

Preventive Therapy for Breast Cancer

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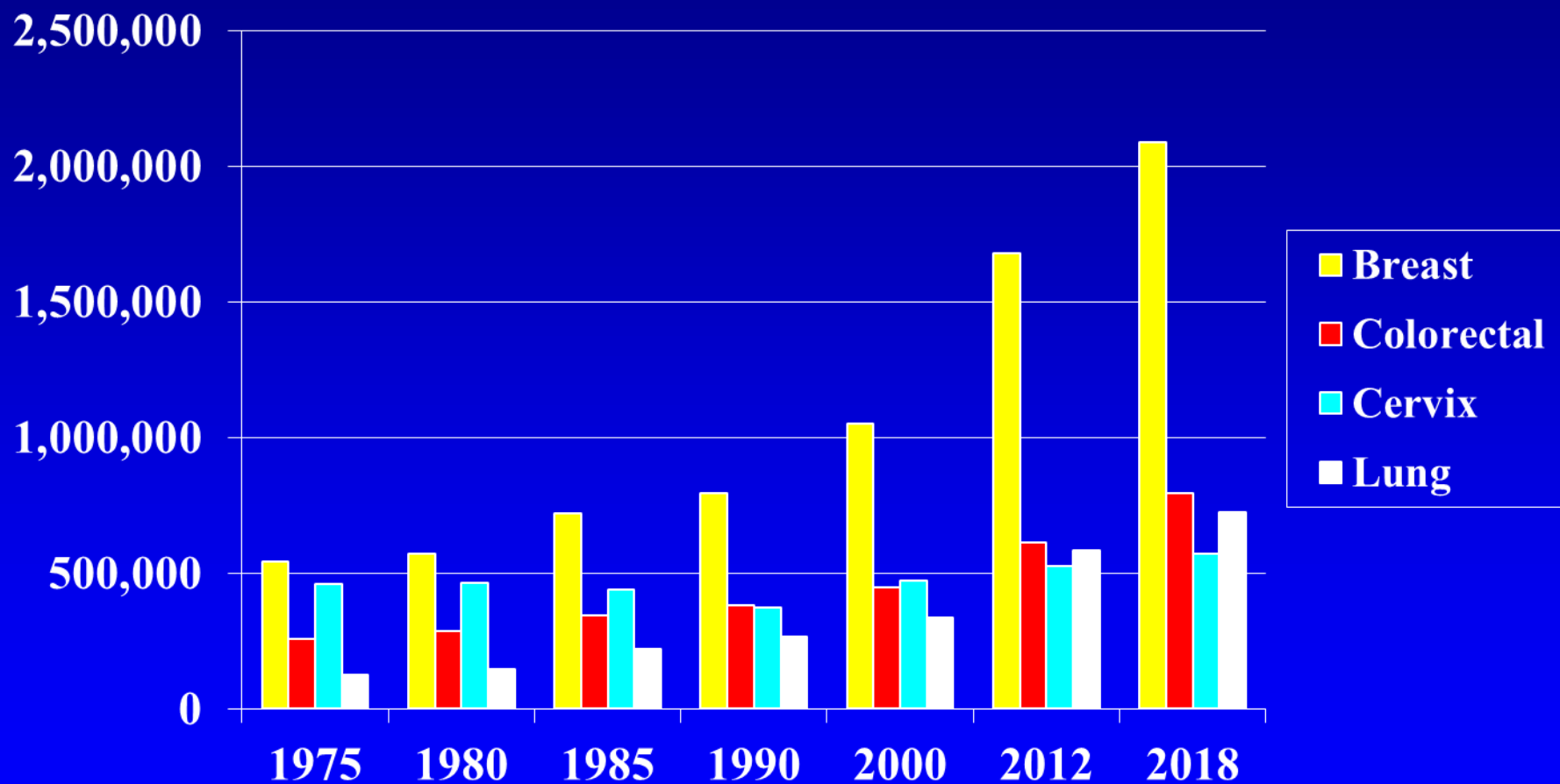
Barts and The London
Queen Mary's School of Medicine and Dentistry



Conflict of Interest

- My institution has received grants and materials from AstraZeneca to support breast cancer treatment and prevention trials

Global Incidence of Breast, Colorectal, Cervix and Lung Cancer 1975 – 2018 (Female)



Two Approaches to Cancer Prevention

- Simple minimally toxic interventions for all
- Focussed interventions on high risk groups

