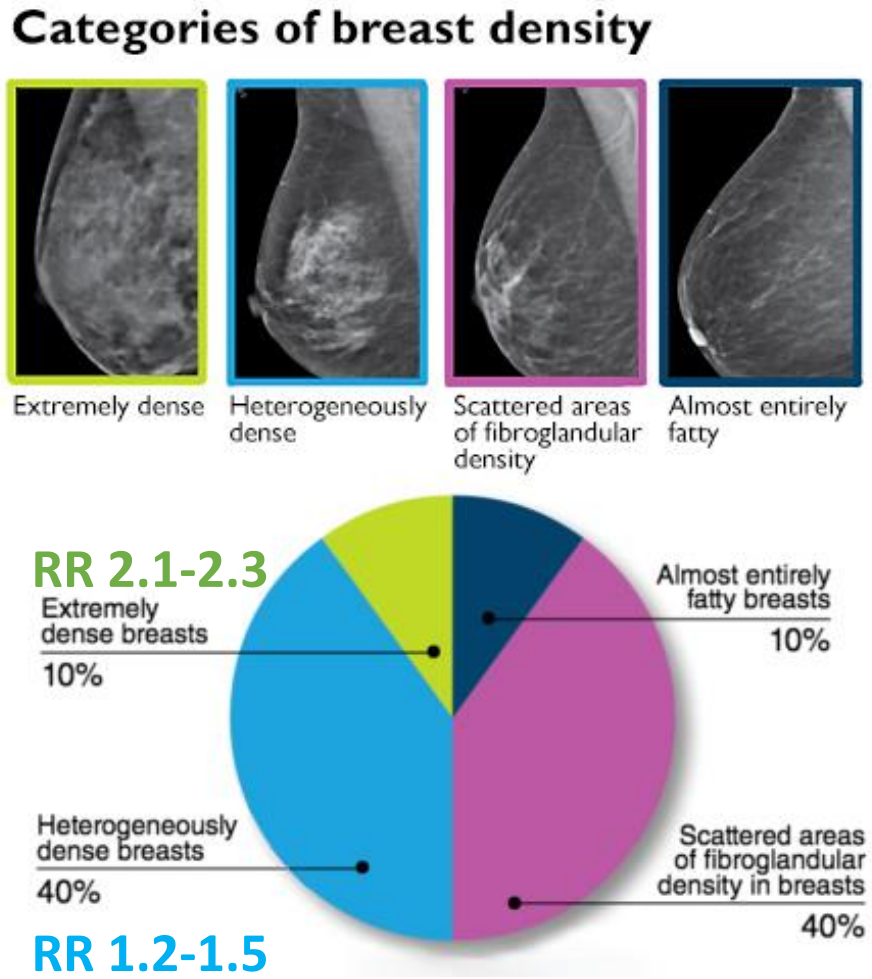
- Determined by mammogram, NOT by physical exam
- Relative risk of ~2
- No evidence that additional testing improves mortality

Increased:

- Estrogen/MHT
- Alcohol

Decreased:

- Antiestrogen therapy (Tam/AI)



Factors with Increased Risk

Factor	Relative risk or Effect
Combined Hormone Therapy *Mod	1.2-1.3
Menarche <13 vs 15yo	1.2-1.3
Obesity (>82 kg vs. <59 kg) *Mod	2.85
Alcohol intake (1/day vs. 0) *Mod	1.12
Parity (Nulliparous vs. Parous) *Mod	2
Smoking (ever) *Mod	1.1
Tall Stature (69 vs 63 inch)	1.2
Higher insulin resistance *Mod	1.3

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017. Height: 10997541

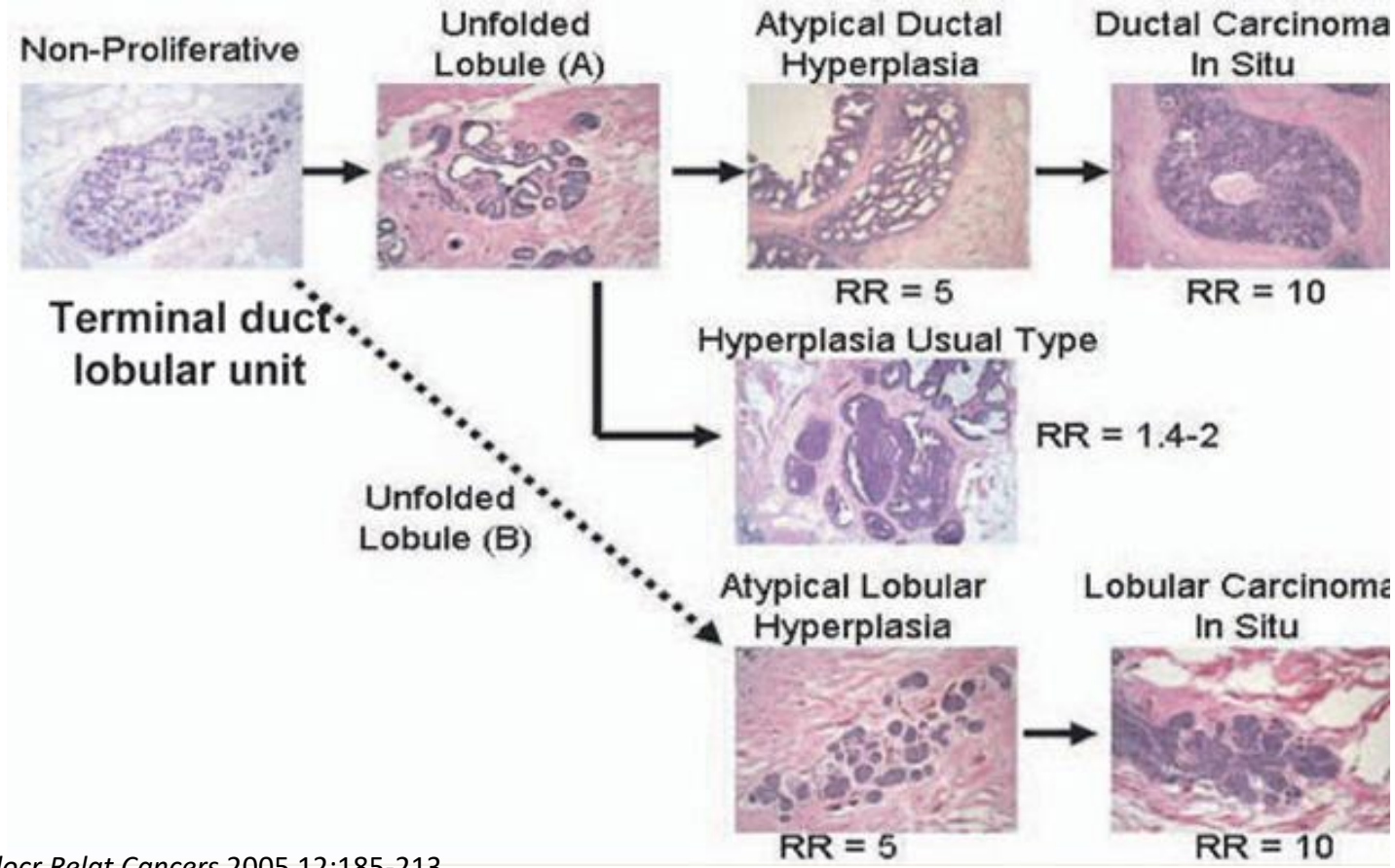
Modifiable Factors with Decreased Risk

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/year
Exercise (exercising strenuously ≥ 4 hrs/week)	RR reduction is 30% to 40%

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

Atypica and In Situ Carcinoma

Proliferative lesions & Intraepithelial Neoplasia



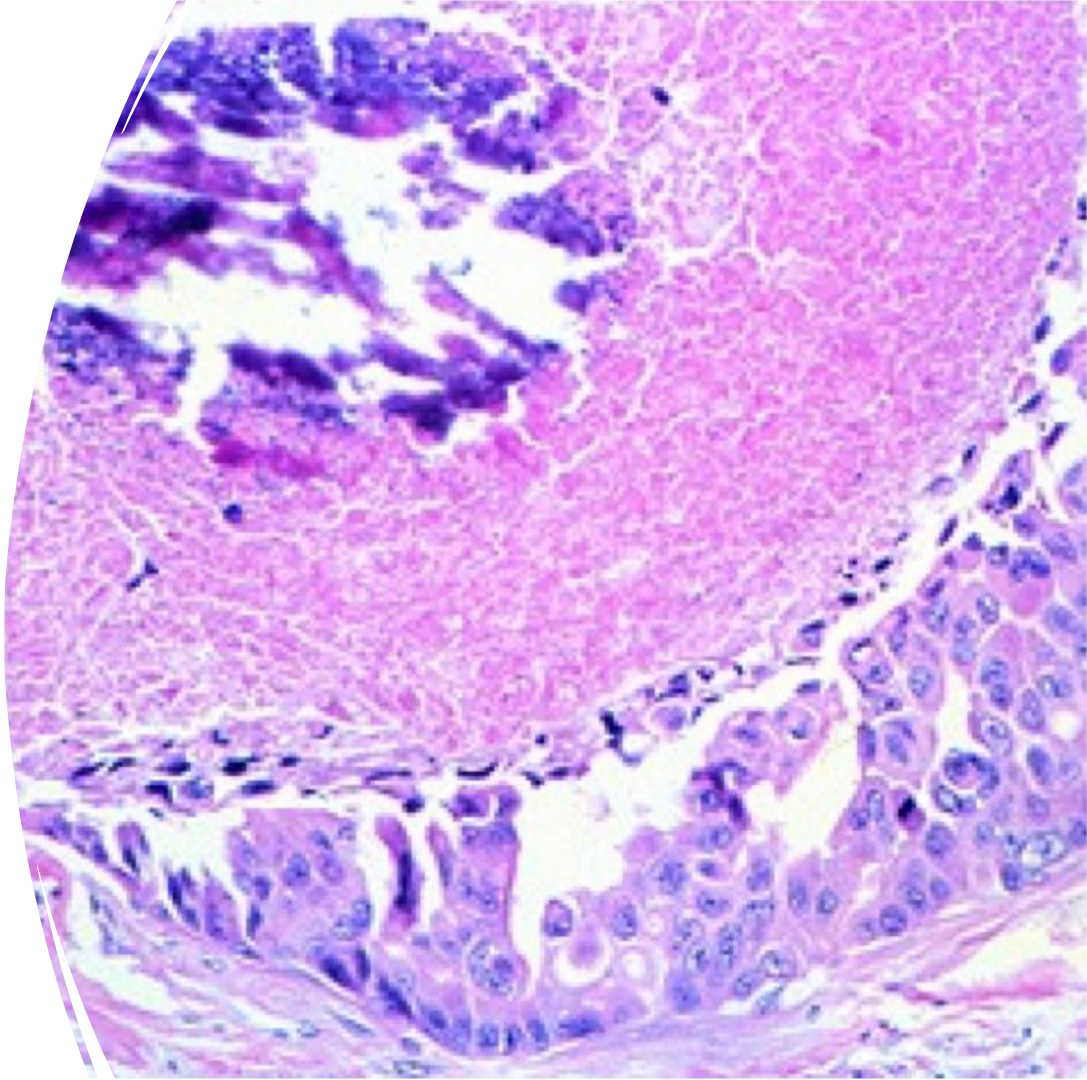
Fabian, *Endocr Relat Cancers* 2005 12:185-213

Management of DCIS & Proliferative Breast Disease

	Risk for Invasive Ca	Upstaging to Invasive Ca	Surgery for Diagnosis/Tx	Treatment & Prevention
DCIS	Precursor	10-20% to IC	Excision Clear margins (2mm)	Treatment
pLCIS or Florid LCIS	?precursor	?	Excisional Bx/ clear margins	Treatment
LCIS (classic)	↑Risk 10x Bilaterally	<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

