VII Jornada EN Cáncer DE Mama Hereditario
FORMATO DIGITAL

Update on endocrine prevention of breast cancer

Ente Ospedaliero Ospedali Galliera Genova
Ospedale di rilievo nazionale e di alta specializzazione

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Disclosure

- I have no conflict of interest to disclose

- I declare institutional funding from the following entities:

  AIFA, EU-TRANSCAN, AIRC, US NCI, Italian Ministry of Health, Umberto Veronesi Foundation, Berlucchi Foundation, International Breast Cancer Study Group, Indena SpA, Roche, Pfizer, Janssen, Novartis, Sanofi Aventis, Quintiles, Gilead, MacroGenics

[CANCER RESEARCH 36, 2699–2702, July 1976]

Approaches to Prevention of Epithelial Cancer during the Preneoplastic Period[1]

Michael B. Sporn

Lung Cancer Branch, Carcinogenesis Program, National Cancer Institute, Bethesda, Maryland 20014

[CANCER RESEARCH 51, 6215–6218, December 1, 1991]

Perspectives in Cancer Research

Carcinogenesis and Cancer: Different Perspectives on the Same Disease

Michael B. Sporn

Therapeutic prevention=chemotherapy of dysplasia.

Use of natural, synthetic, or biological chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer

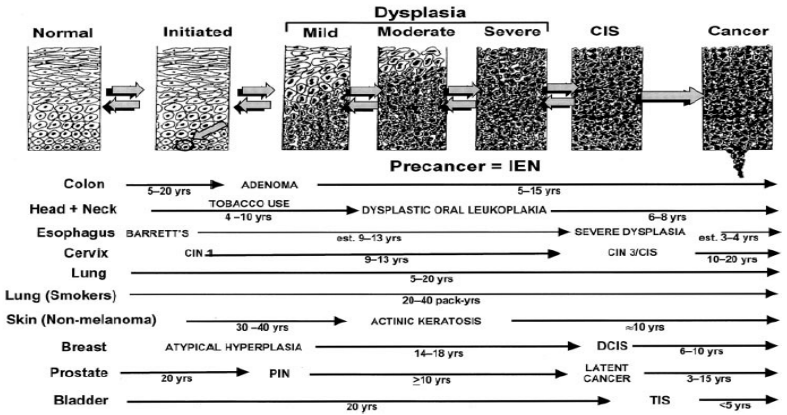


Table 1 Why IEN?

- Near-obligate cancer precursor
- Risk marker for cancer
- Disease requiring surveillance and treatment interventions

ursor to Cancer

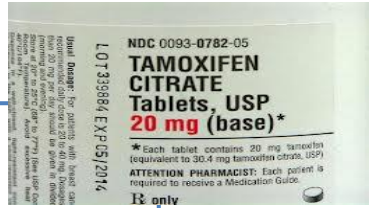
elial tissue as moderate to severe

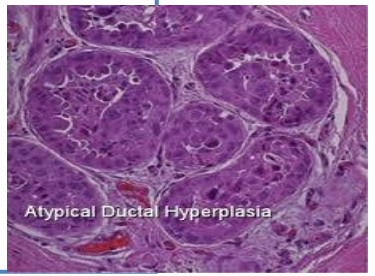
Key Ingredients in cancer preventive medicine: the ABC paradigm

1. Effective non-toxic Agents

2. Measurable for individuals based on Biomarker response

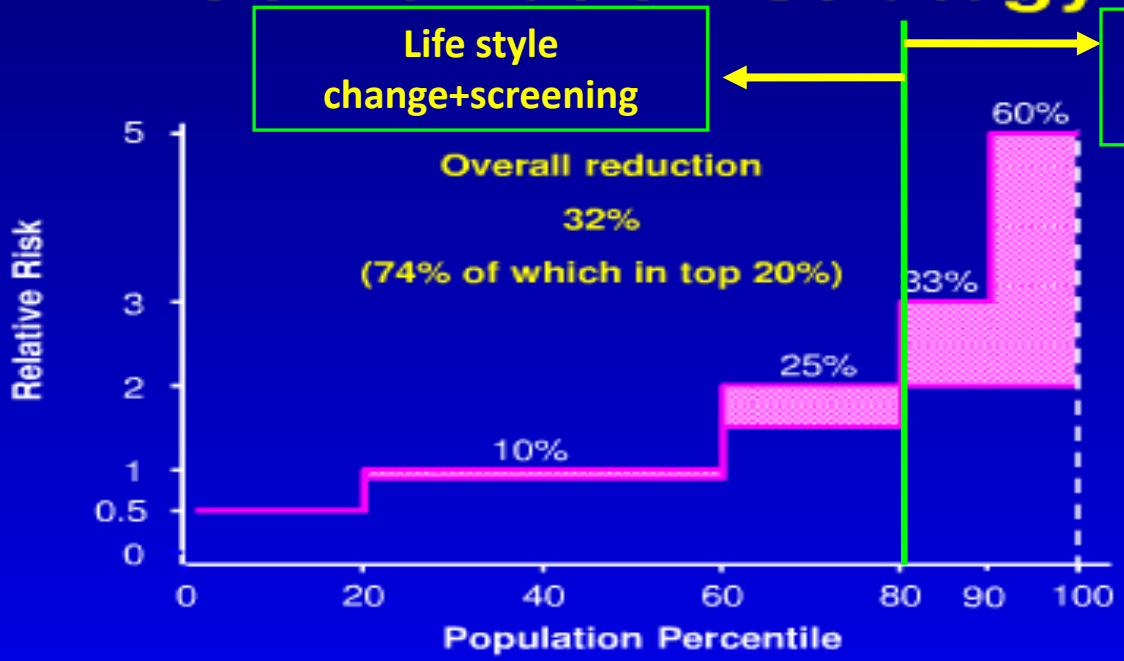
3. Precise identification of high-risk Cohorts





De Censi A et al. Ecancer medicalscience 2015

Combination Strategy



De Censi and Cuzick Ecancer medicalscience 2015

Who should be treated?

- Pre-invasive disease (ADH, LCIS, DCIS)
- Women with high-risk score (e.g., Gail, Tyrer-Cuzick, BCSC)
- Gene mutation carriers: *BRCA* or moderate penetrance: *CHECK2, PALB2, ATM*
- Young women with prior chest radiation
- Women with elevated mammographic density
- Overweight and sedentary women, alcohol drinkers

Risk Assessment Models

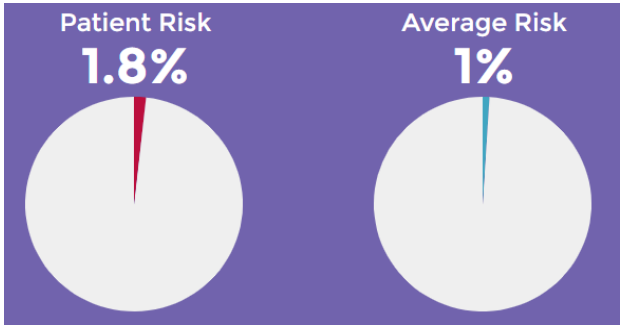
Variables	Gail https://bcrisktool.cancer.gov/calculator.html	Tyrer-Cuzick https://ibis.ikonopedia.com/	BCSC https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm
Age	✓ only > 35 years	✓	✓ only > 35 years
Race/ethnicity	✓	✓ only Ashkenazi	✓
Previous breast biopsy	✓	✓	✓
Presence of ADH or LCIS	✓	✓	✓
Age at first menstruation	✓	✓	
Age at first child	✓	✓	
1st degree family history	✓	✓ also ♂ and 2nd degree	✓
Breast density		✓	✓
BMI		✓	
Menopausal status, MHT usage, ovarian cancer		✓	

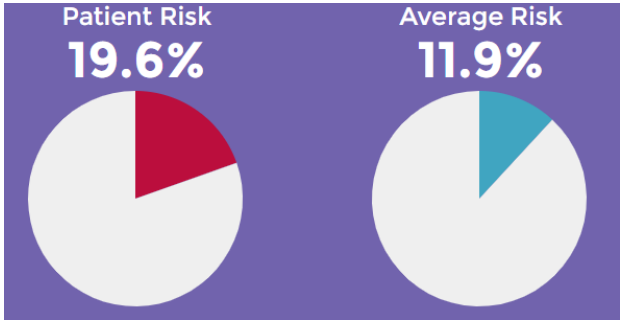
Case 1

- 45 yo., pre-menopausal woman with no history of breast biopsy
- Menarche 11 yo., nulliparous
- Mother with breast cancer (diagnosis at 65 yo.)
- Extremely dense breasts
- Obese, BMI 31 kg/m^2; physically inactive
- Drinks ~2 glasses of wine / day

Case 1

GAIL





TYRER-CUZICK

Ten Year Risk:

This woman's Risk (at age 45): **8.7%**

Average women (at age 45): **2.2%**

Lifetime Risk:

This woman's Risk (to age 85): **35.0%**

Average woman (to age 85): **10.3%**

BCSC

Based on the information provided, the woman's estimated risk for developing invasive breast cancer over the next 5 years is **1.79%**, over the next 10 years is **4.16%**.