Preventive Therapy

Key Ingredients

- Identification of High-risk women
- Effective minimally -toxic prophylaxis

Tyrer –Cuzick (IBIS) Model

New developments for v8

Age

Height Menarche

Age first child

Age Menopause

BMI HRT

BREAST DENSITY

Family History
BRCA testing

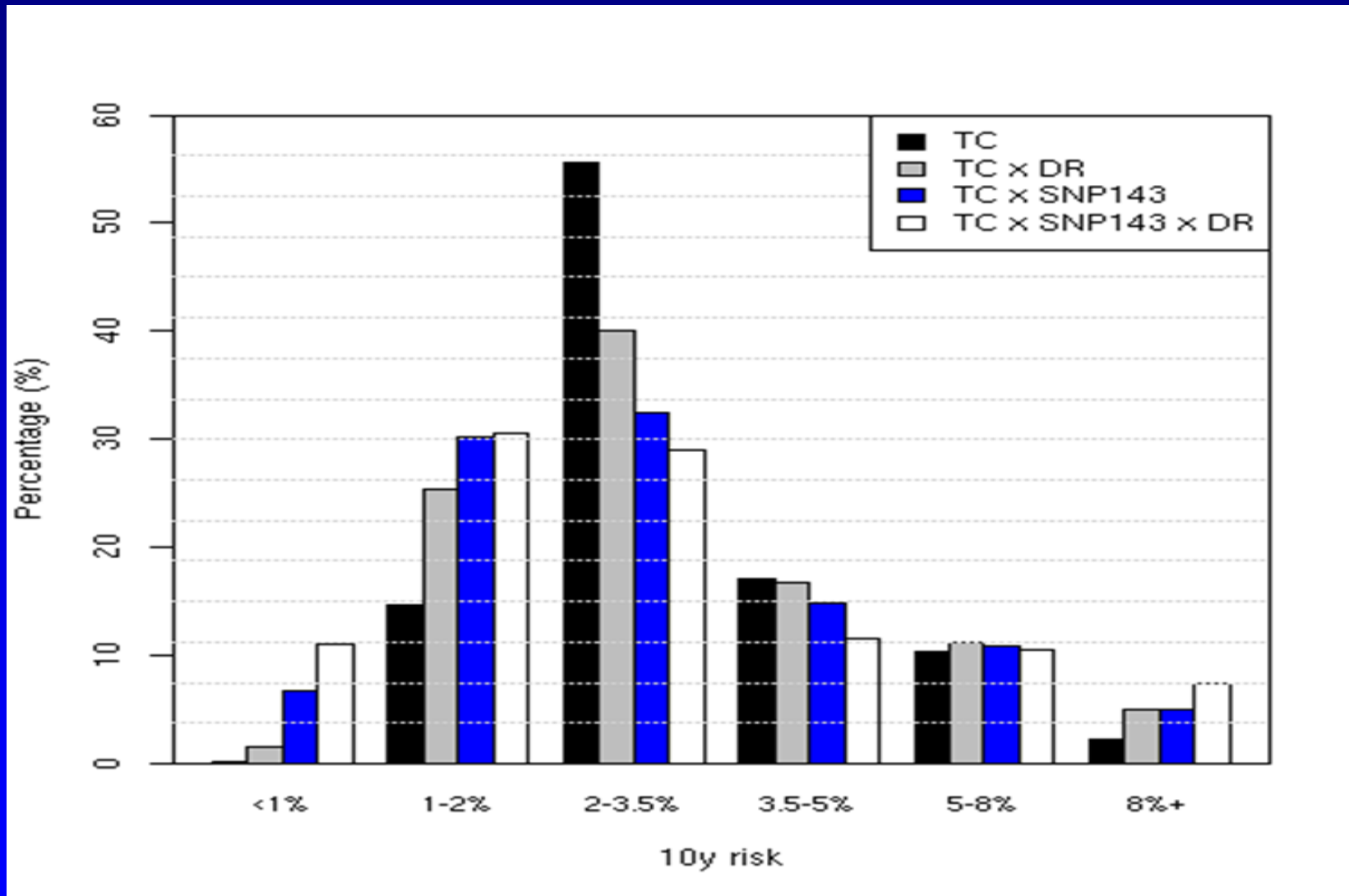
SNPs

Proliferative benign
breast disease

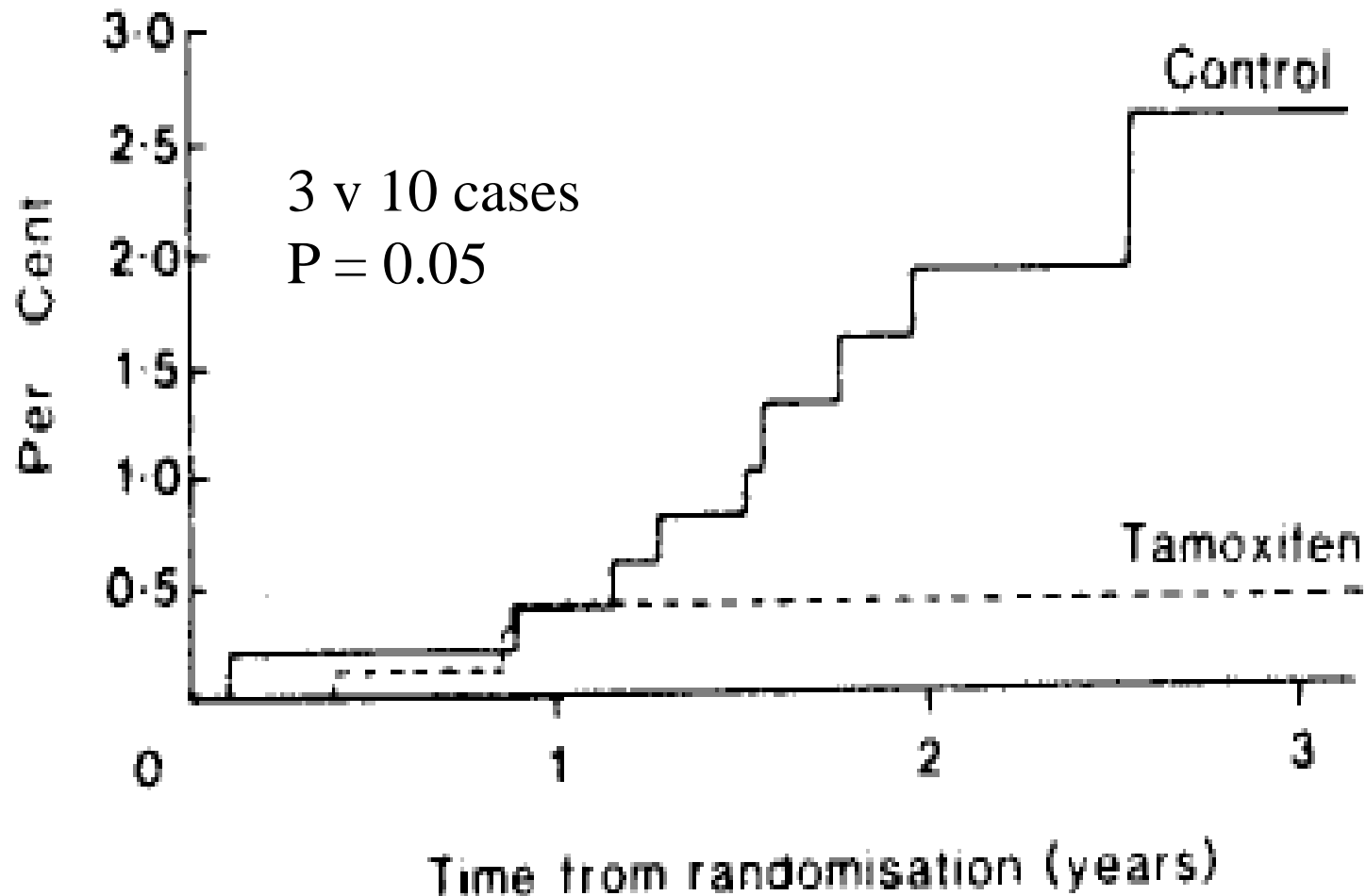
Atypical Hyperplasia

LCIS