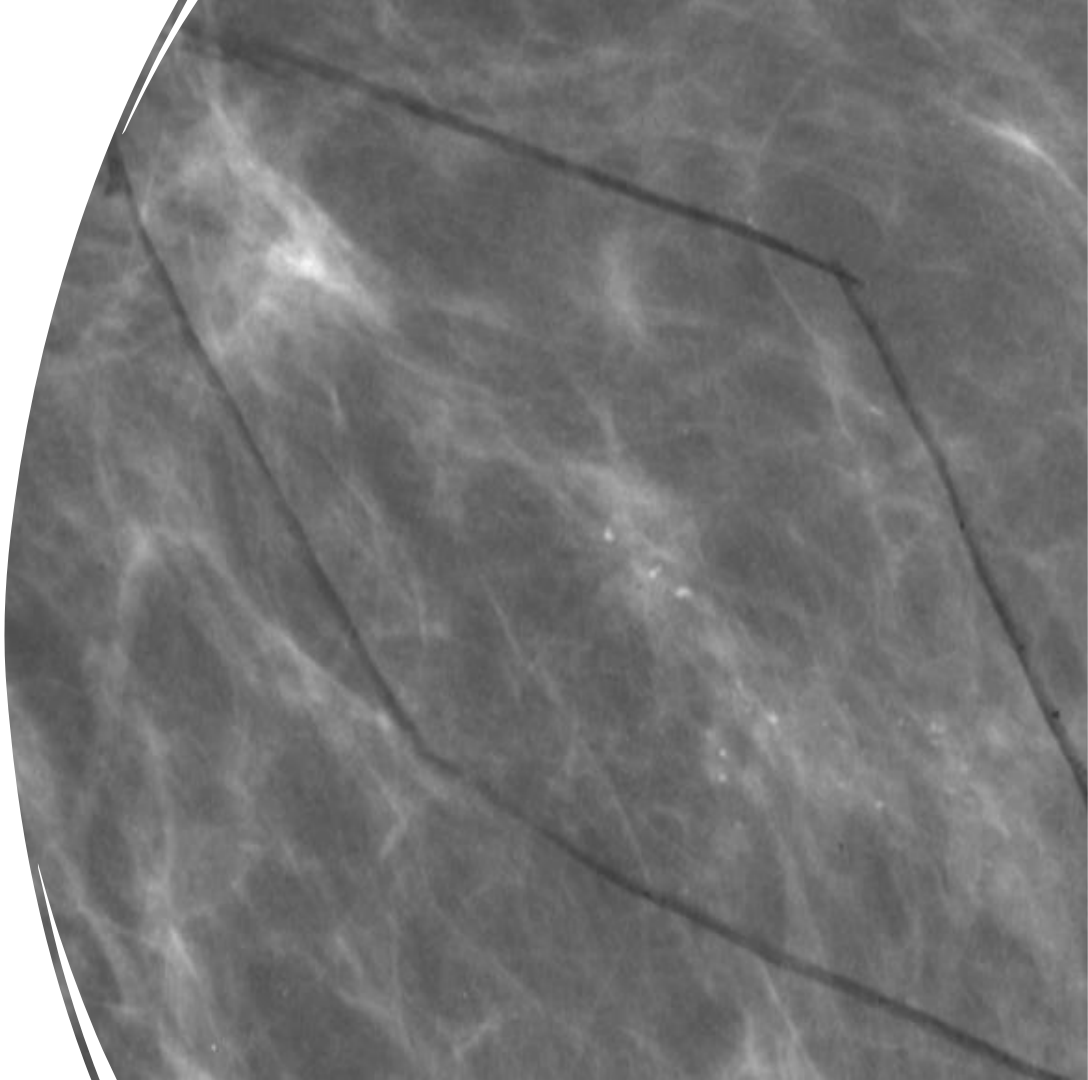
Non-invasive Breast Cancer: DCIS

- Proliferation of malignant cells of the ducts not breaching basement membrane
- Precursor lesion for invasive breast cancer
- 50-75% is ER+ or PR+
- 1970 = 5.8/100k, 2004 = 32.5/100k
- 25% of new breast cancers
- >50K new cases each year
- Equal in risk to IBC for genetic mutations
- Seen in BRCA mutation carriers
- Increases risk of IBC 2-fold
- Requires Surgery
- Radiation and Endocrine therapy discussed



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
  - Mastectomy or BCS
  - Similar BC Mortality outcomes
- Surgical Margins, **2 mm**
  - lower rates of local recurrence
  - 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
  - with mastectomy
  - features in needle biopsy concerning for invasive disease

* Note that if invasive disease (except mic) is found at time of surgery – treatment should be managed as per IBC guidelines (specifically no tumor on ink)

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.

Margin Recommendations for IDC, DCIS, LCIS

	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

*For pleomorphic Lobular Carcinoma In Situ (LCIS), the optimal width of margins is not known.

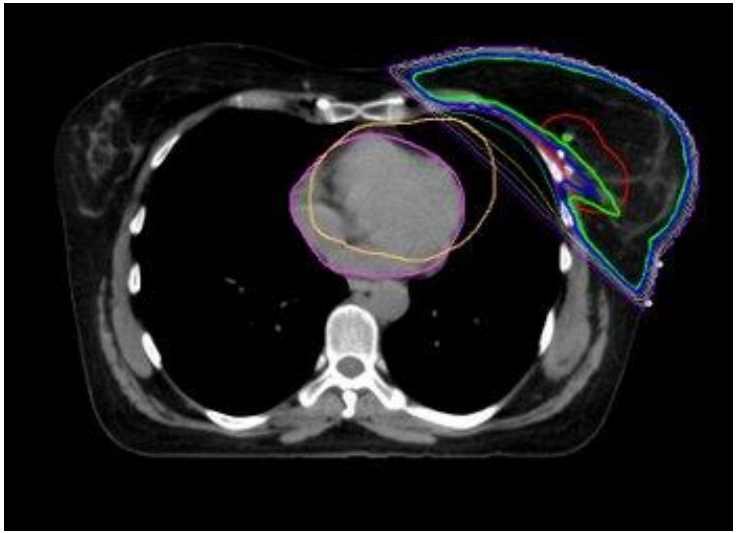
NCCN, Breast Cancer Guidelines 4.2023 BINV-F

Treatment of DCIS: Benefit of Radiation

- Evaluated in 3 trials: NSABP B-17, EORTC 10853, UK trial

- In NSABP B-17, pts with DCIS were randomized to lumpectomy +/- breast radiation
  - 12 yrs follow up, radiation s/p BCS decreased 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

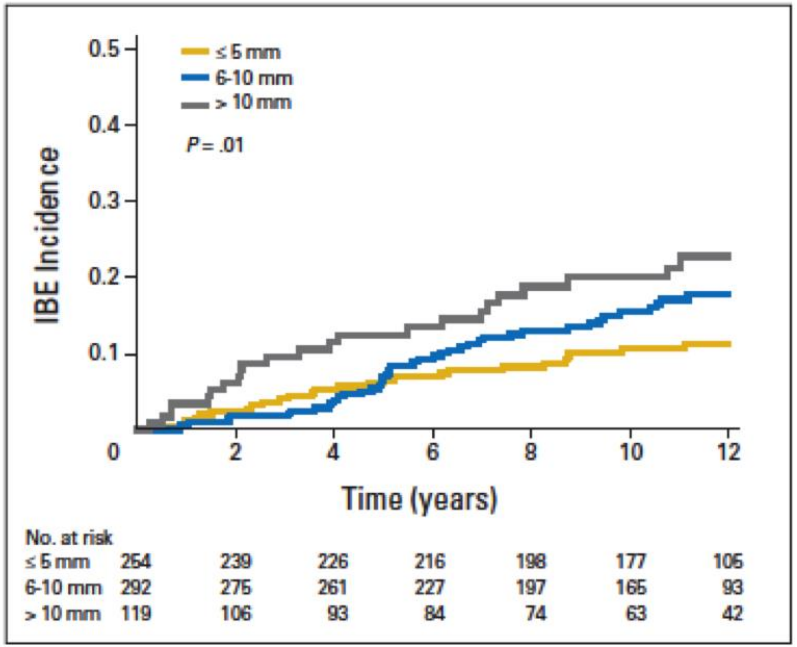
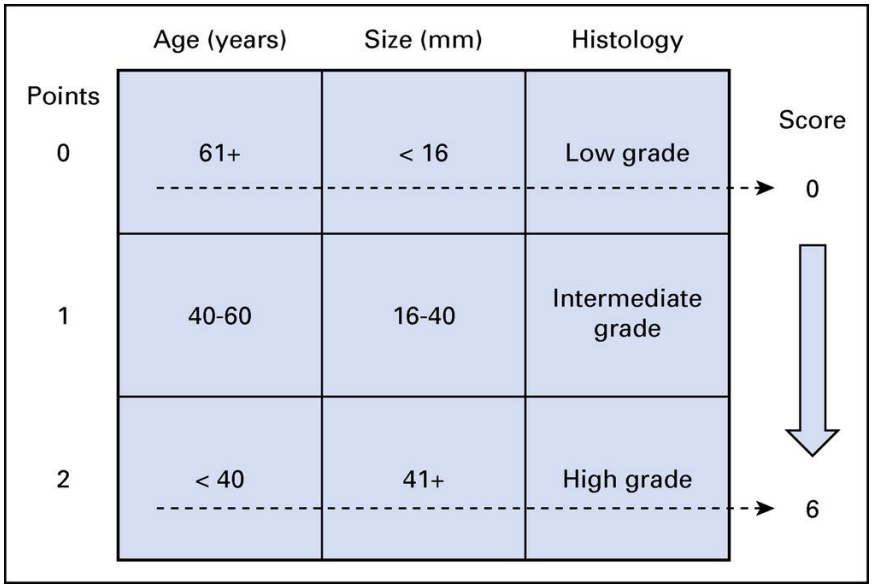


Fig 2. Ipsilateral breast events (IBEs) according to tumor size. The numbers at risk are given beneath the *x*-axis.

- Prospective trial of 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

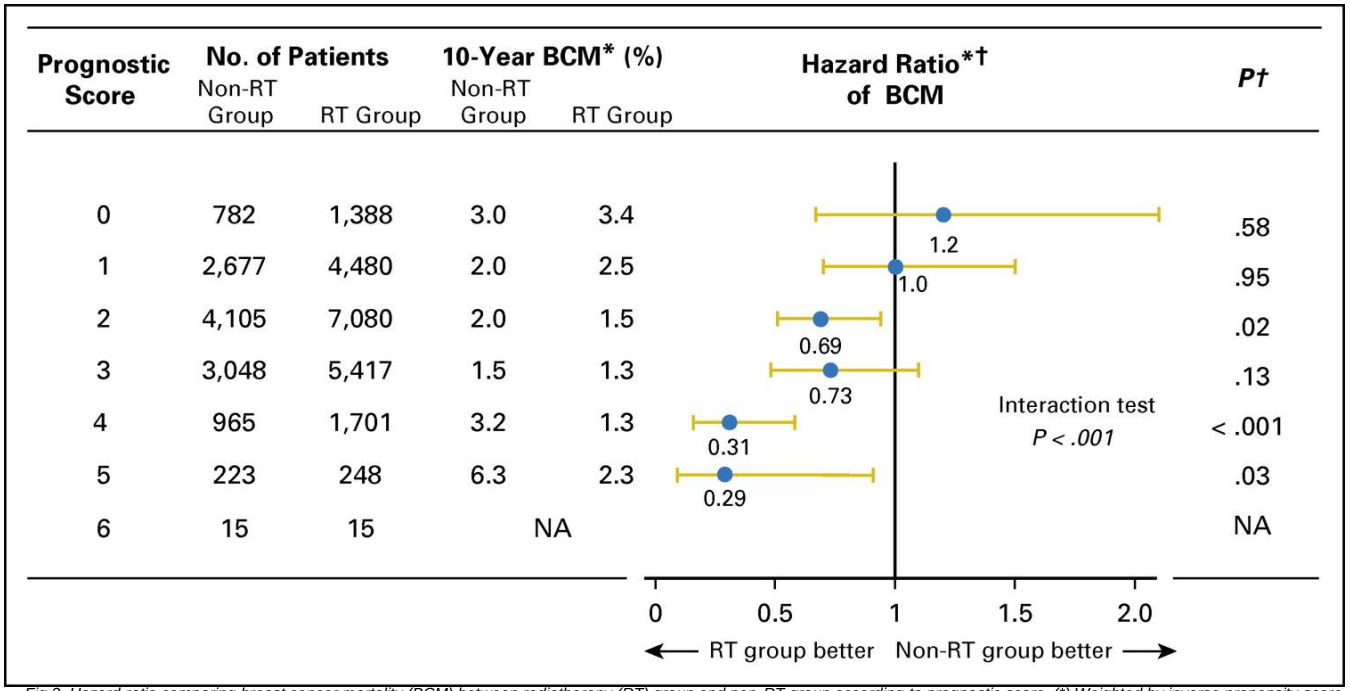
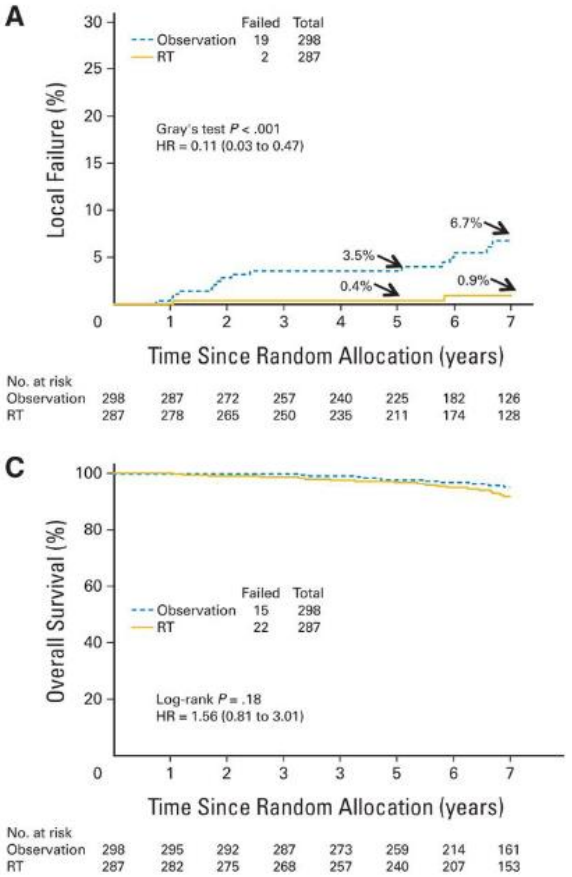