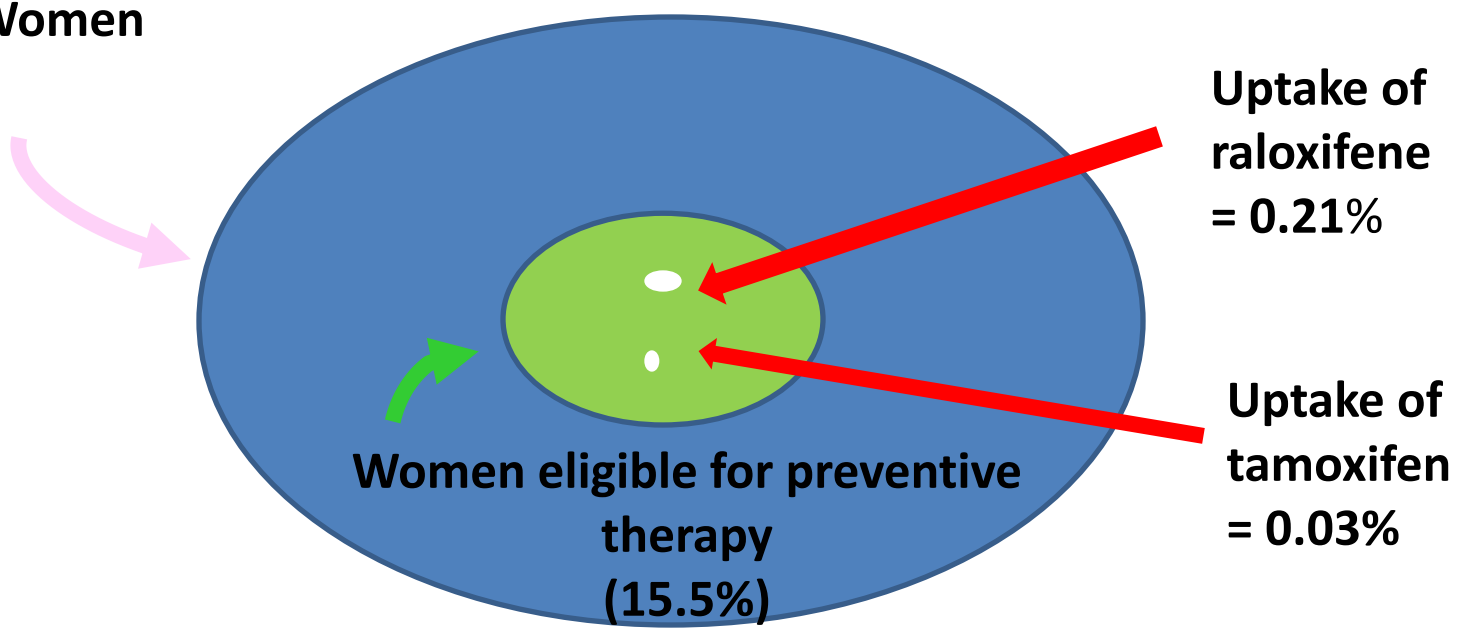
The average 5-year risk for a woman the same age and race/ethnicity is **0.89%**. The average 10-year risk for a woman the same age and race/ethnicity is **2.09%**.

Andrea De Censi MD,
Medical Oncology, Galliera Hospital,
Genoa, Italy

Prevention Studies

Study	N=	Risk factors	Invasive cancer	HR
P-1 Tam-Pl	13,388	>60yrs, Gail, LCIS	54.6 mo 89 vs 175	0.51
IBIS-1 Tam-Pl	7,152	FH, LCIS, AH, G0+FH, br bx + FH	50 mo 64 vs 85	0.75
P-2 Tam-Ral	19,747	Postm, ,AH Gail, LCIS	81 mo 247 vs 310	RR:1.24 P=0.01
B-24 Tam-Pl	1804	DCIS	74 mo 15 vs 23	0.63 P=0.22
MAP-3 Exe-Pl	4560	>60yrs, AH, Gail, LCIS, DCIS (mast)	35 mo 11 vs 32	0.35 P=0.004
IBIS-2 Arim-Pl	3864	40-70 yrs, FH, AD/LH, D/LCIS, breast density	60mo 48 vs 85	0.47 P=0.0001

What Has Been the Uptake of Breast Cancer Anti-estrogen Preventive Therapy?



Waters et al. Breast Cancer Res Treat, 2012

ASCO Use of Endocrine Therapy for BC Risk Reduction

Clinical considerations for use of endocrine prevention agents

– **Risk Threshold for Considering Endocrine Therapy for Primary BC Prevention**

- 5-year risk of ≥ 3%
- 10-year risk of ≥ 5%
- Gail or IBIS/Tyrer-Cuzick model
- Women with AH or LCIS have a four- to 10-fold increase in BC risk
- Low dose Tamoxifen may be an alternative in women with noninvasive disease
- No endocrine therapy for women >70 years old
- 5 years is the standard but 3 years may be considered based on MAP3 and low dose Tam studies

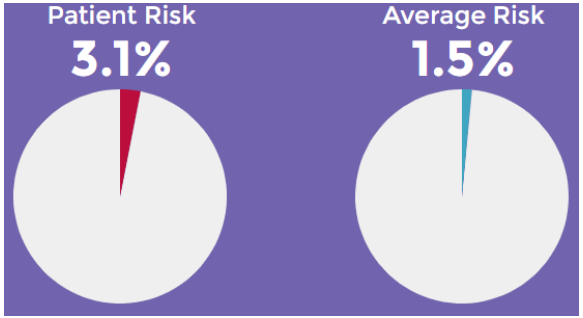
Visvanathan et al. JCO 2019

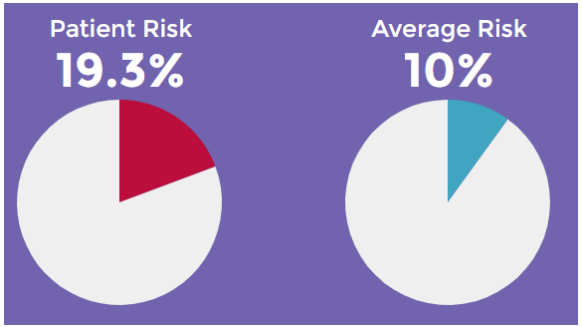
Case 2

- 56 yo., post-menopausal women with ADH
- Menarche 12 yo., First pregnancy 26 yo., Menopause: 53 yo.
- Scattered fibroglandular densities
- Obese, BMI 35 kg/m^2
- Prediabetes, on Metformin
- No family history

Case 2

GAIL





TYRER-CUZICK

Ten Year Risk:

This woman's Risk (at age 56): **11.8%**

Average women (at age 56): **3.2%**

Lifetime Risk:

This woman's Risk (to age 85): **27.8%**

Average woman (to age 85): **8.2%**

BCSC

Based on the information provided, the woman's estimated risk for developing invasive breast cancer over the next 5 years is **3.14%**, over the next 10 years is **6.58%**.

The average 5-year risk for a woman the same age and race/ethnicity is **1.62%**. The average 10-year risk for a woman the same age and race/ethnicity is **3.43%**.

NSABP-P1 events and incidence rates of invasive BC in prior LCIS or ADH

Characteristic		No. At risk/No. of events		Rate per 1000 women		RR	95% CI
		Placebo	Tam	Placebo	Tam		
Prior LCIS	Baseline	413	416				
	On Tam	**29**	**16**	11.7	6.3	**0.54**	**0.27-1.02**
Prior ADH	Baseline	615	581				
	On Tam	**38**	**9**	10.4	2.6	**0.25**	**0.10-0.52**

Fisher B et al. JNCI 2005; 97: 1652-62

	7-year risk in placebo group*	Number of women who developed breast cancer		Hazard ratio (95% CI)
		Anastrozole group (n=1920)	Placebo group (n=1944)	
Age (years)				
≤60	4·1%	20	44	0·47 (0·28–0·80)
>60	6·7%	20	41	0·46 (0·27–0·78)
Body-mass index (kg/m²)				
<25	4·7%	10	23	0·43 (0·20–0·90)
25–30	5·2%	14	28	0·49 (0·26–0·94)
>30	6·9%	16	34	0·47 (0·26–0·85)
Lobular carcinoma in situ or atypical hyperplasia				
No	4·9%	35	66	0·52 (0·31–0·78)
Yes	12·1%	5	19	0·31 (0·12–0·84)
Ductal carcinoma in situ				
No	5·2%	34	72	0·47 (0·31–0·71)
Yes	9·7%	6	13	0·44 (0·17–1·15)
Previous use of hormone replacement therapy				
No	6·0%	17	47	0·36 (0·20–0·62)
Yes	5·3%	23	38	0·61 (0·37–1·03)
Less than 12 months before enrolment	9·0%	3	12	0·30 (0·08–1·07)
All				