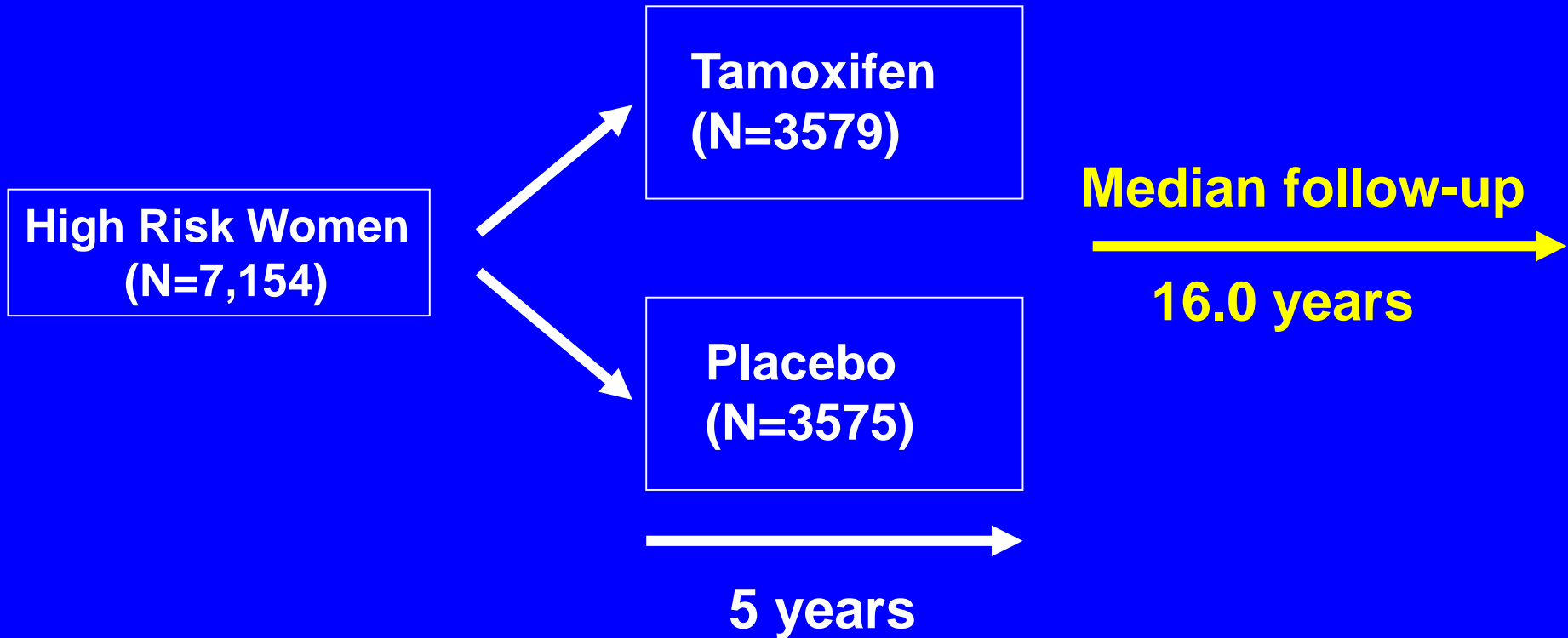
10-year risk using questionnaire data (TC), mammographic breast density (DR) and a 143 gene SNP panel



Cumulative Incidence of Contralateral Breast Cancer in an Adjuvant Tamoxifen Trial