Fig 2. Hazard ratio comparing breast cancer mortality (BCM) between radiotherapy (RT) group and non-RT group according to prognostic score. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital 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

RTOG 9804: RCT of Radiation vs Not for low-risk DCIS

- Eligibility was low-risk DCIS
  - screen-detected DCIS
  - low to intermediate nuclear grade
  - tumor size ≤2.5 cm
  - margins >3 mm
- 585 pts, closed to low accrual
- Slight increase in local recurrence
- No survival effect

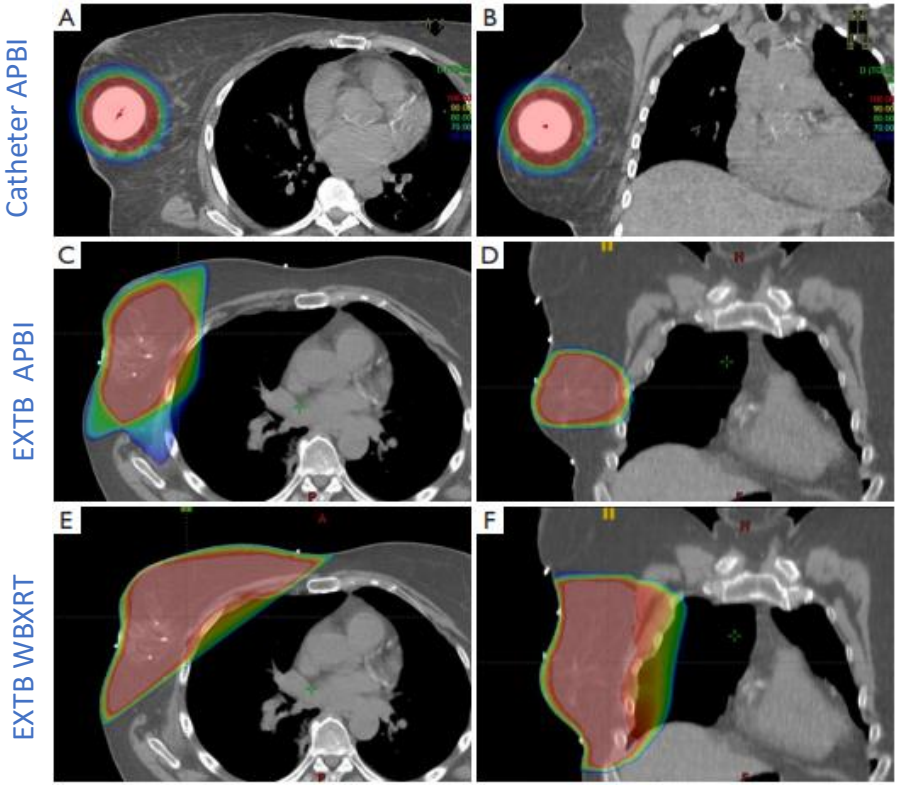


McCormick, JCO 2015

Another option, APBI

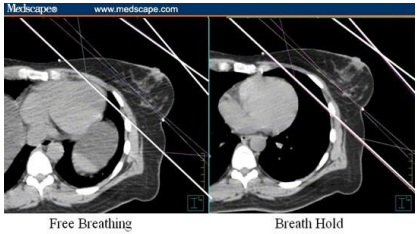
- Suitable for low-risk DCIS
  - screen-detected DCIS
  - low to intermediate nuclear grade
  - tumor size ≤2.5 cm
  - margins >3 mm.

- 4 RCT: multi-catheter APBI is non-inferior in local control compared with WBRT
  - NSABP B-39/RTOG 0413 (25% DCIS)
  - OCOG-RAPID (18% DCIS)
  - University of Florence (8.8% DCIS)
  - GEC-ESTRO (6% DCIS)



Bennion, Gland Surgery, 2018

Treatment of DCIS: Radiation



Radiation is used for most DCIS

- Decreases risk of local recurrence by 50-70%
- Recurrences are ½ IBC & ½ DCIS
- 45-50 Gy over 4.5-5 weeks, +/- boost
- NNT is 9 to prevent 1 local recurrence[1]

APBI may be considered

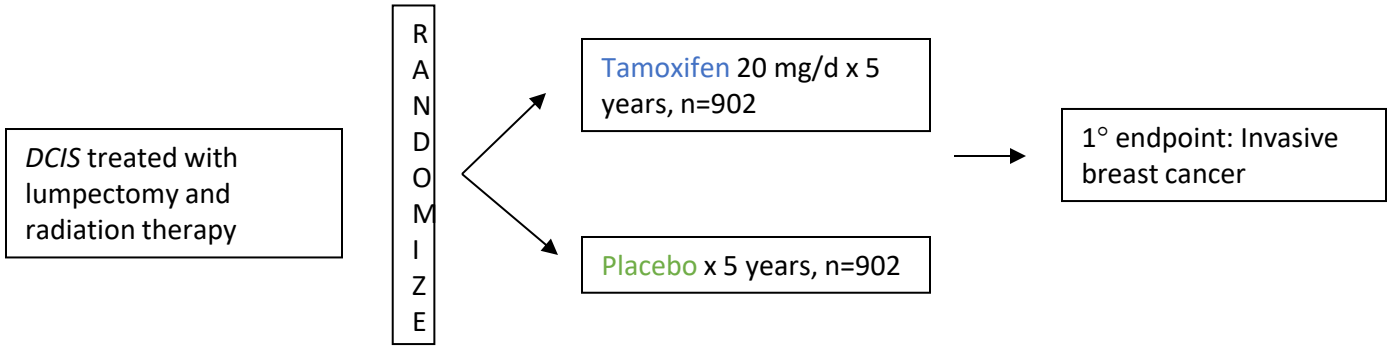
- If low risk
- Screen detected
  - low to int grade
  - <2.5cm
  - Margins >3mm

Omission of Radiation in low-risk patients can be considered:

- ER+ receiving endocrine therapy
- Low or Int grade DCIS
- <1.6-2.5 cm of disease
- Older Age (>60)
- 1cm margins
- OncotypeDX DCIS is not standard, but can be used

1. Goodwin, Breast 2009; Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for BCS With Whole-Breast Irradiation in Ductal Carcinoma In Situ. J Clin Oncol 2016;34:4040-4046

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.

Tamoxifen for DCIS: 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	11	10	**0.88** (0.33-2.28)

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

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

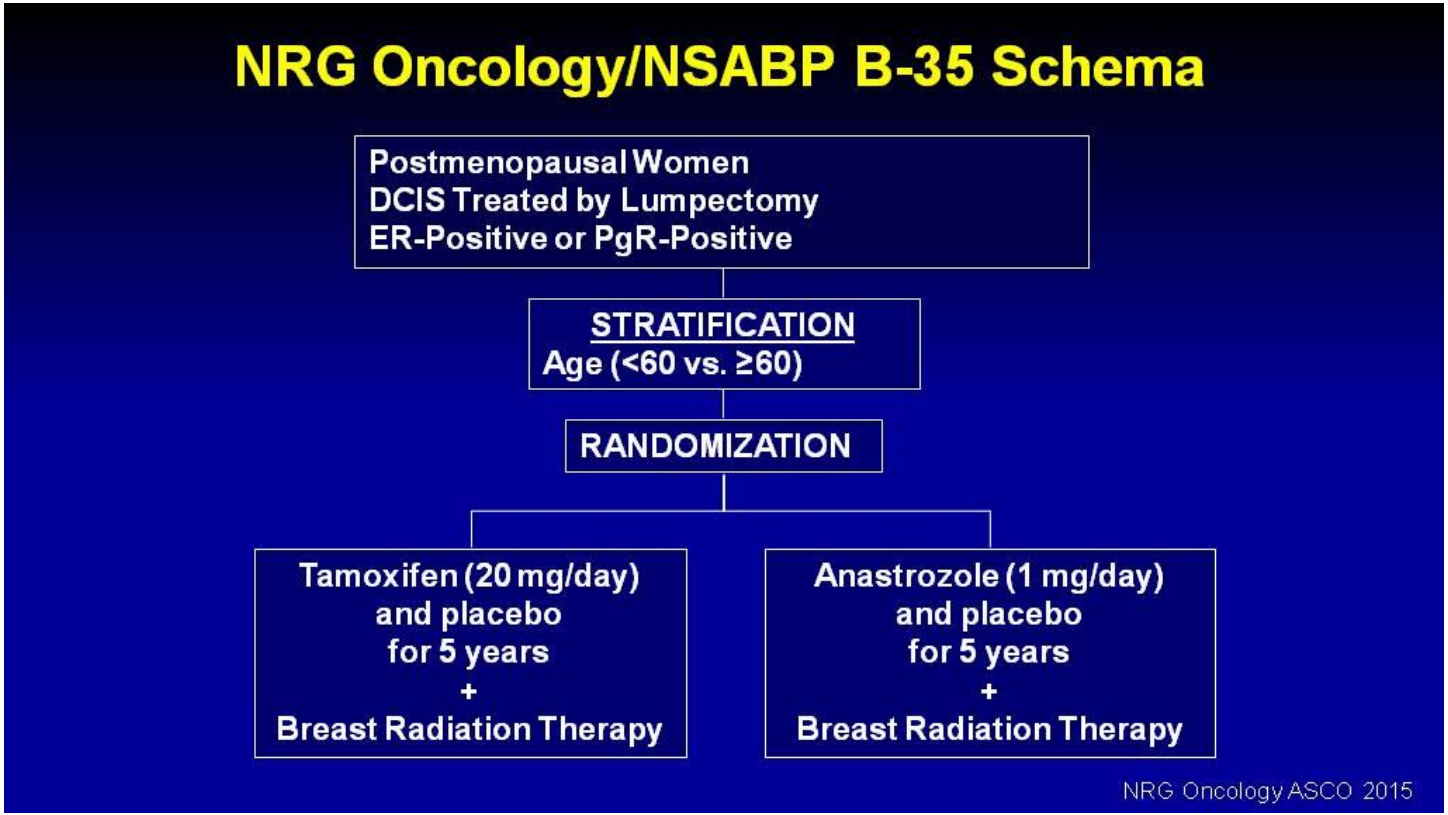
	DCIS (HR)	IBC (HR)
Ipsilateral side	**0.75** (0.61-0.92)	**0.79** (0.61-1.01)
Contralateral side	**0.50** (0.28-0.87)	**0.57** (0.39-0.83)

N = 3375 women

No OS benefit HR = 1.11 (0.89-1.39)

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

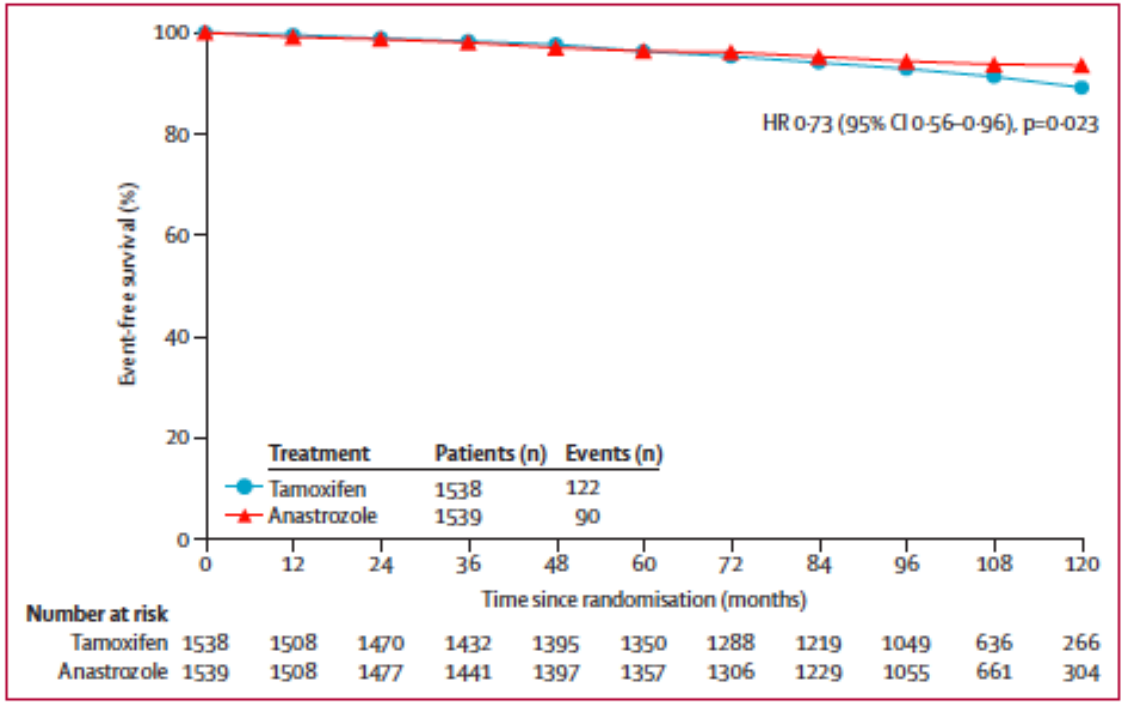
Treatment of DCIS: Tamoxifen vs AI



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: Tam vs. AI



Breast Cancer Free Interval

	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.