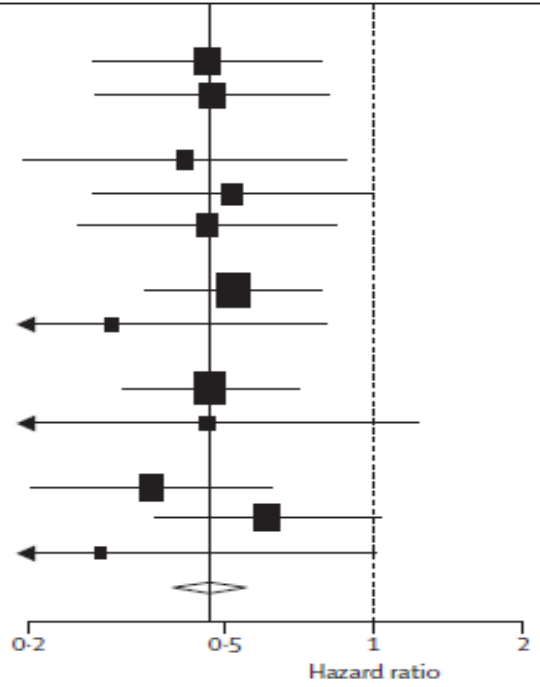
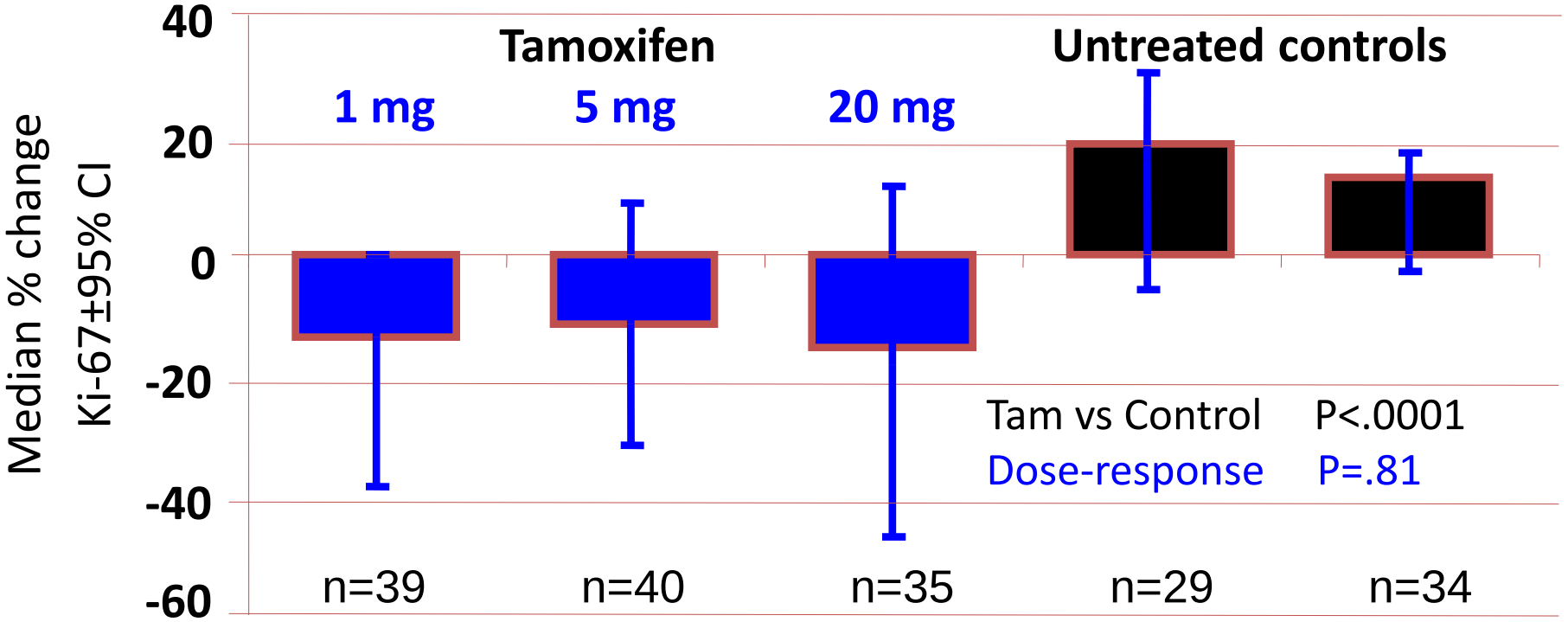


Figure 5: **Subgroup comparisons**
*Cumulative risk calculated with Cox proportional hazards model.

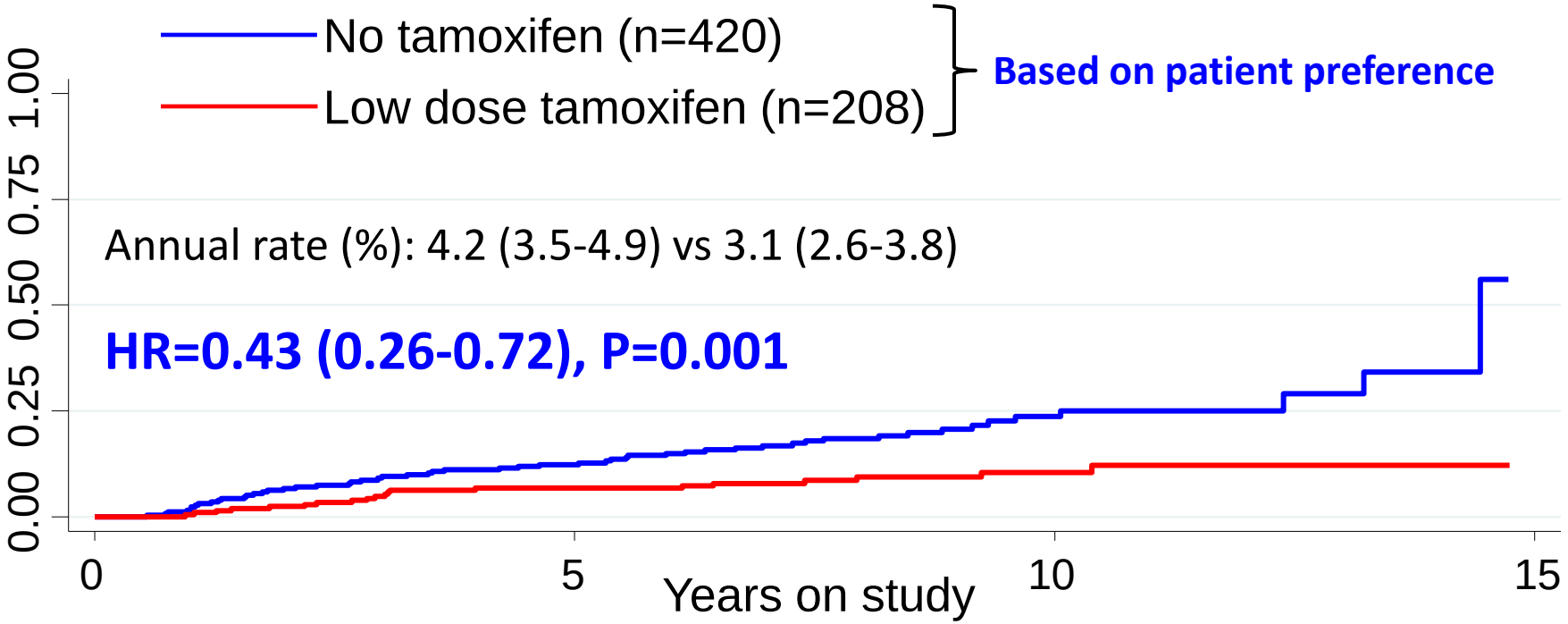
Cuzick et al Lancet 2013

Lower doses non inferior to 20 mg/d in decreasing ki-67 in a randomized presurgical trial



DeCensi et al. *JNCI* 95: 779, 2003

Effect of 10 mg on alternate days on ipsilateral recurrence in high risk DCIS>50 yrs



Guerrieri Gonzaga et al. *Int J Cancer* 139:2127-34, 2016

Randomized placebo controlled trial of low dose tamoxifen ("Babytam") - Study Tam01

Primary endpoint: Incidence of invasive breast cancer or DCIS

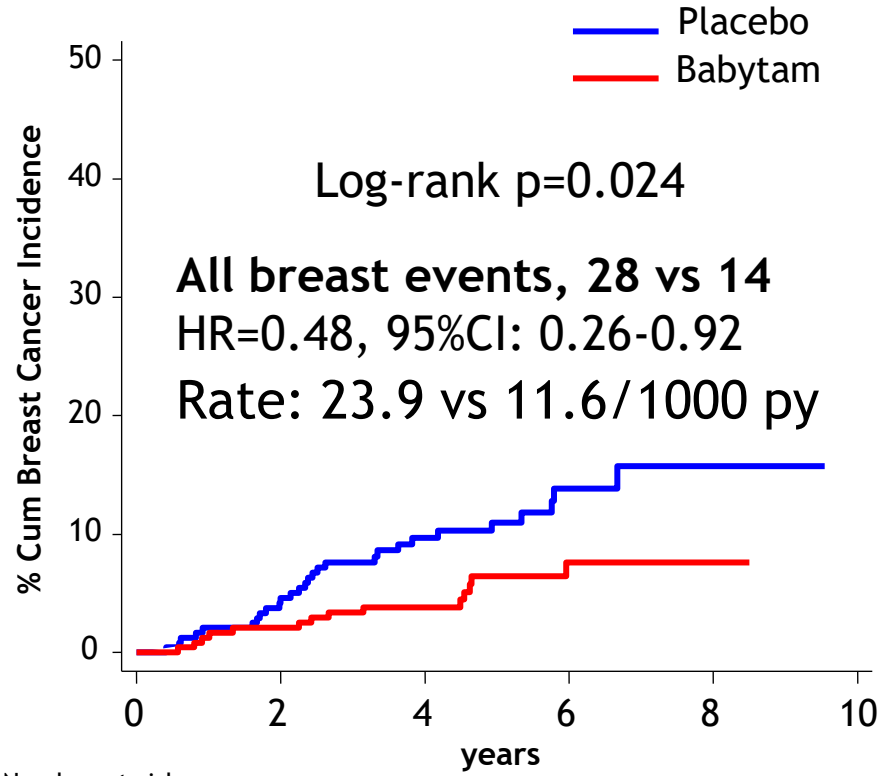
- 500 participants enrolled from 14 centers in Italy
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

DeCensi et al. JCO 37; 2019

Main subject and tumor characteristics (n = 500)