IBIS-I study design

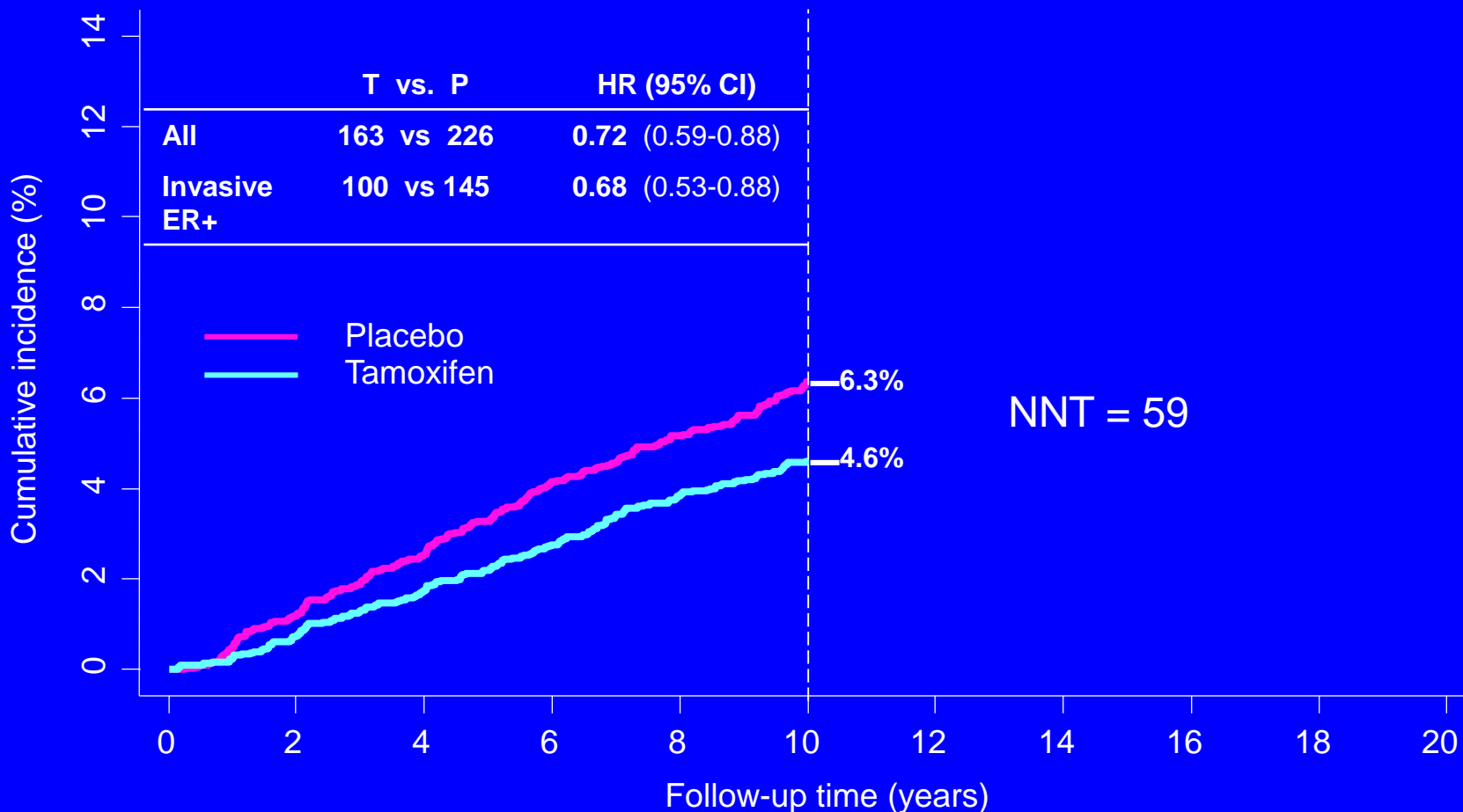


Endpoints:

Primary: Breast cancer incidence (incl. DCIS)