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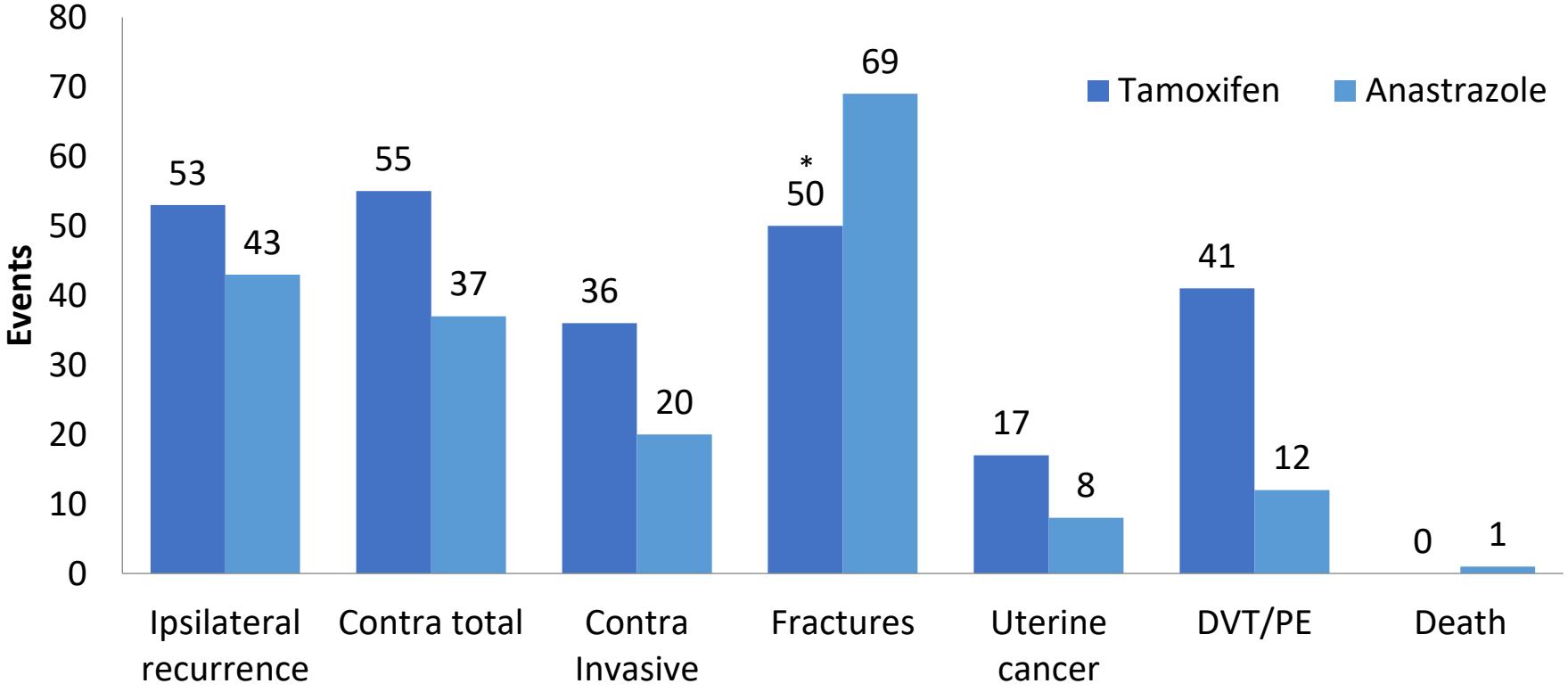


Adapted from presentation by Richard Margolese at 2015 ASCO Annual Meeting

Conclusions: Tamoxifen vs Anastrozole for DCIS

Anastrozole is slightly 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

Low-dose Tamoxifen for Breast Atypia and Intraepithelial Neoplasia

Primary endpoint: Incidence of invasive breast cancer or DCIS

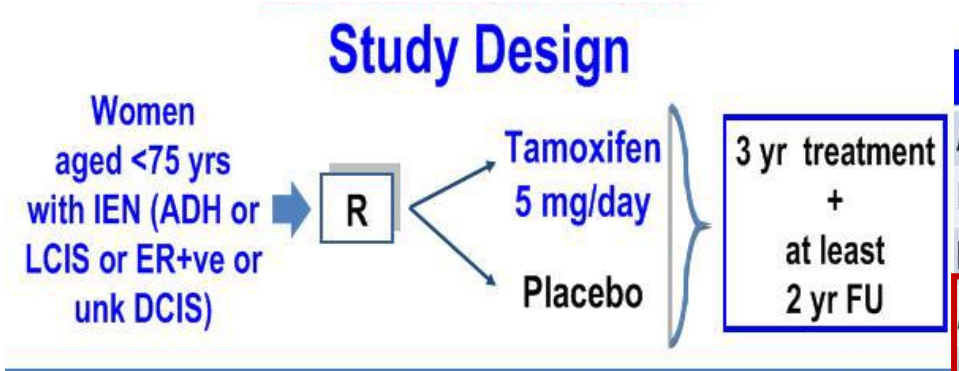
- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

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

Low-dose Tamoxifen for Breast Atypia and Intraepithelial Neoplasia



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JCO, 2019, DeCensi

Results: Low Dose Tamoxifen

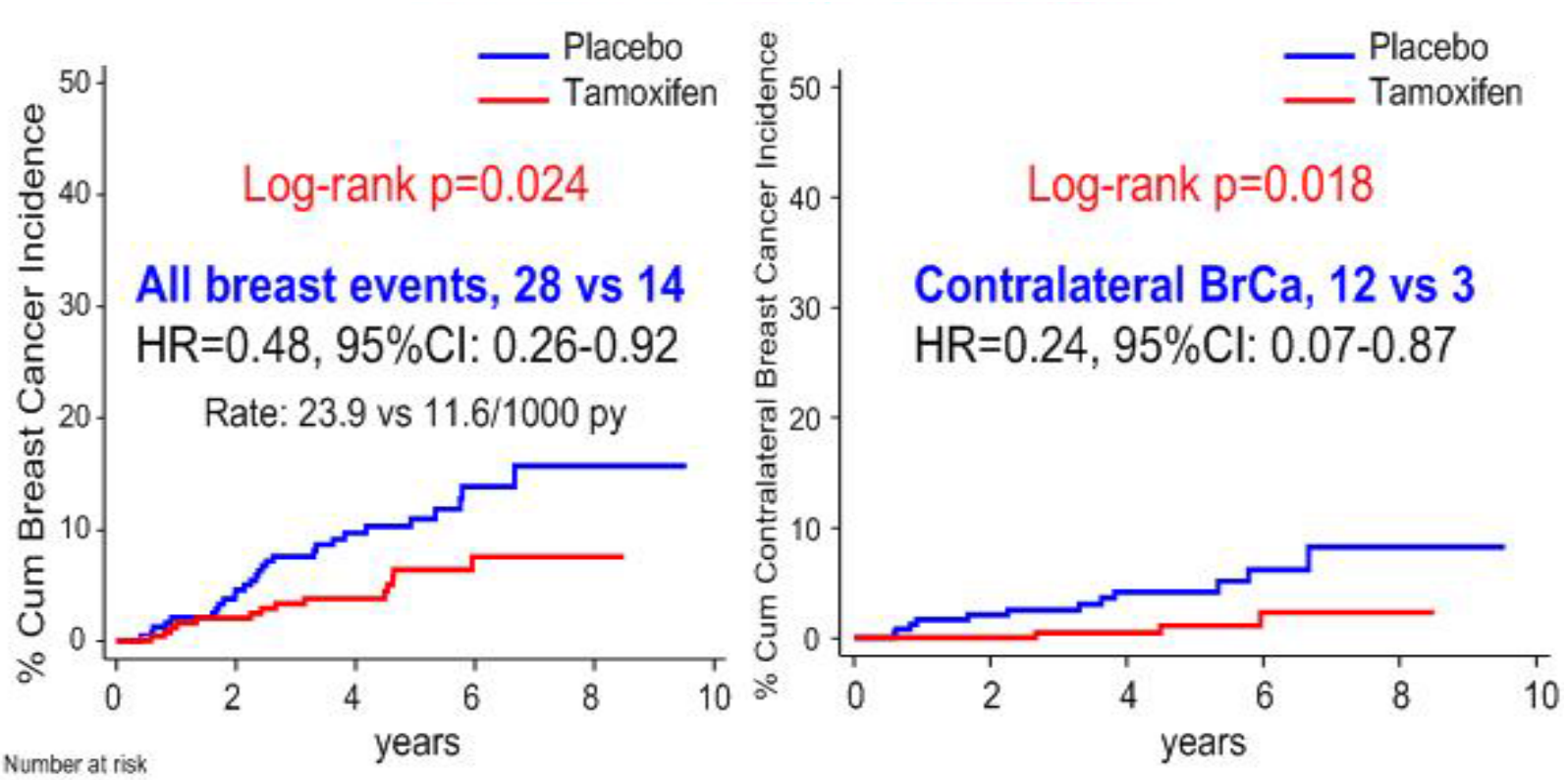


TABLE 3. Serious Adverse Events by Allocated Arm

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).

Low Dose Tam: Risk and Results by Pathology

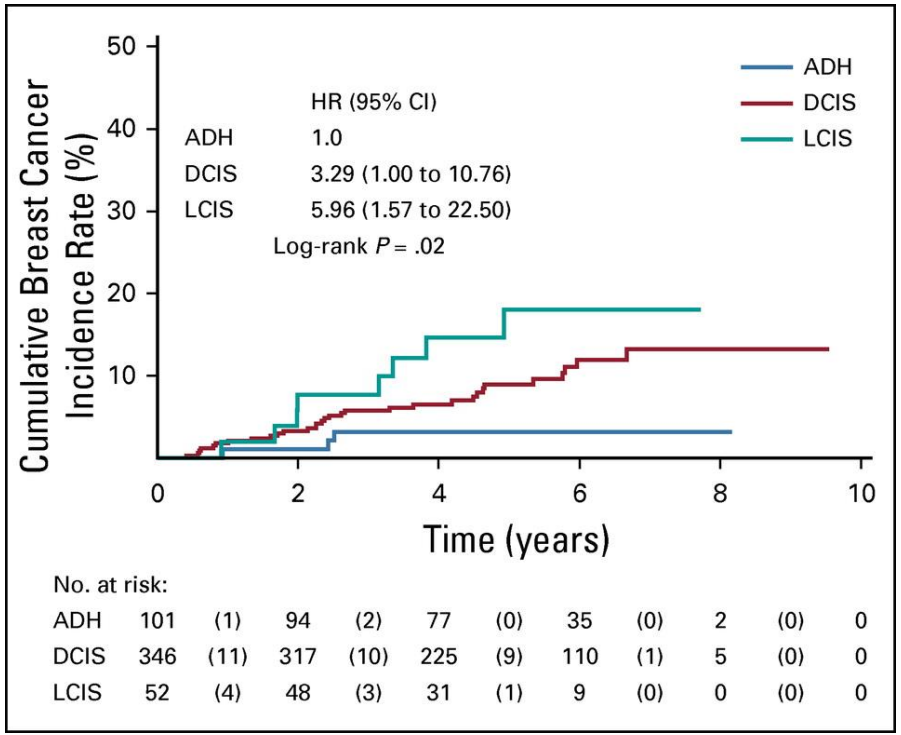
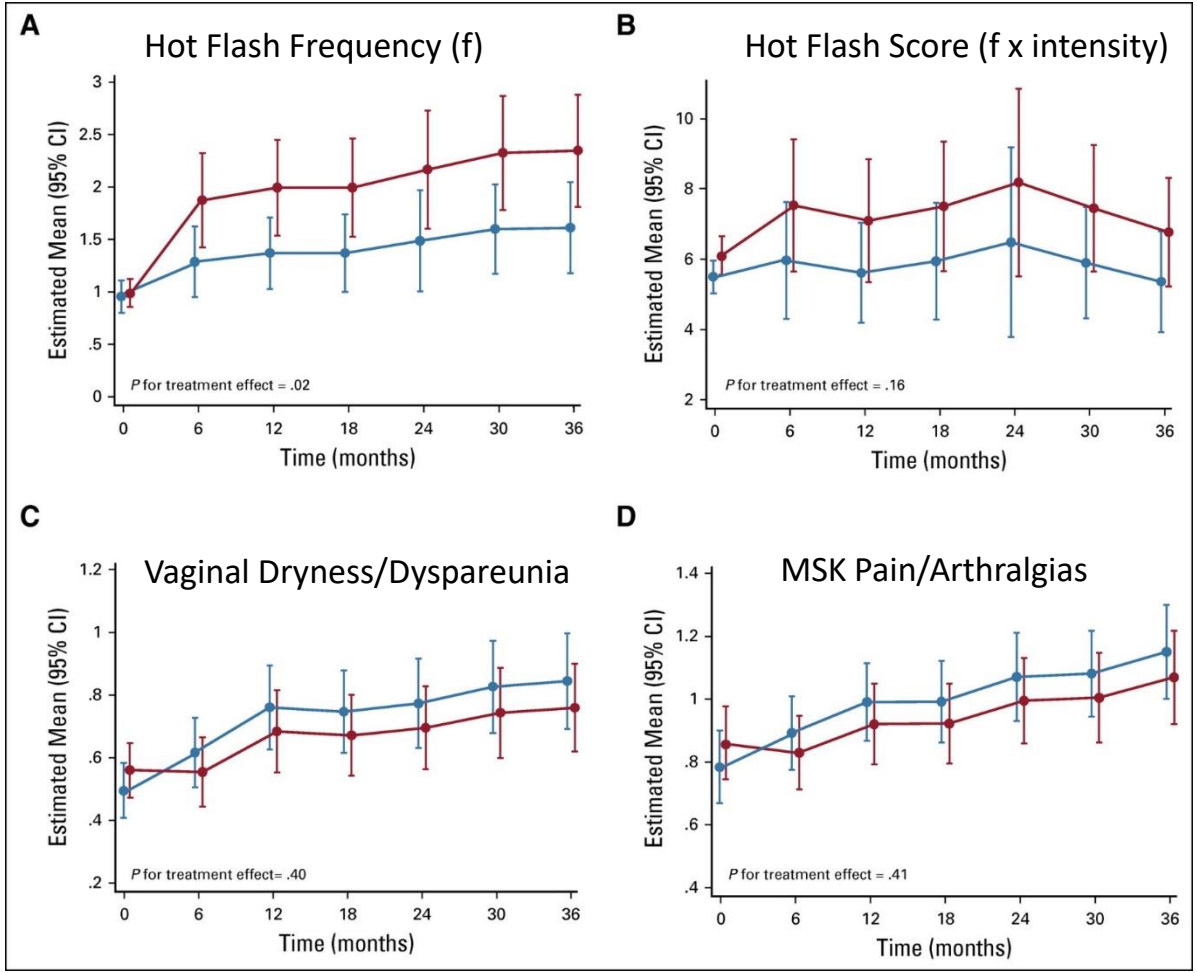