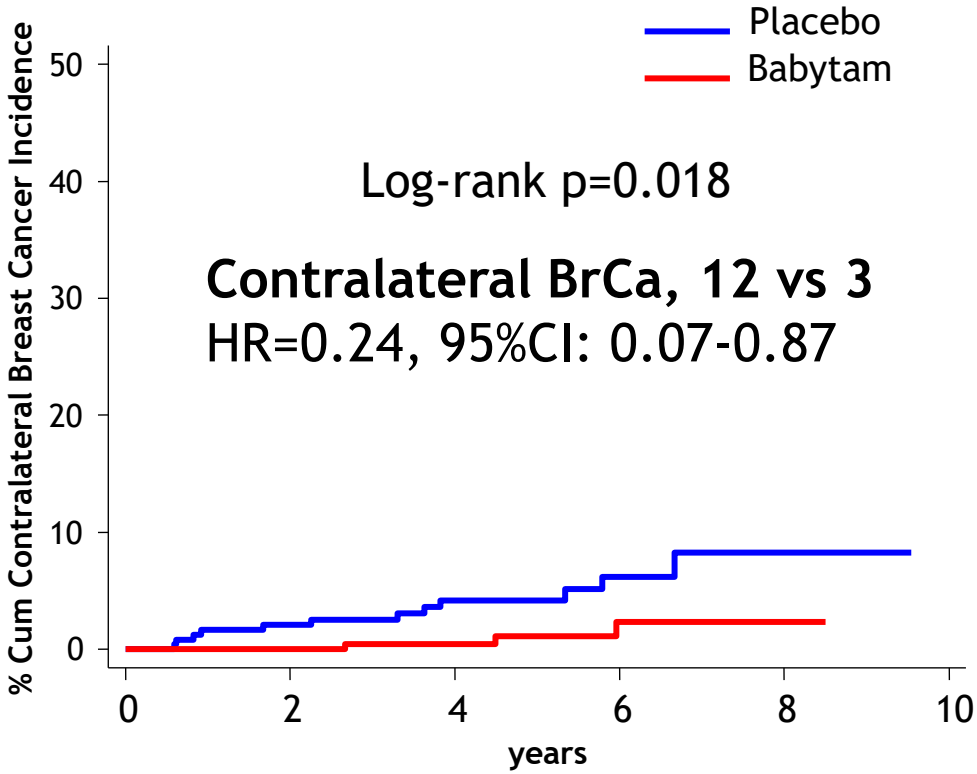
	Babytam N=253	Placebo N=247
Age, mean (SD)	54 (9.6)	54 (9.1)
Pre-menopausal, %	46	44
BMI, mean (SD)	25.7 (4.8)	25.3 (4.2)
ADH, %	20	20
LCIS, %	11	10
DCIS, %	69	70
ER/PR+ve/unk DCIS, %	66 / 34	67 / 33
Radiotherapy for DCIS, %	61	61

DeCensi et al. JCO 37; 2019



Number at risk

Pla	247	225	161	78	4	0
Tam	253	234	172	76	3	0



	247	225	161	78	4	0
	253	234	172	76	3	0

DeCensi et al. JCO 37; 2019

Serious adverse events

	Babytam	Placebo
Endometrial cancer	1	0
DVT or PE	1	1
Other neoplasms	4	6
Coronary heart disease	2	2
Other	3	5
Death	1	2
Total	12	16

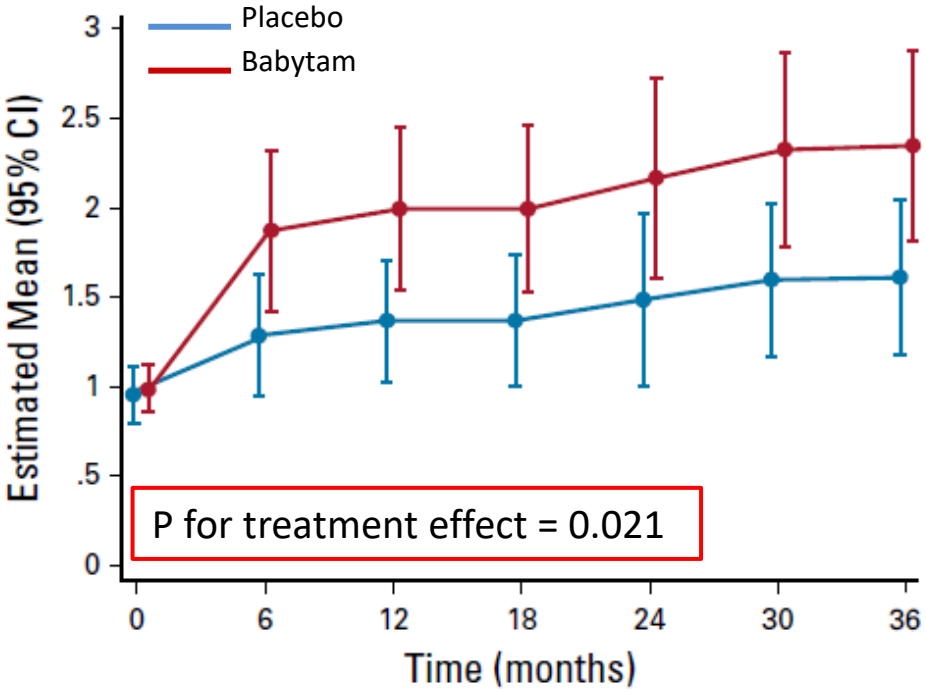
With 20 mg/d, expected Endometrial Cancer: **2.7**[1];

Expected DVT+PE: **2.4**[1]

[1]NSABP-P1 trial (Fisher et al. *JNCI* 90:1371-88, 1998)