Secondary: Other cancers, BC mortality, all cause mortality, adverse events

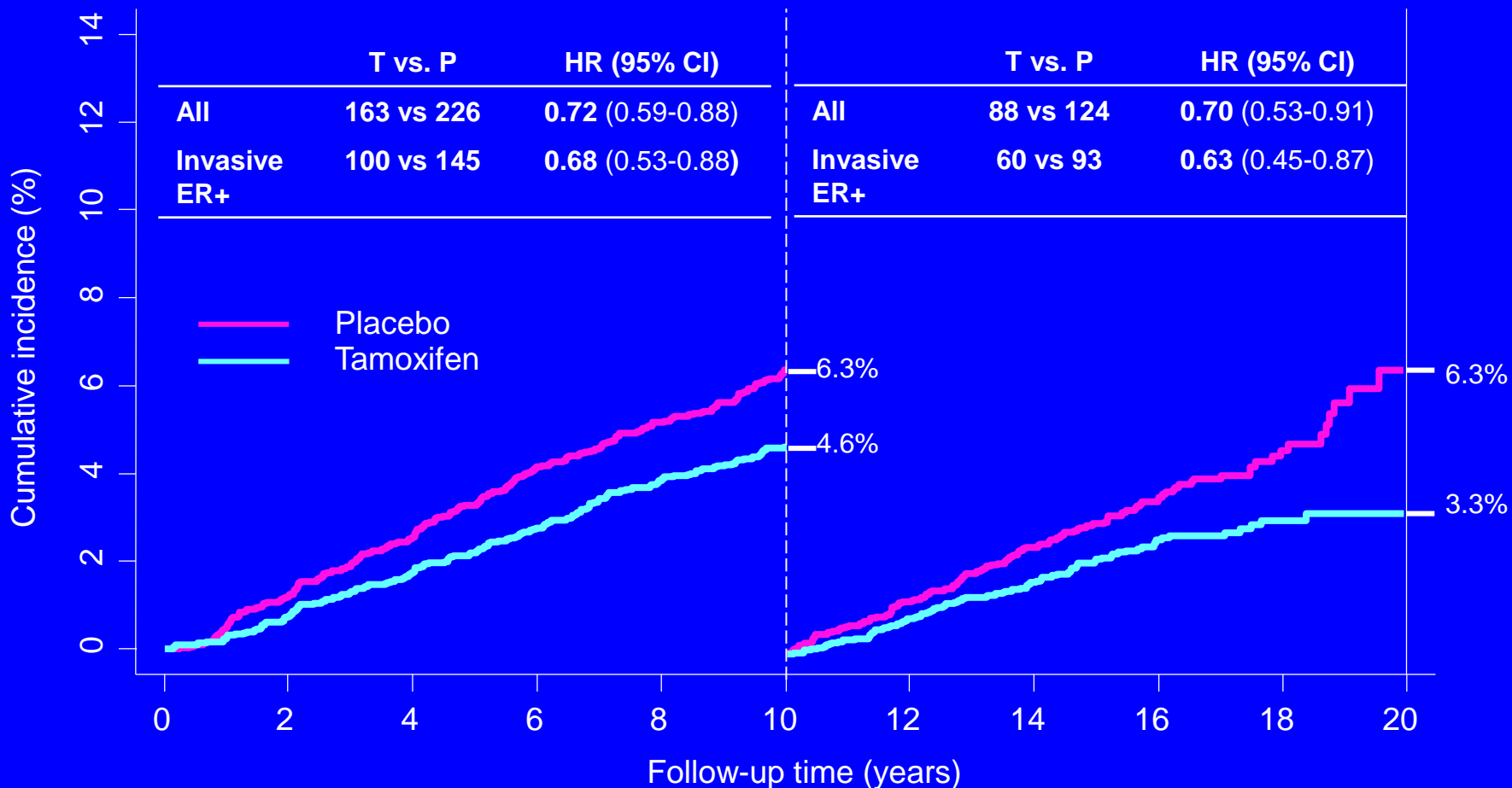
Cumulative Incidence for All Breast Cancer



Number at risk

Placebo	3575	3527	3474	3410	3358	3296	3239	2850	1901	725	165
Tamoxifen	3579	3542	3495	3446	3385	3344	3293	2890	1918	748	168