TABLE A1. Prespecified Subgroup Analyses

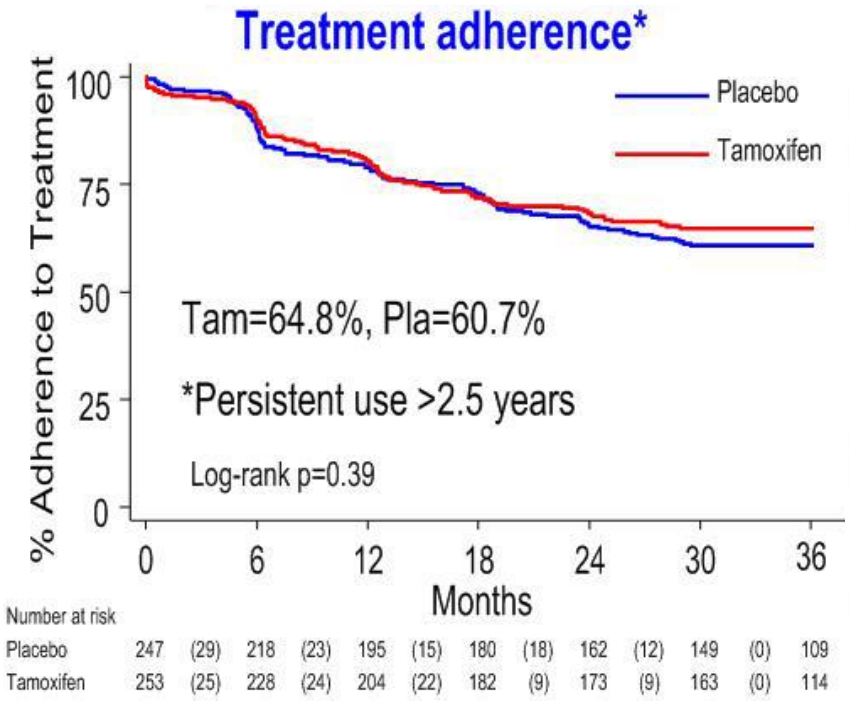
Subgroup	No. of Patients	*P**	HR (95% CI)
Diagnosis within 12 months since random assignment	458	.16	0.41 (0.20 to 0.82)
Diagnosis between 12 and 60 months	42		1.59 (0.27 to 9.53)
ADH + DCIS	447	.54	0.53 (0.26 to 1.08)
LCIS	52		0.31 (0.06 to 1.51)
ER positive	333	.84	0.51 (0.24 to 1.10)
ER unknown	166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



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

Standard of Care:

- **Surgical resection** (2mm margin)
  - BCS or Mastectomy
  - SLNB indicated in mastectomy

Share Decision Making: (No Survival Benefit)

- **Radiation**
  - Most get radiation
  - APBI is an option for lower risk patients (>50, low/int grade DCIS, screened, margins >3mm)
  - Omission possible for low-risk patients

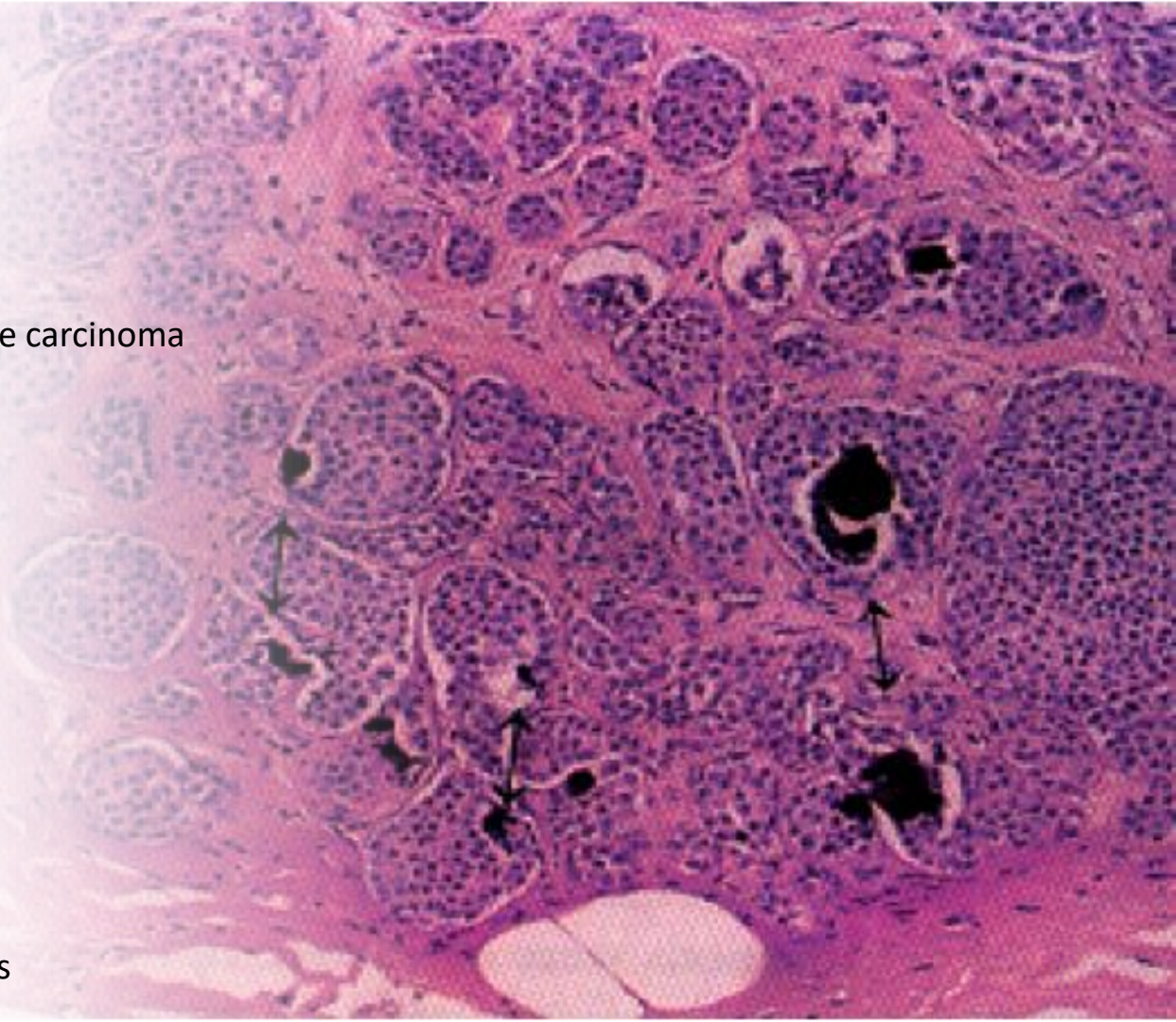
- **Endocrine therapy**
  - Motivation is Recurrence is ~1%/year, ½ are Invasive
  - BCT for ER+ DCIS: Offer treatment with Tamoxifen (20mg or 5mg) or AI
  - Unilateral Mastectomy: Consider for Risk-reduction therapy (Tam, Ral or AI)
  - Bilateral Mastectomies without invasive component: No role

Management of DCIS & Proliferative Breast Disease

	Risk for Invasive Ca	Upstaging to Invasive Ca	Surgery for Diagnosis/Tx	Treatment & Prevention
DCIS	Precursor	10-20% to IC	Excision Clear margins (2mm)	Treatment
pLCIS or Florid LCIS	?precursor	?	Excisional Bx/ clear margins	Treatment
LCIS (classic)	↑Risk 10x Bilaterally	<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

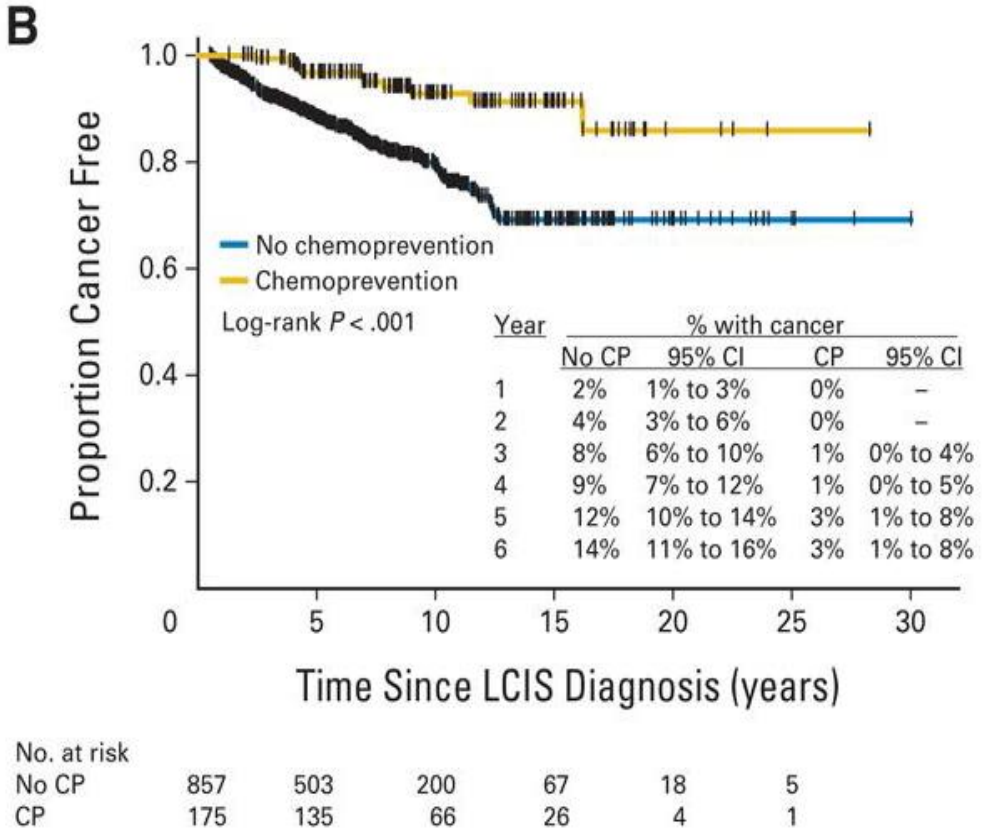
LCIS: Proliferative Breast Disease

- Risk factor for BC
- Not a direct precursor of invasive carcinoma
  - Can be monitored
  - Upgrade rate <3%
- Restaged by AJCC
  - NOT a Cancer
- 7-11 Fold increase of Cancer
  - 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 yrs
- Chemoprevention reduced incidence of breast cancer
  - 7% vs. 21% at 10 yrs
  - HR 0.27



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

Pleomorphic LCIS or Florid LCIS

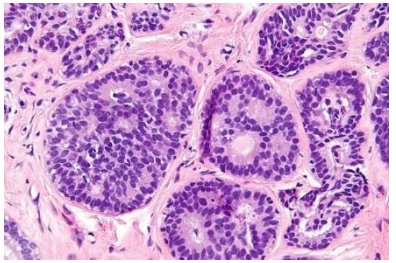
- Pleomorphic LCIS
    - •central necrosis and calcs
- Florid LCIS
    - •distention of involved ducts/lobules
    - • mass forming
- Any non-classic LCIS or rad/path discordant lesion should be surgically excised
- **Typically treated similarly to DCIS**

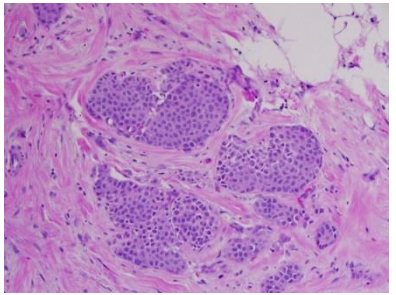
Chemoprevention = Medical Risk Reduction

Who should we consider medical risk reduction for?