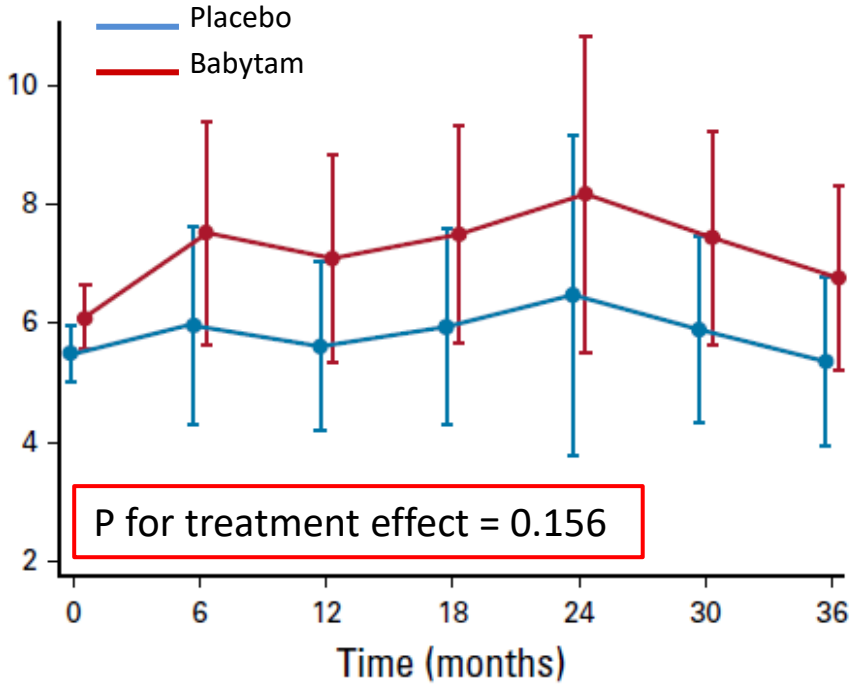
DeCensi et al. JCO 37; 2019

Daily hot flashes frequency



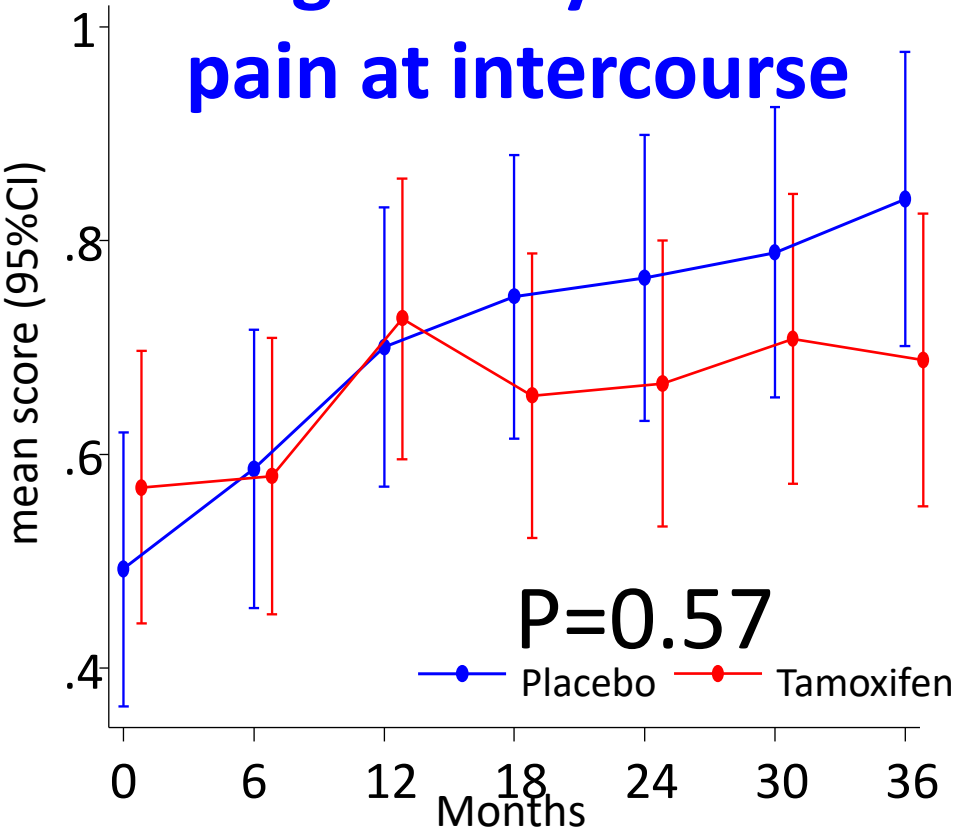
Daily hot flashes score

Frequency by Intensity

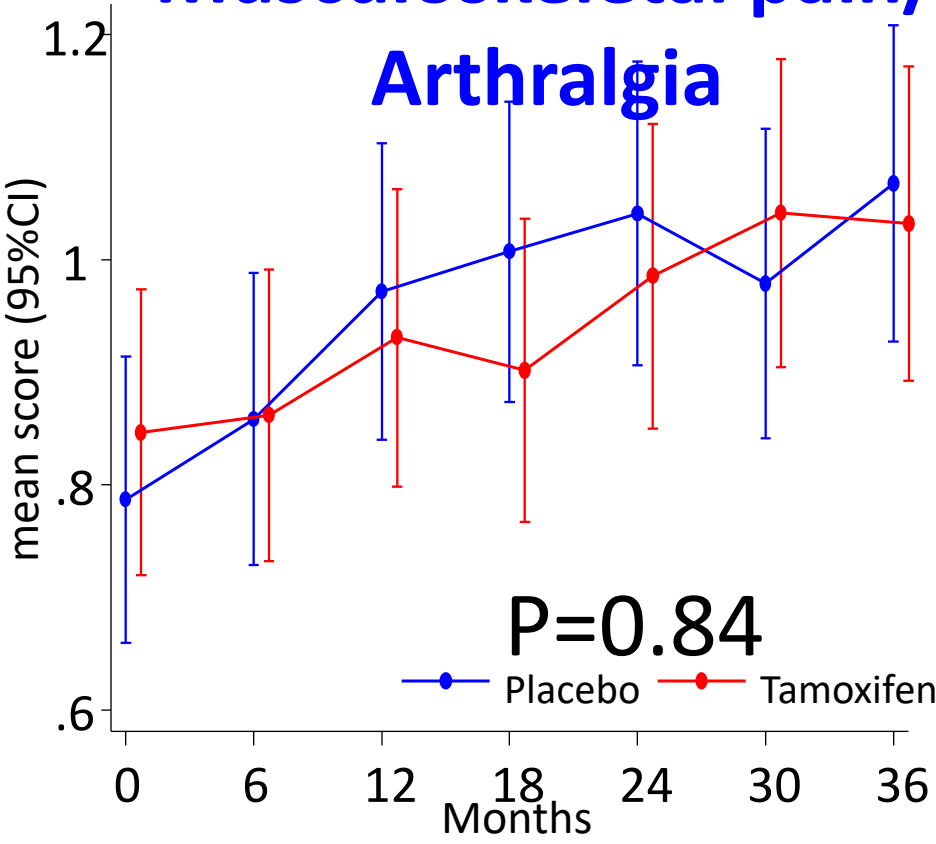


DeCensi et al. JCO 37; 2019

Vaginal dryness or pain at intercourse

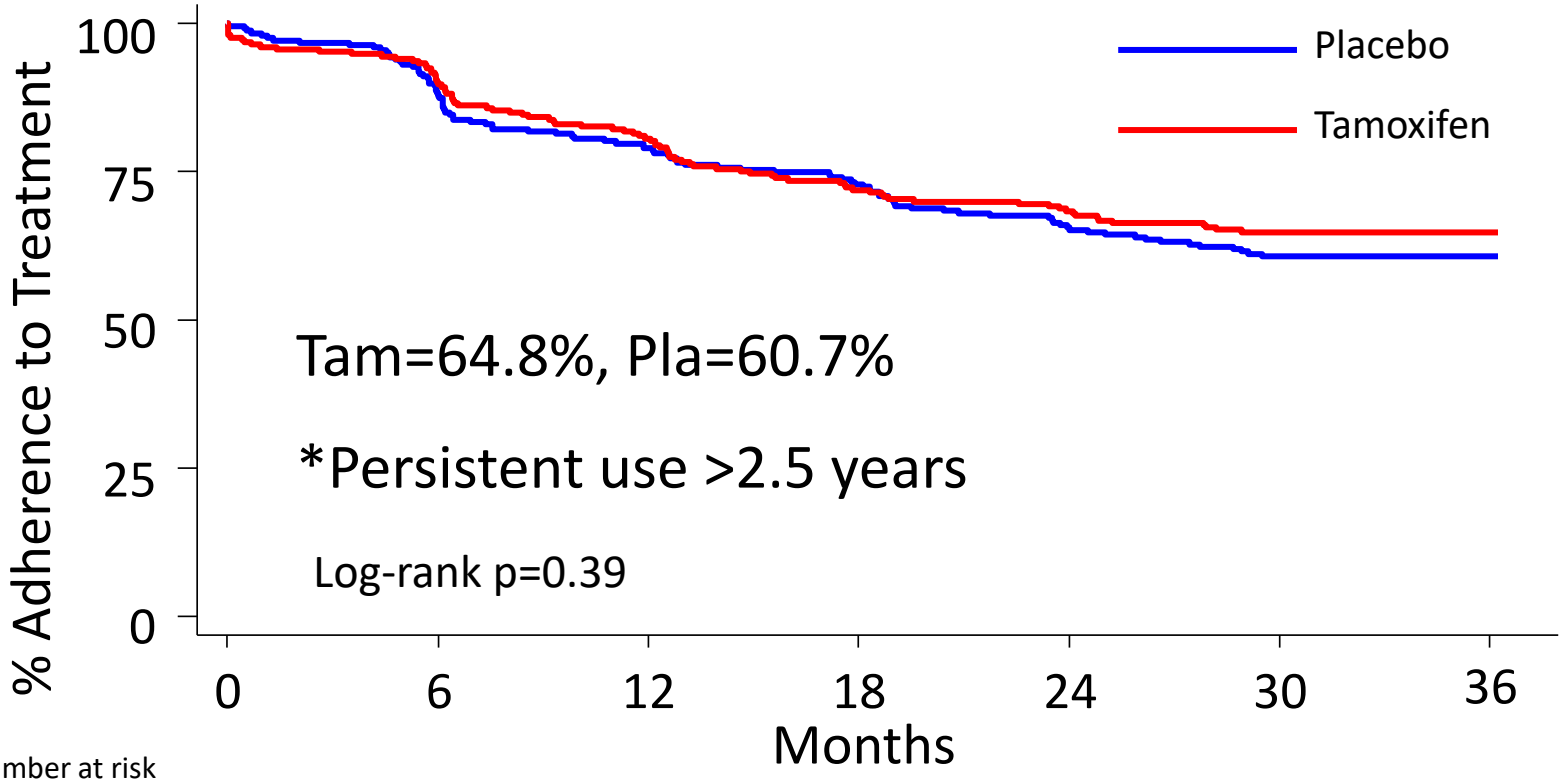


Musculoskeletal pain/ Arthralgia



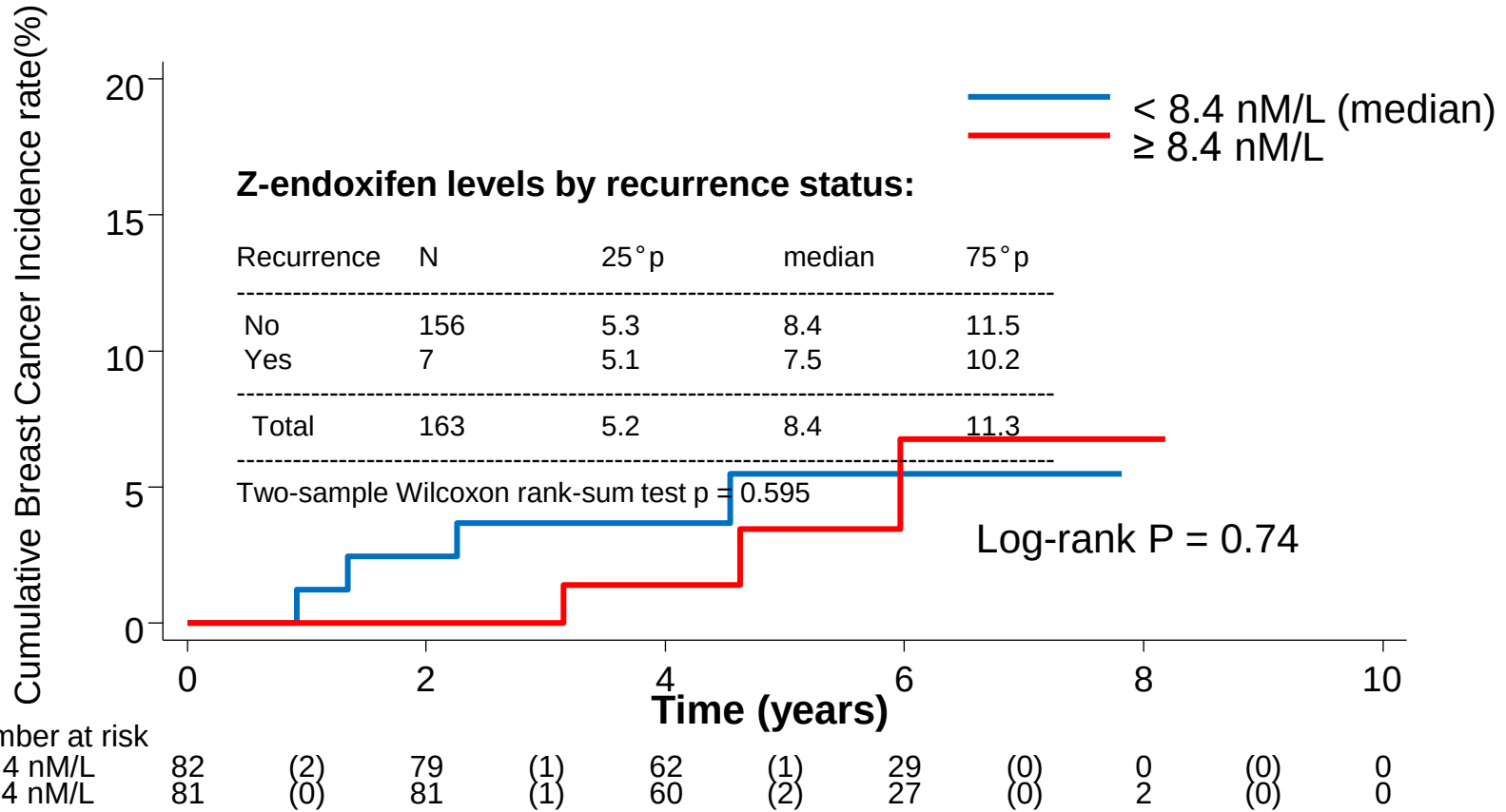
BCPSC, Stanton et al. JNCI 97:448-456, 2005
DeCensi A et al. JCO, 2019