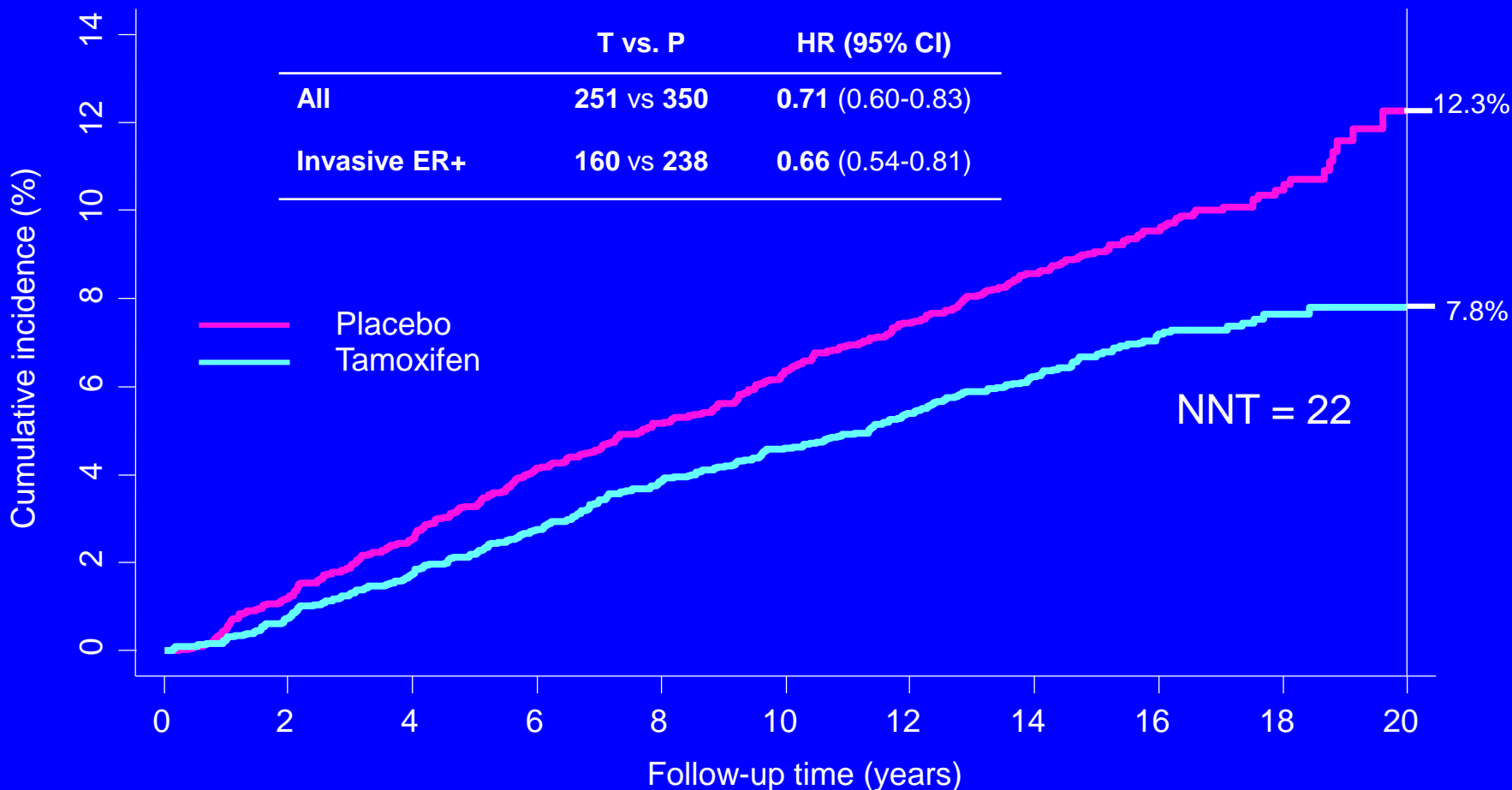
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Effect of tamoxifen on breast cancer risk

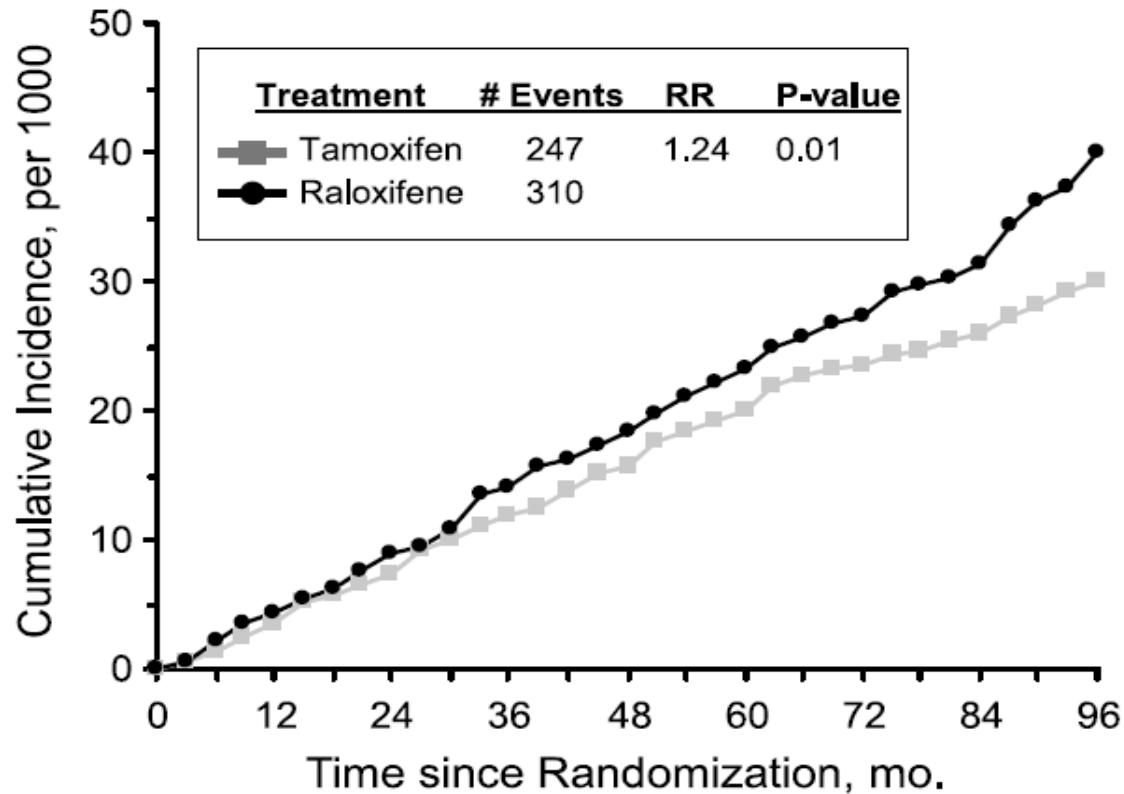
according to reduction in density at 12-18 months