ASCO/NCCN guidelines:

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





Gaps in our recommendations?

- Not strong/specific recommendations for less penetrant mutations
- Case-control data suggests there may be benefit in BRCA2 P/LP carriers

Breast Cancer Risk Assessment Models

Gail Model

- Estimates 5 year and lifetime risk
- Incorporates age, family history (1st degree), benign breast disease, age of menarche, age of first pregnancy, and race
- http://www.cancer.gov/bcrisktool/

Breast Cancer Surveillance Consortium Risk Calculator

- Estimates 5 year and 10 year breast cancer risk
- Incorporates 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

Tyrer-Cuzick, IBIS Breast Cancer Risk Evaluation Tool

- Estimates 5 year and lifetime risk
- Incorporates 1st and 2nd degree relatives, reproductive factors, BMI, LCIS
- http://www.ems-trials.org/riskevaluator/

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.

Comparing the Breast Cancer Risk Models

	Demo-graphics	Gyn history	Breast history	Family history	Body Factors	Pros	Cons
Gail/ BCRISK	Age Race	Menarche Parity/Age	Biopsy/ atypia	1º relative Yes/no	-	Fast – 8 Qs Gives lifetime risk	Misses • Fm Hx details • Body factors • Gyn hx • Density
BCSC	Age Race	Menarche	Biopsy/ atypia Density	1º relative Yes/no	-	Fast – 5 Qs Phone App	Lacks lifetime risk Misses • Fm Hx details • Body factors • Gyn hx
Tyrer Cuzick /IBIS	Age Race	Menarche Menopause HRT (duration) Parity/Age	Biopsy/ atypia Density Genetics	1º and 2º with Br or Ov CA • Relationships • Ages • Non-affected	Height Weight	Gives lifetime risk Comprehensive • FM HX • LCIS • Menopause • HRT • Body Factors	Time User Dependent Overestimates • Race • Young • LCIS

When NOT to use these tools

- History of radiation therapy to the chest
- History of DCIS or Breast Cancer (LCIS only with TC)
- Known pathogenic mutation associated with higher risk of breast cancer

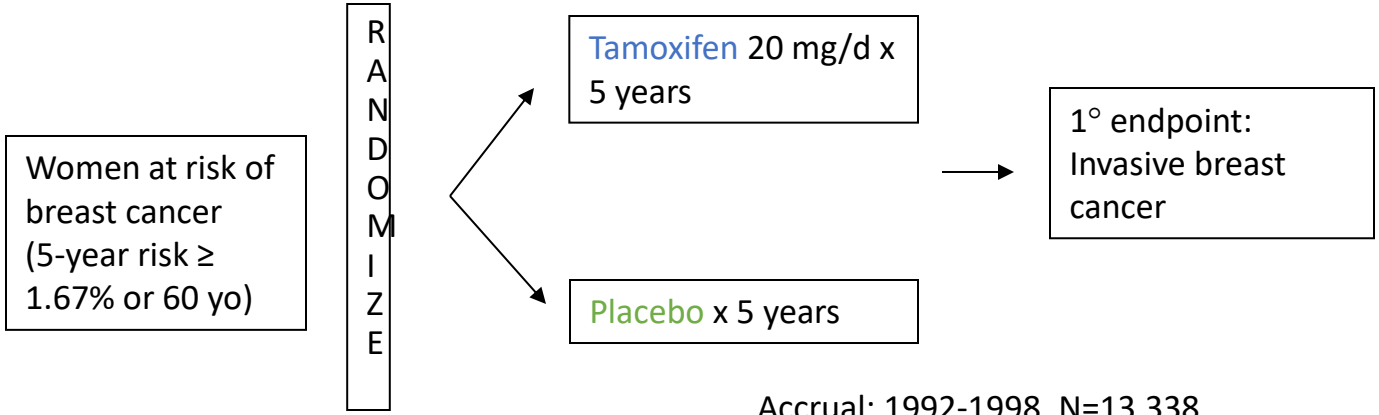
What these tools DON’T include:

- Alcohol use and Exercise

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)

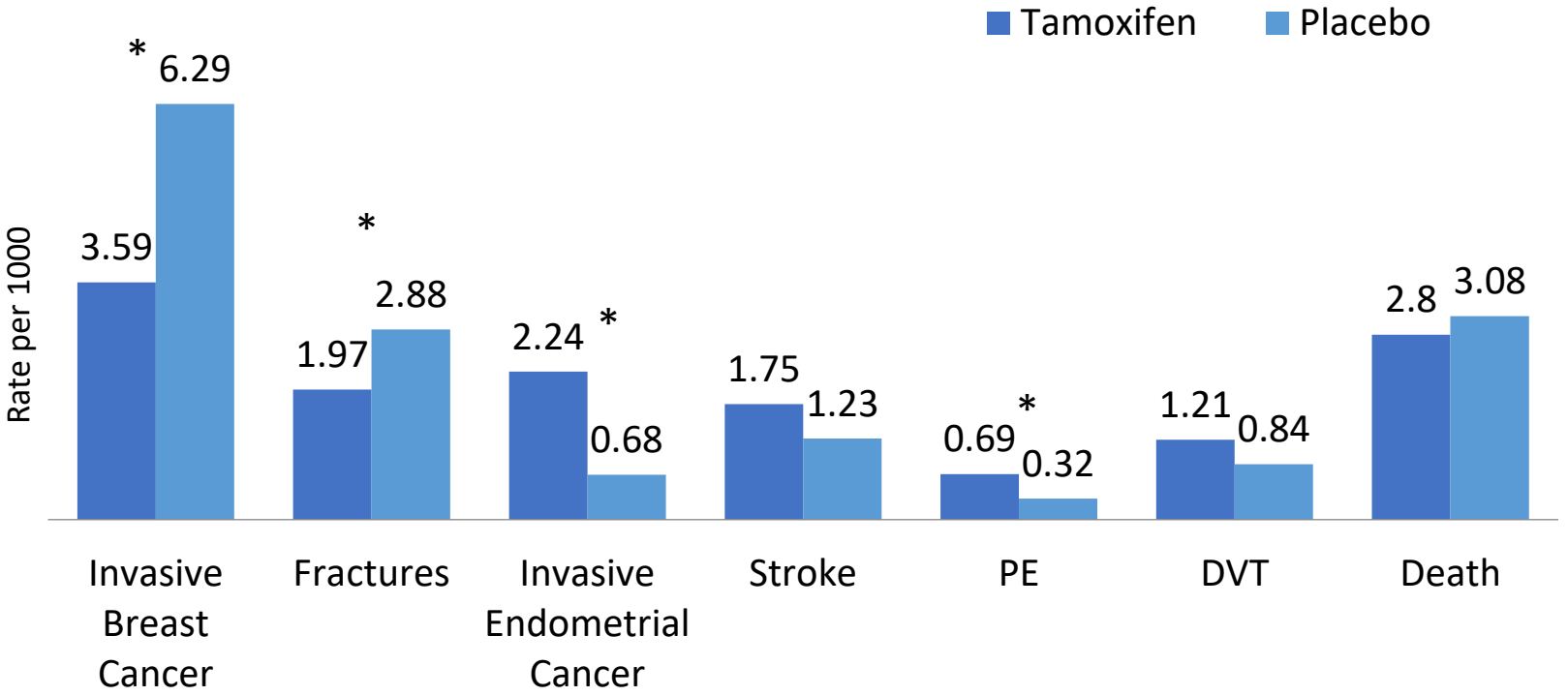


Accrual: 1992-1998, N=13,338
Closed early after interim analysis
Median follow-up 54.6 months

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

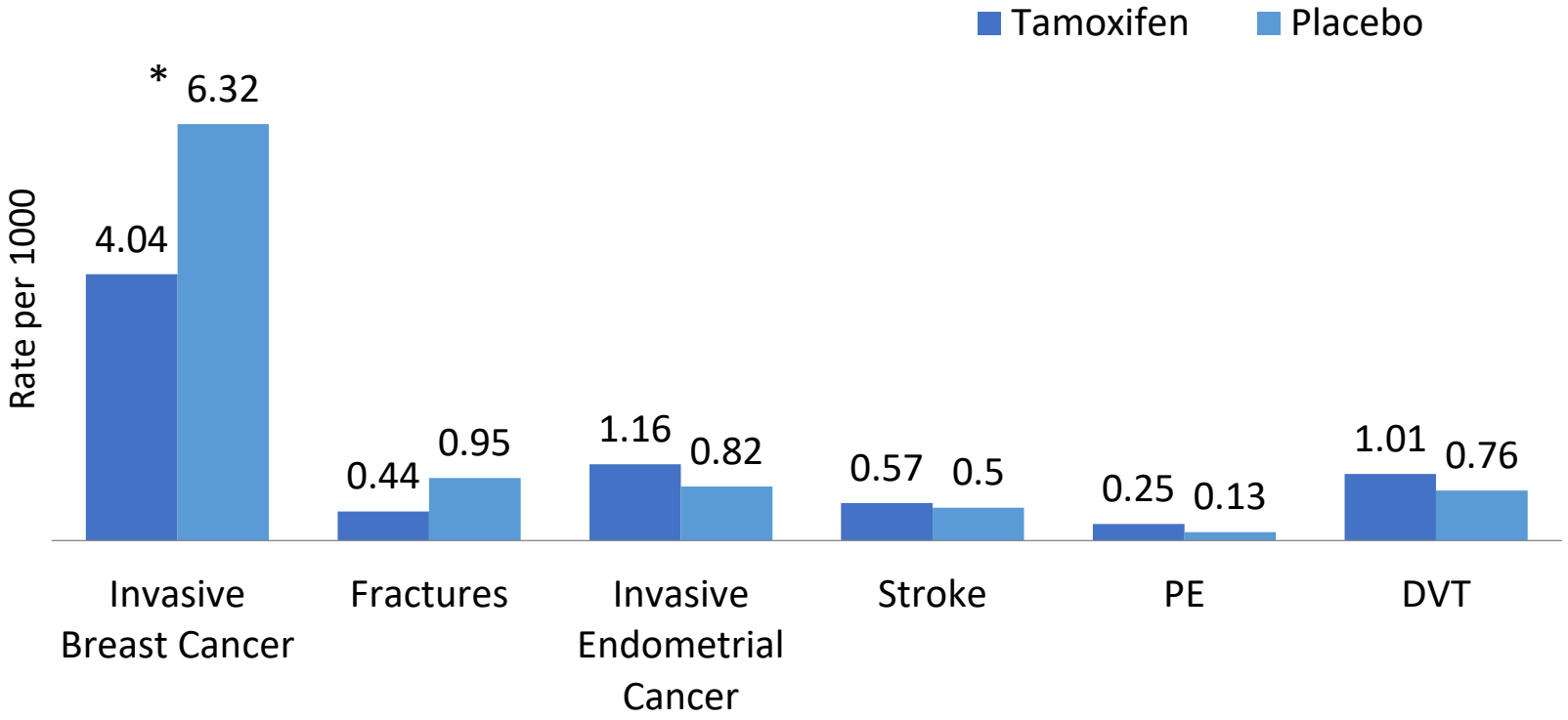
Fisher B *et al*. 1998 *J Natl Cancer Inst* **90**:1371.