Treatment adherence*



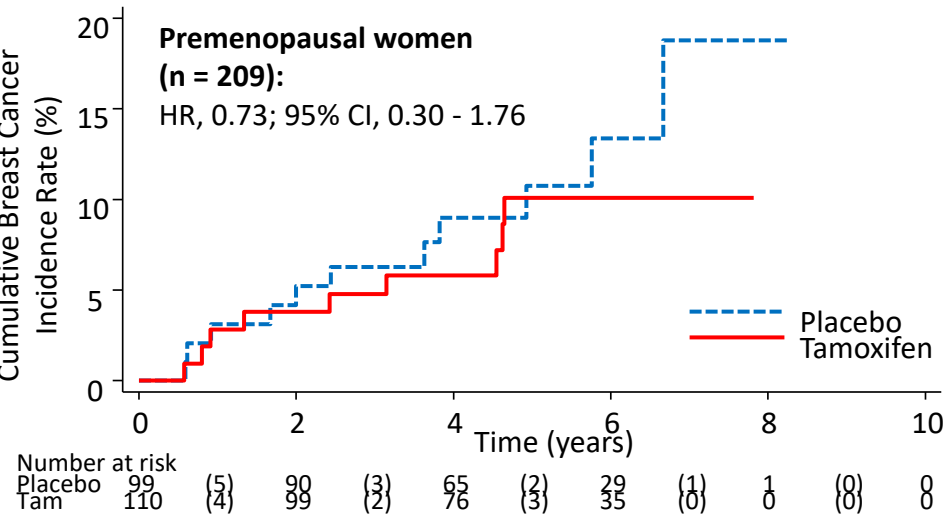
Number at risk													
Placebo	247	(29)	218	(23)	195	(15)	180	(18)	162	(12)	149	(0)	109
Tamoxifen	253	(25)	228	(24)	204	(22)	182	(9)	173	(9)	163	(0)	114

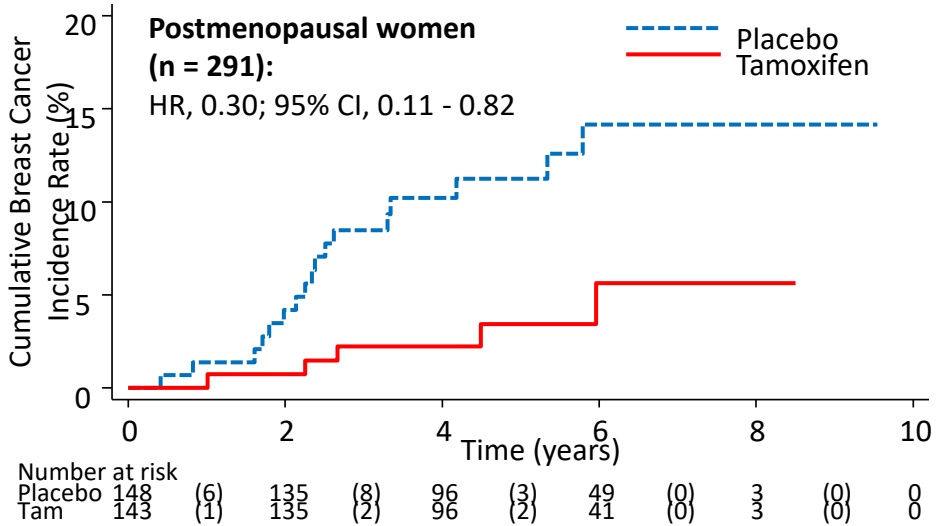
Cumulative breast cancer recurrence curves in the tamoxifen arm according to Z-endoxifen, nmol/L and by recurrence status (yes/no)



De Censi A et al. NPJ Breast Cancer. 2021 Mar 25;7(1):34.

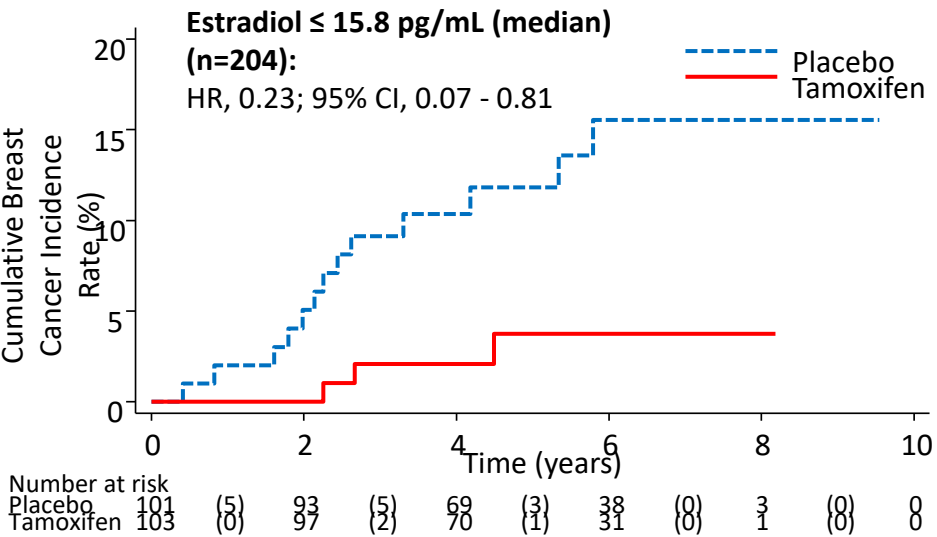
Cumulative incidence of breast cancer by allocated arm and menopausal status

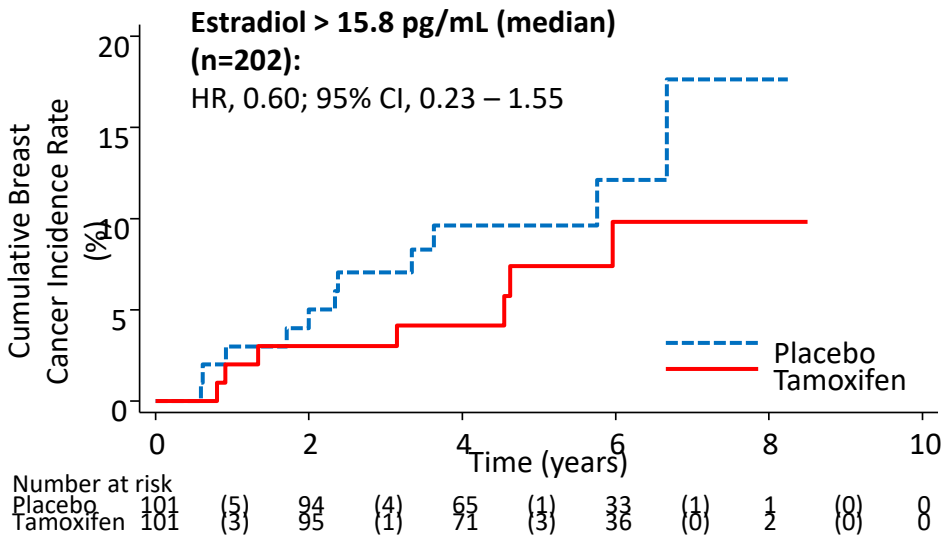




De Censi A et al. Clin Cancer Res. 2021 Feb 19. Online ahead of print.

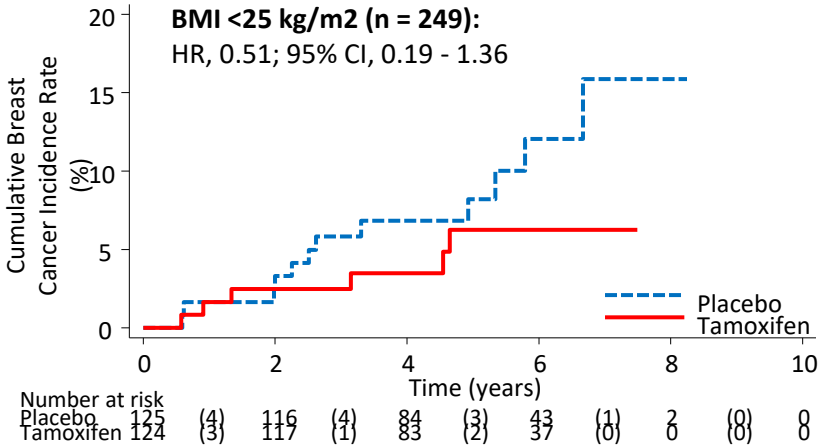
Cumulative incidence of breast cancer by allocated arm and baseline estradiol level

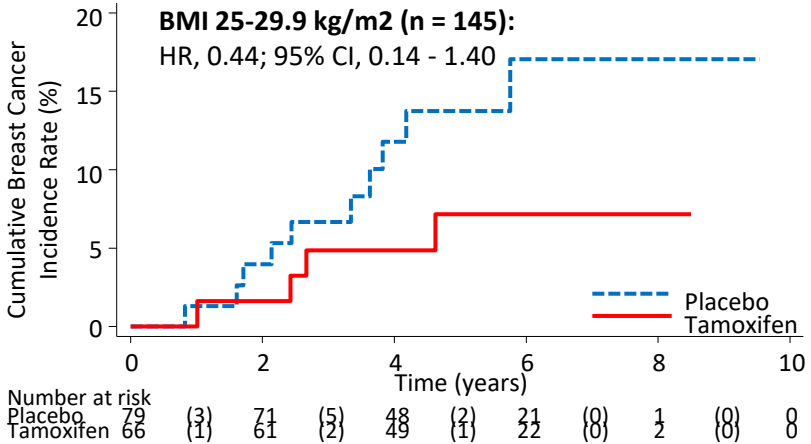


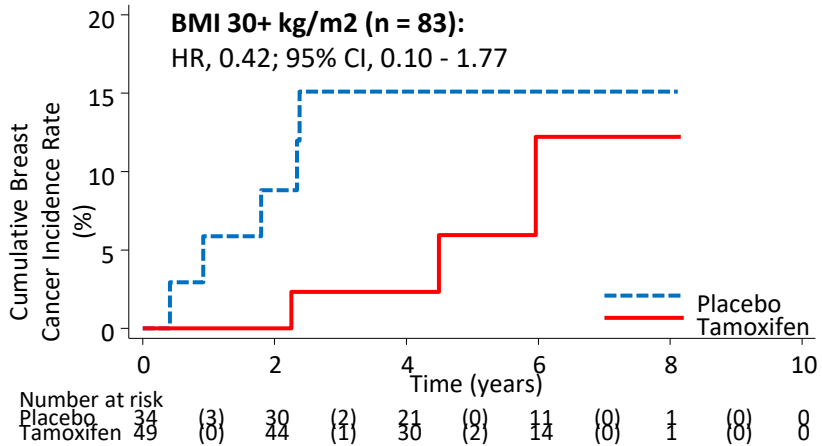


De Censi A et al. Clin Cancer Res. 2021 Feb 19. Online ahead of print.

Cumulative incidence of breast cancer by allocated arm and baseline BMI

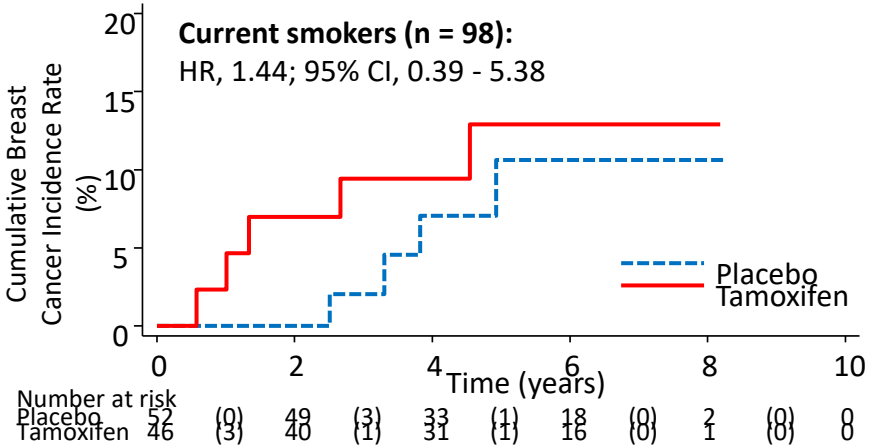


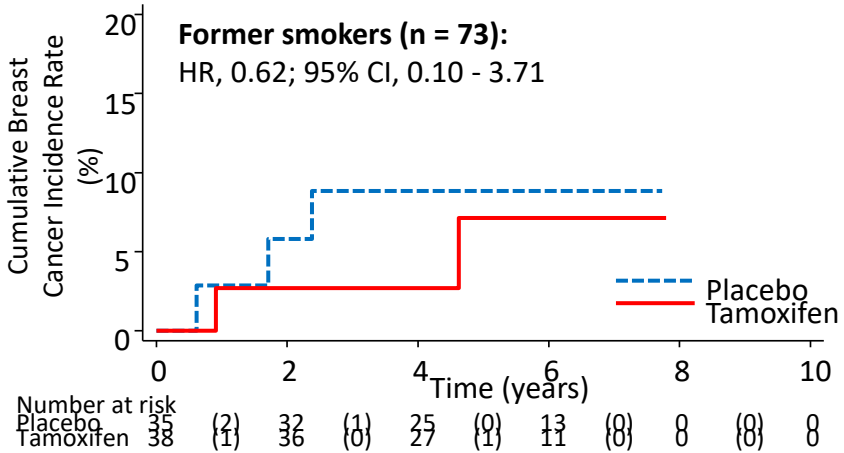


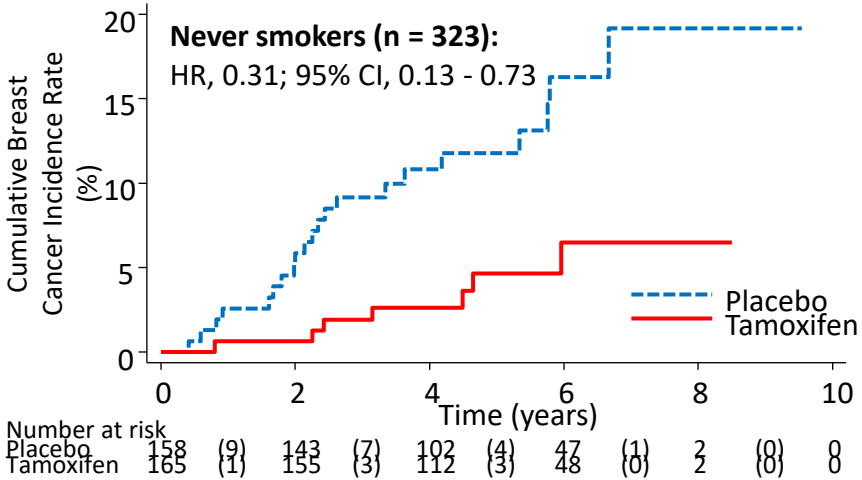


De Censi A et al. Clin Cancer Res. 2021 Feb 19. Online ahead of print.

Cumulative incidence of breast cancer by allocated arm and smoking status





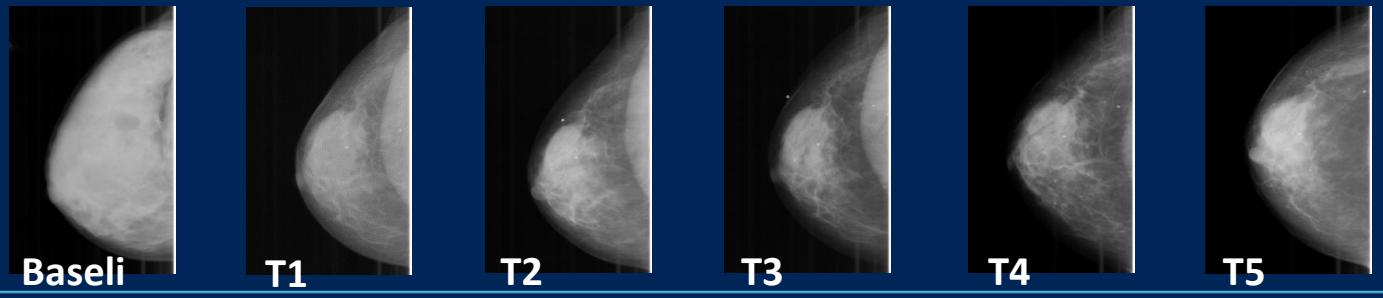


De Censi A et al. Clin Cancer Res. 2021 Feb 19. Online ahead of print.

Breast Density Decline As A Biosensor of Treatment Response: Clinical Considerations

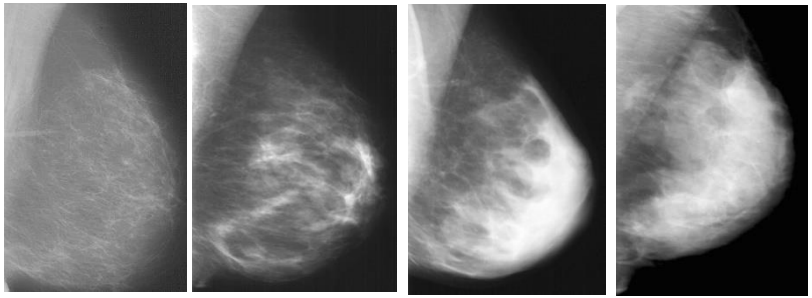
- **What do Tamoxifen-associated breast density declines mean for the patient?**
  - Associated with reduced breast cancer risk (IBIS-I, chemoprevention: Cuzick et al. *JNCI* 2011)
  - Improved breast cancer outcomes (adjuvant Rx: Mullooly et al. *JCO* 2016)
  - Improved mammographic sensitivity (low-dose Tam: Eriksson et al. *Cancers* 2021)
  - Most density decline occurs within 12-18 months post-Tam; measure from single time point may be sufficient

(Nyante et al. *CEBP* 2016)



Predictive markers in prevention.
The case for mammographic density and tamoxifen

OR for developing breast cancer for tamoxifen versus placebo arm overall and by breast density reduction category in specific subgroups



Variable	No. of control subjects/No. of case subjects	Tamoxifen, all	Tamoxifen, breast density reduction <10%		Tamoxifen, breast density reduction ≥10%	
		OR (95% CI)†	No. of case subjects	OR (95% CI)‡	No. of case subjects	OR (95% CI)§
Overall	929/120	0.73 (0.49 1.08)	35	1.13 (0.72 1.77)	13	0.37 (0.20 0.69)