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



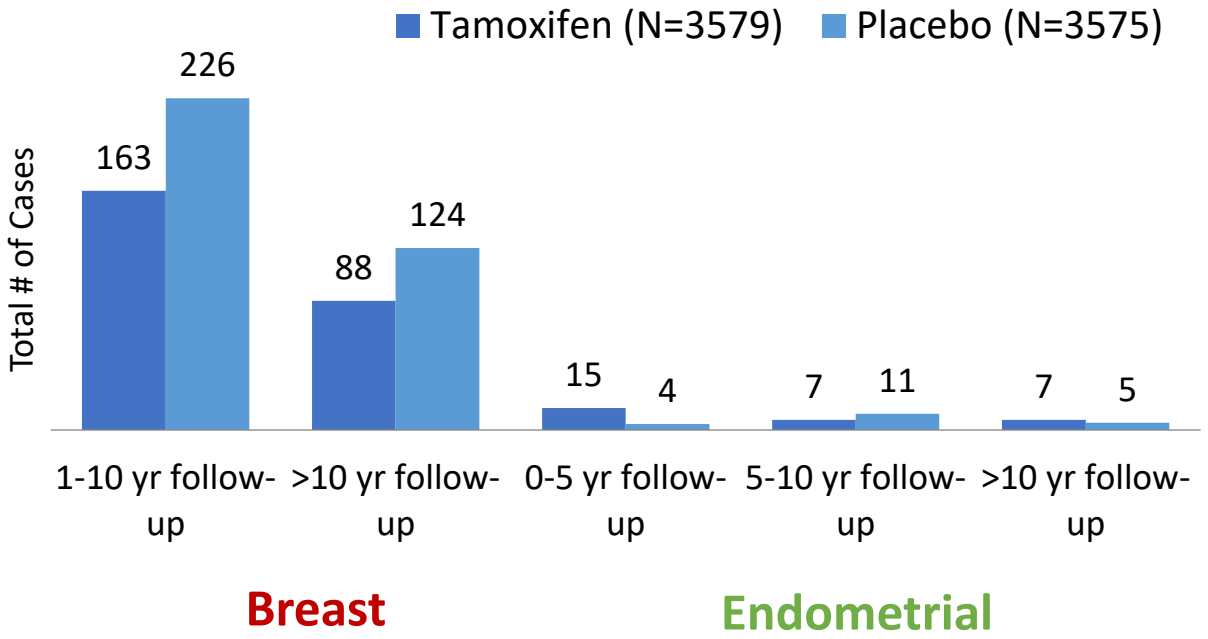
Fisher B *et al. Journal of the National Cancer Institute*, Vol. 97, No. 22, November 16, 2005

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



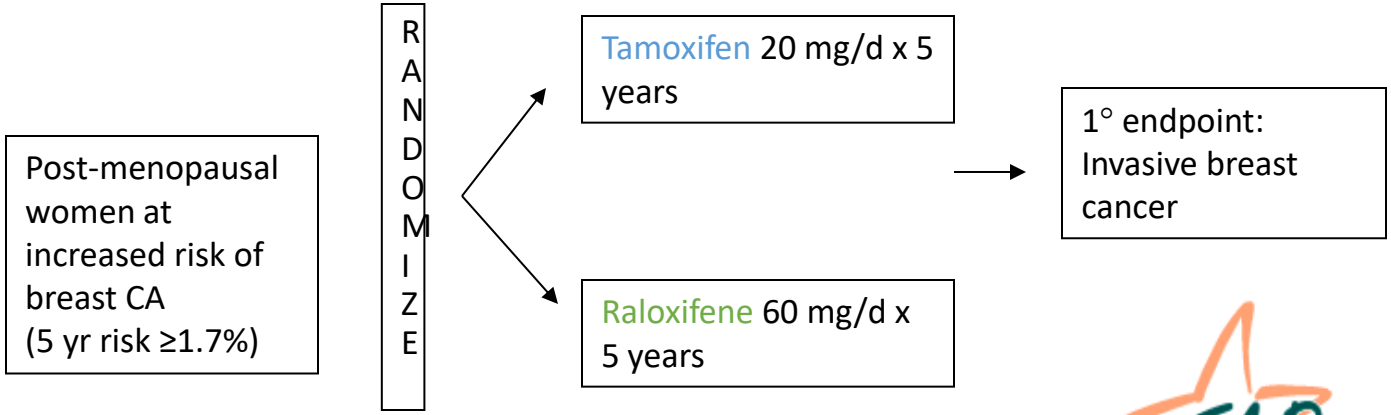
Fisher B *et al., Journal of the National Cancer Institute*, Vol. 97, No. 22, November 16, 2005

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)

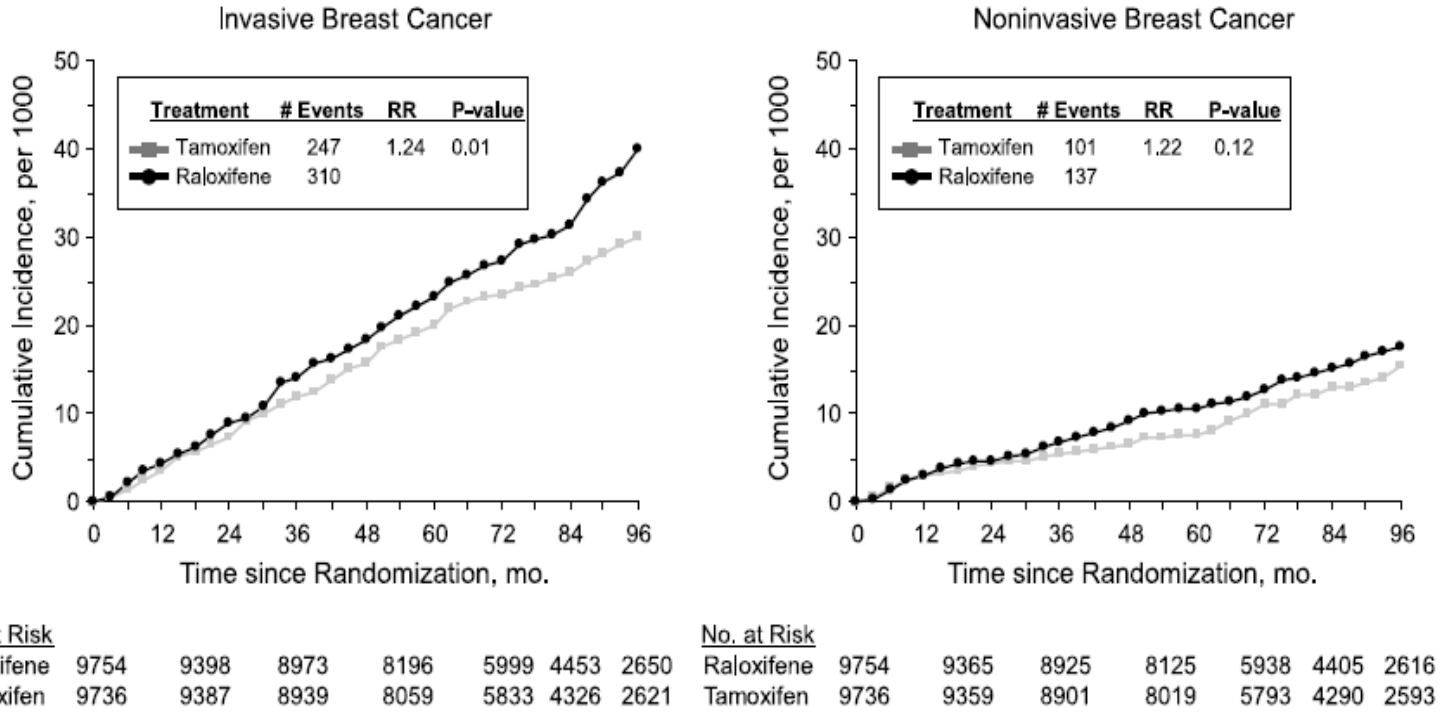


- Accrued 19,471 patients between July 1999-Nov 2004
- Mean age participants at randomization 58.5 years
- 93% of participants were white
- Mean predicted 5-year risk of IBC was 4.03%

STAR
Study of Tamoxifen And Raloxifene

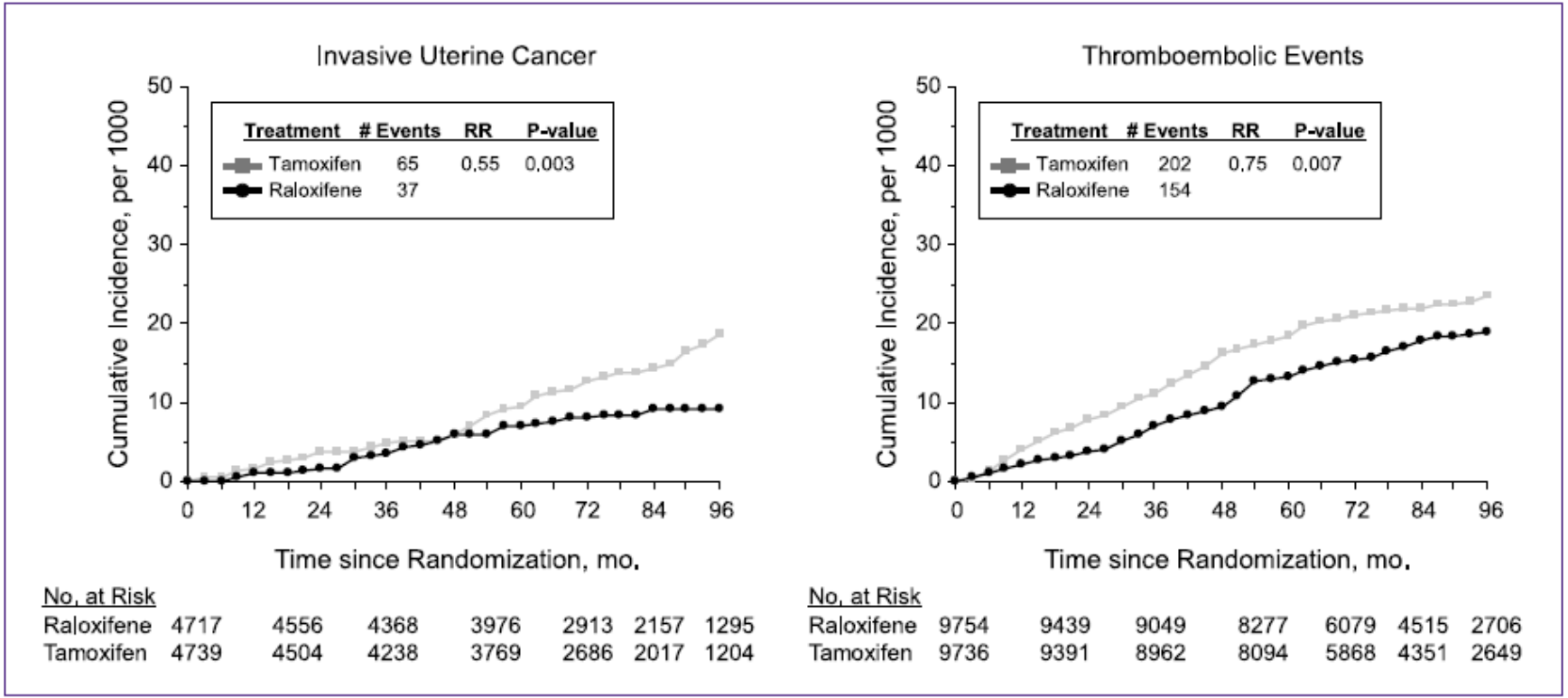
Vogel VG *et al*. 2006 *JAMA* **295**:2727. Vogel VG *et al. Cancer Prev Res (Phila)* **3**:696-706, 2010.

STAR Long Term Update 2010: Tamoxifen is more effective



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

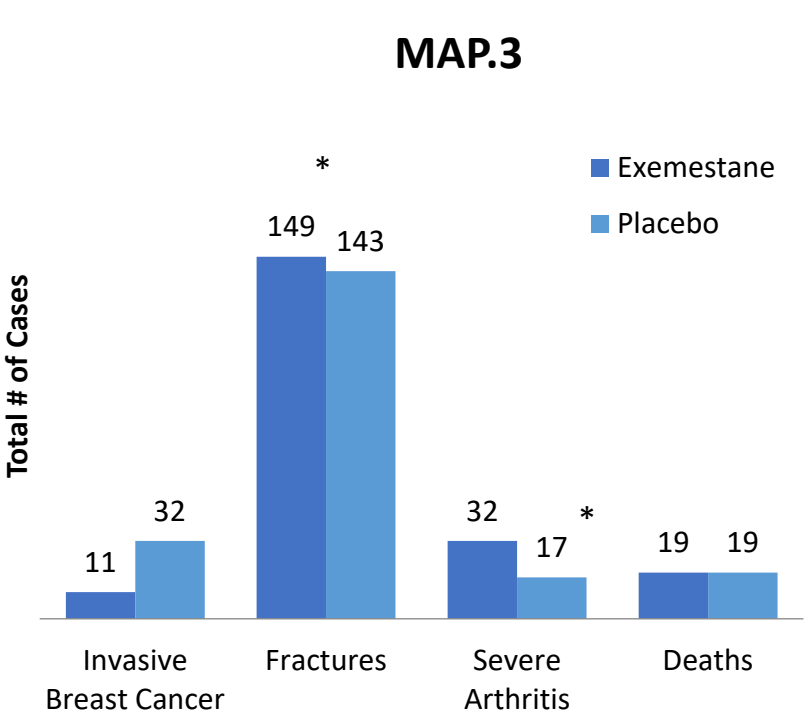
…and more toxic

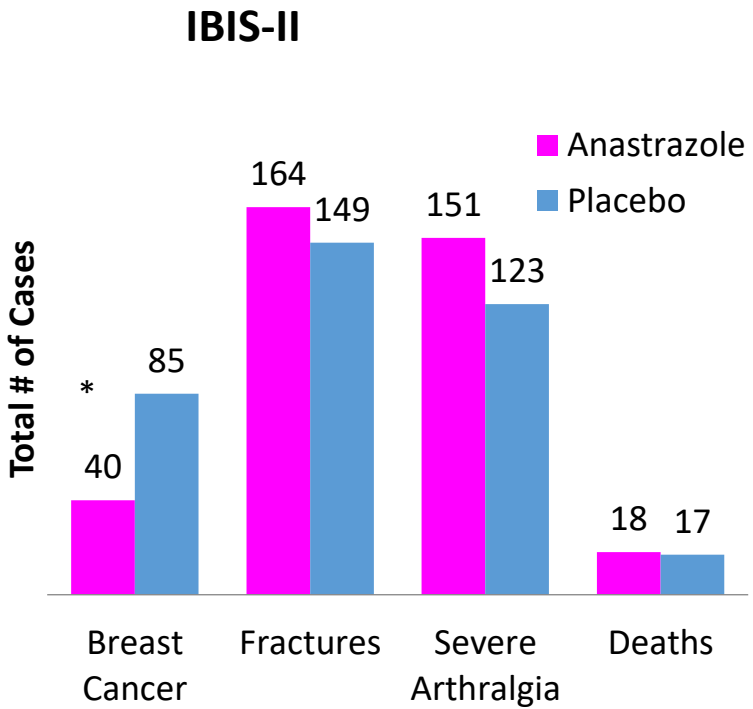


*Hysterectomy for benign disease was double in Tamoxifen group, RR = 0.45 (0.37-0.54)