Cuzick et al, JNCI 2011;103:744–752

cancers

MDPI

Article

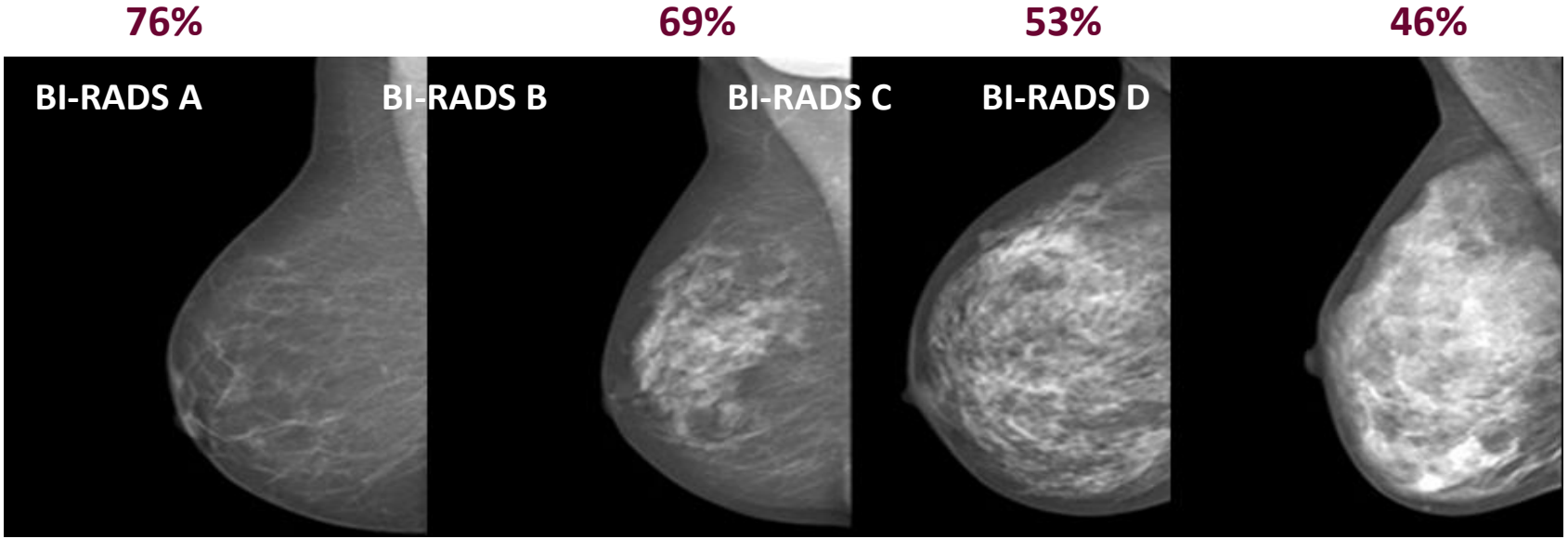
Use of Low-Dose Tamoxifen to Increase Mammographic Screening Sensitivity in Premenopausal Women

Mikael Eriksson [1,*], Kamila Czene [1], Emily F. Conant [2] and Per Hall [1,3]

Received: 22 December 2020
Accepted: 12 January 2021
Published: 15 January 2021

Screening sensitivity is strongly reduced by the amount of dense tissue in the breast

Screening sensitivity in premenopausal women, digital mammography



Dense tissue classified into BI-RADS categories. A = almost entirely fatty, D= extremely dense

Interval cancers were reduced by 24% in women who responded to therapy with a relative reduction of ≥20% mammographic density

Percent reduction of interval cancers	Relative density response, %			
BI-RADS category	≥10	≥20	≥30	≥50
A+B	-31	-34	-35	-43
C	-7	-11	-22	-34
D	-29	-35	-42	-53
A to D combined	-19	-24	-31	-42

BI-RADS categories: A = almost entirely fatty, D= extremely dense

Erikkson et al 2021

Tamoxifen lowers by 30% overdiagnosis in high risk women undergoing screening Mx

Effects of Tamoxifen on Benign Breast Disease in Women at High Risk for Breast Cancer

Elizabeth Tan-Chiu, Jiping Wang, Joseph P. Costantino, Soonmyung Paik, Cheryl Butch, D. Lawrence Wickerham, Bernard Fisher, Norman Wolmark

Table 1. Rate of benign breast disease diagnosis by treatment group*

Type of benign breast disease	No. of events		Average annual rate per 1000 person-years		RR (95% CI)
	Placebo	Tamoxifen	Placebo	Tamoxifen	
Adenosis	222	133	8.51	5.01	0.59 (0.47 to 0.73)
Cyst	578	391	22.98	15.17	0.66 (0.58 to 0.75)
Duct ectasia	106	77	4.03	2.89	0.72 (0.53 to 0.97)
Fibrocystic disease	466	318	18.30	12.21	0.67 (0.58 to 0.77)
Fibroadenoma	98	76	3.72	2.85	0.77 (0.56 to 1.04)
Fibrosis	266	232	10.26	8.83	0.86 (0.72 to 1.03)
Hyperplasia	343	209	13.29	7.93	0.60 (0.50 to 0.71)
Metaplasia	293	152	11.34	5.74	0.51 (0.41 to 0.62)
Any first event†	1014	750	42.13	30.16	0.72 (0.65 to 0.79)

Journal of the National Cancer Institute, Vol. 95, No. 4, February 19, 2003

AACR American Association for Cancer Research

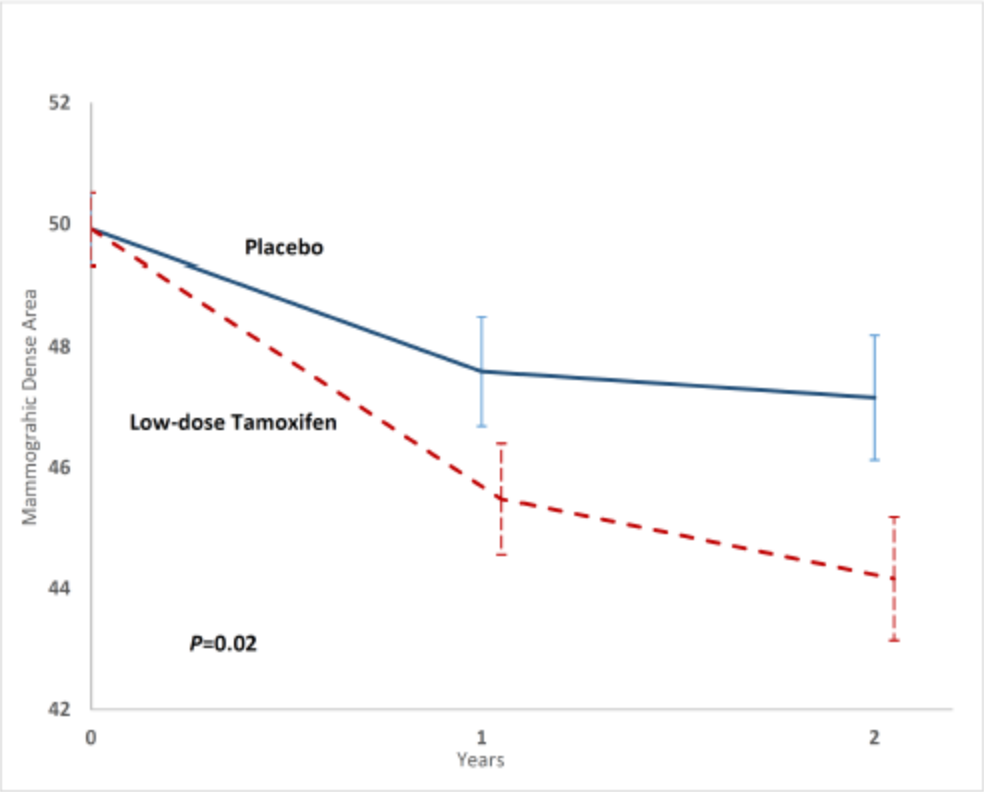
Clinical Cancer Research

A Randomized Phase IIb Study of Low-dose Tamoxifen in Chest-irradiated Cancer Survivors at risk for Breast Cancer

Smita Bhatia, Melanie R Palomares, Lindsey Hageman, et al.

Clin Cancer Res Published OnlineFirst December 3, 2020.

Figure 2A


52
50
48
46
44
42
Mammograhic Dense Area
Placebo
Low-dose Tamoxifen
P=0.02
0
1
2
Years

MDA2014-04-01 STUDY DESIGN

180 Postmenopausal women; confirmed Tis-2, N0-1, Mx, ER-positive breast cancer

R

Exemestane 25mg daily

Exemestane 25mg /week

Exemestane 25mg three times a week

4/6 weeks

SURGERY

Conclusions

- Babytam (10 mg eod or ½ tablet) is practice changing in pre-invasive disease and likely to increase uptake in healthy women at high risk (and possibly in low risk breast cancer who don't tolerate full dose)
- Screening and prevention should go hand in hand during a teachable moment where women are already engaged in health behaviours
- Low dose tamoxifen increases mammographic sensitivity
- Combining chemoprevention with life style changes (optimizing weight, being physically active and limiting alcohol) and personalized breast imaging may be the way forward
- A comparison with AI in terms of efficacy and safety in the prevention setting is warranted

Acknowledgements

Matteo Clavarezza
Mauro D'Amico
Carlotta Defferrari
Alberto Gozza
Silvia Zanardi
Nicoletta Provinciali
Irene Briata
Tania Buttiron Webber
Silvia Caviglia
Davide Corradengo
Giorgia Dario
Silvia Giuliano
Laura Paleari
Matteo Puntoni

Bernardo Bonanni
Massimiliano Cazzaniga
Aliana Guerrieri Gonzaga
Harriet Johansson
Matteo Lazzeroni
Davide Serrano
Nicoletta Colombo

Wolfson Institute of Preventive Medicine

Jack Cuzick
Mangesh Thorat
Ivana Sestak

Nicoletta Gandolfo
Marina Gualco
Flavio Guasone
Stefano Spinaci

Leslie Ford
Eva Szabo
Brandy Heckman-Stoddard
Barbara Dunn
Howard Parnes

Powel
Brown


Thank you!