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

Risks and Benefits of AIs

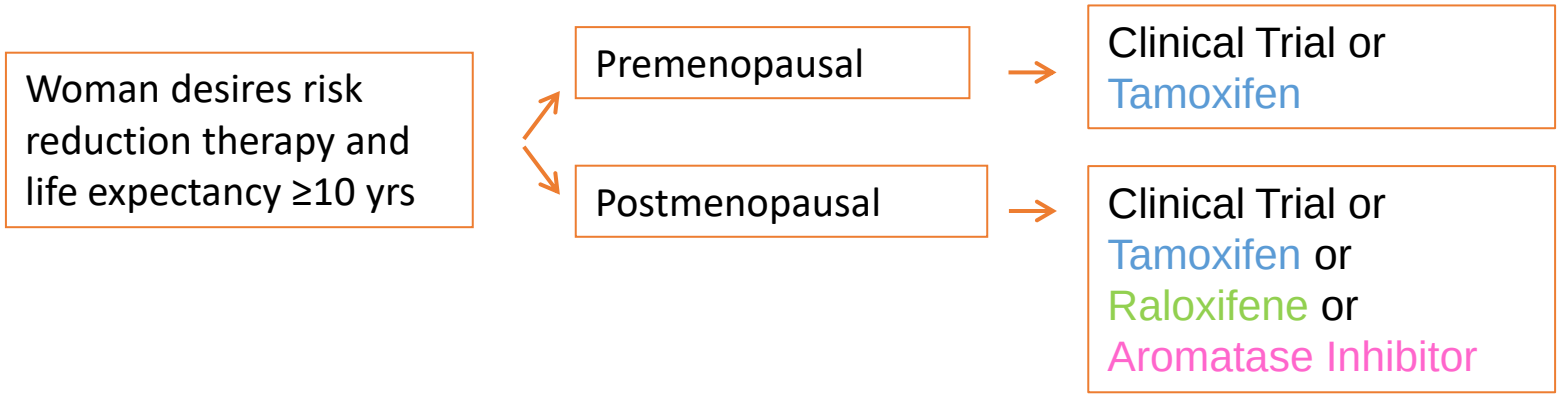




No Direct comparison of AI to Tamoxifen for prevention, but extrapolation from treatment data for Breast cancer is often used.

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

Summary: Medical Risk Reduction



Adapted from NCCN Guidelines Version 4.2023.

Who should get Medical Risk Reduction?

Ideal candidates

Tamoxifen

- Premenopausal (40-50) women with high risk of cancer
- 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

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?

Modifying Weight changes BC Risk (NHS)

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

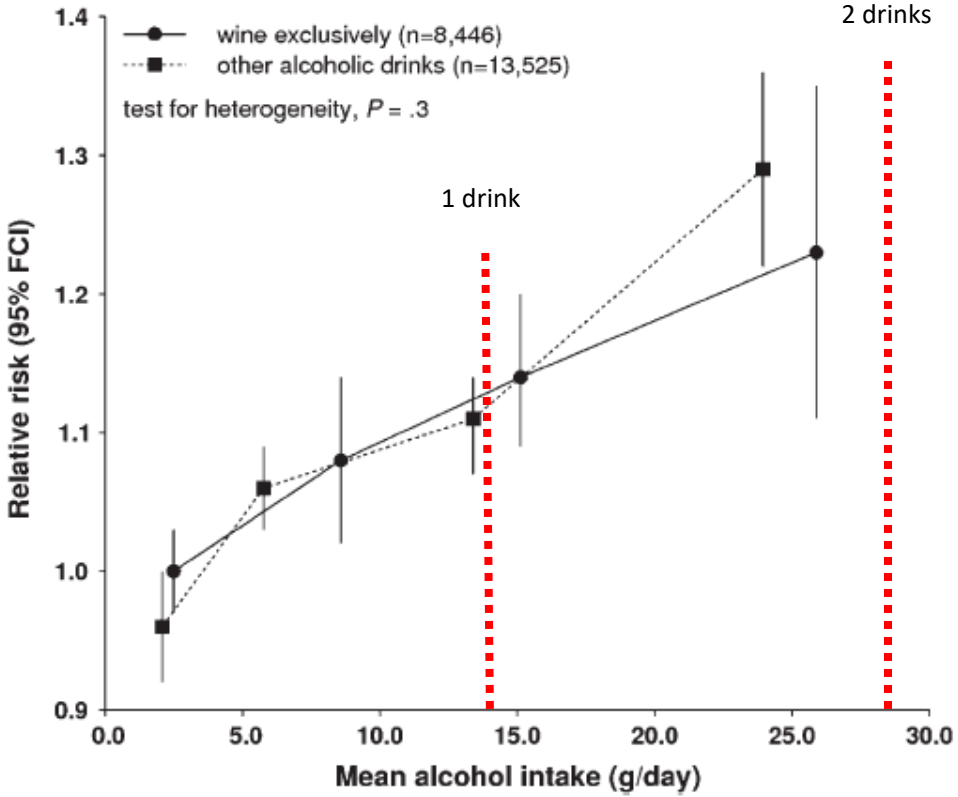
Weight Change Since Age 18 y, kg	Simple Update*			Stable Change†	
	No. of Cases	Age-Adjusted RR	MV-Adjusted RR (95% CI)‡	No. of Cases§	MV-Adjusted RR (95% CI)‡
Overall					
Loss					
≥10.0	53	0.72	0.84 (0.62-1.13)	48	0.80 (0.58-1.11)
5.0-9.9	99	0.88	0.94 (0.75-1.18)	84	0.90 (0.69-1.17)
2.0-4.9	152	0.97	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.

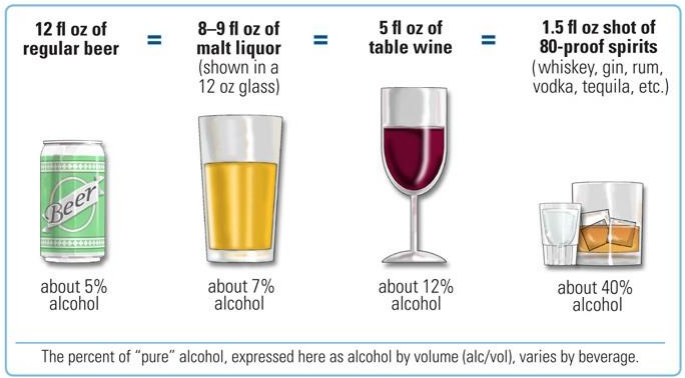
Million Women Study Results



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

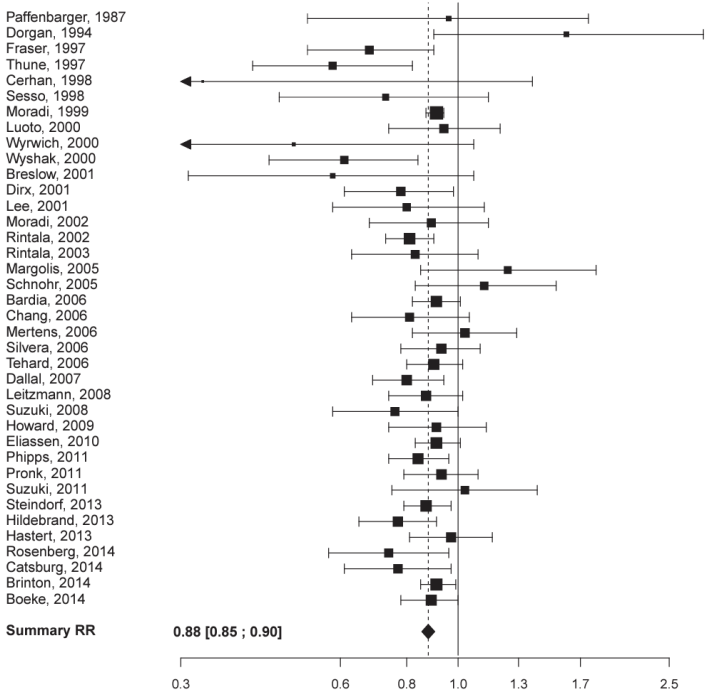
Alcohol increases Breast Cancer Risk

- Risk appears to exist as low as 3-6 drinks/week
- 2013 meta-analysis of 110 studies light alcohol intake (RR 1.05, 95% CI 1.02-1.08)
- Dose dependent
- Binge drinking confers a higher risk
- US, population attributable risk is ~2%, Italy it is ~11%
- Maybe related to folic acid intake

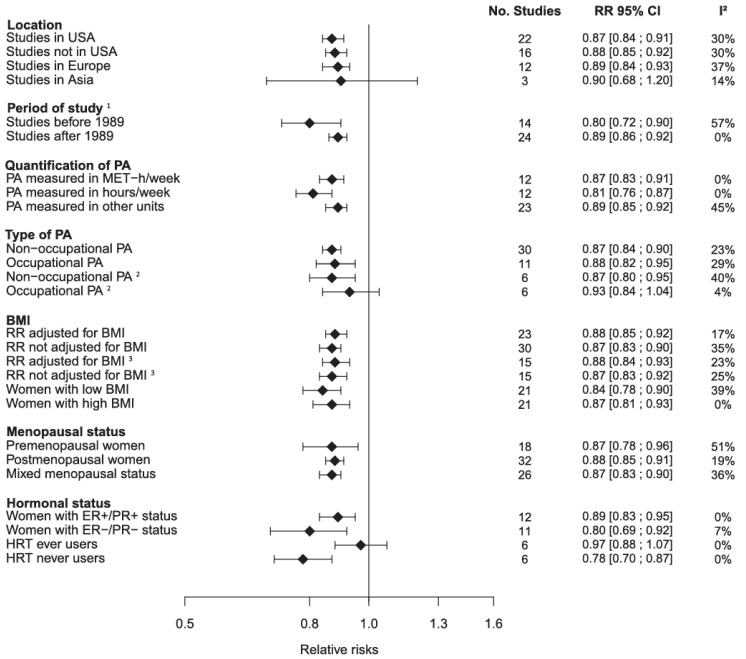


http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink

Physical Activity decreases Breast Cancer Risk



RR = 0.88 (0.85-0.90)



Holds for:

- Type/Measurement of PA
- Regardless of BMI
- Type of Cancer (ER+/ER-)

Pizot et al, E J of Ca, 2016

Overall Take Home Points

1) DCIS
   - requires surgery to a clear/2mm margin in BCS or mastectomy
   - radiation should be considered
   - considerTamoxifen/AI for ER+ DCIS /p BCT

2) LCIS
   - significant risk factor for developing breast cancer
   - surgical removal is not indicated
   - Medical Risk Reduction should be considered/recommended

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

4) Counsel on lifestyle choices: Exercise, Weight, & Alcohol

New Survivorship Webpage:

Breast Cancer Survivorship

When finishing treatment for breast cancer, most people feel different than they did before diagnosis. Oftentimes, it is difficult to adjust to the “new normal.” Fred Hutch's Breast Cancer Program created this educational resource guide to help you through this transition. This guide covers a variety of topics and includes outside resources. We invite you to explore the resources at your own pace, in a place that works for you.

ON THIS PAGE

Nutrition | Physical Activity | Genetics | Integrative Medicine | Lymphedema | Cognitive Changes | Fatigue | Neuropathy

Fred Hutch Cancer Center

Donate Now

Nutrition

Nutritional overview provided by Raymond Palko, MS, RD, CSO, CD.

Evidence-based studies have shown that by increasing physical activity, choosing healthy foods, and maintaining a healthy weight, you can reduce your or risk of getting cancer again. While there is no one-size-fits-all strategy, following these general guidelines will help:

- Choose whole, plant-based foods.
- Eat less processed foods and moderate amounts of animal-based foods
- Limit alcohol intake.
- Stay active on a regular basis by doing something you enjoy, such as walking, riding a bicycle, practicing yoga, or something else.

Online Resources

- Cook for your Life
- Eat Healthy and Get Active, American Cancer Society
- Eat Right to Fight Cancer, Oncology Nutrition
- Eat Right. Academy of Nutrition and Dietetics
- Healthy Eating, American Institute for Cancer Research
- Rebecca Katz

Nutrition Videos

- https://www.fredhutch.org/en/diseases/breast-cancer/breast-cancer-survivorship.html

Thanks!

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WASHINGTON