Group	OR	95% CI†	P-value
Placebo	Ref	-	-
Tamoxifen, Reduction < 10%	1.03	(0.66-1.61)	0.89
Tamoxifen, Reduction ≥ 10%	0.37	(0.20-0.69)	0.002

$X^2(\text{heterogeneity}) = 8.32, p=0.004$

†Adjusted for age and density at entry, and bmi

STAR-Invasive Breast Cancer 81-month follow up



No. at Risk

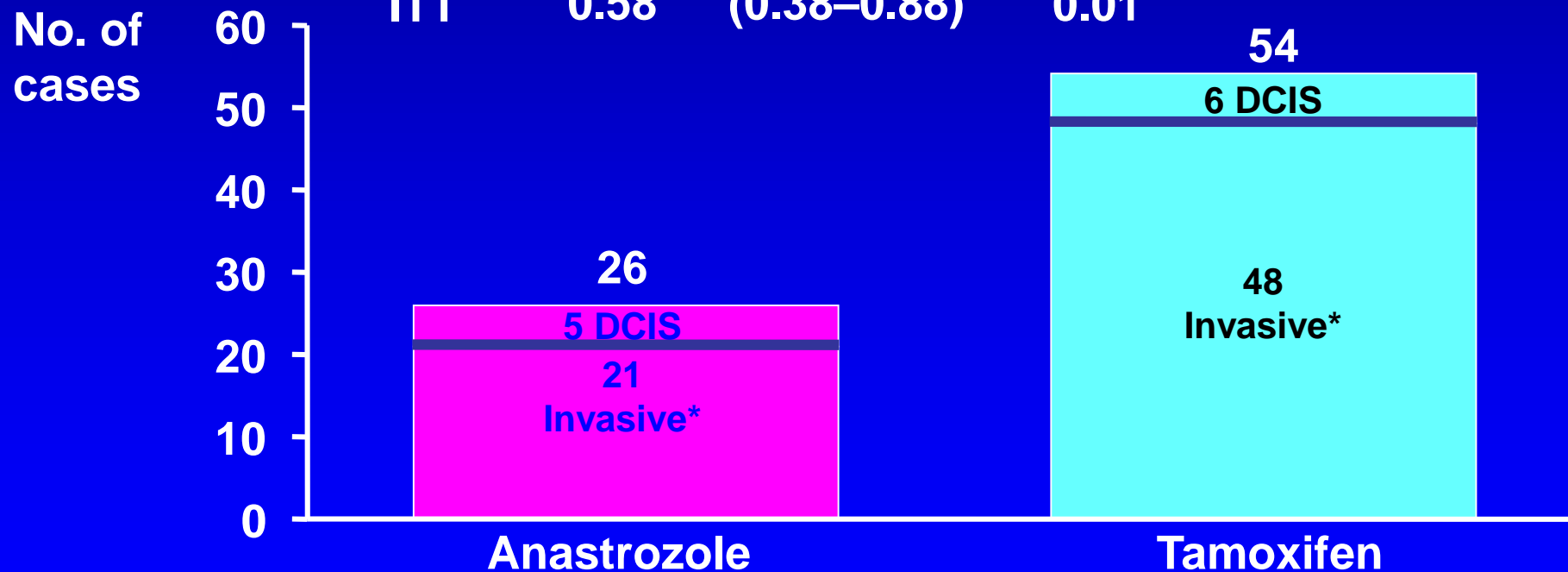
Raloxifene	9754	9398	8973	8196	5999	4453	2650
Tamoxifen	9736	9387	8939	8059	5833	4326	2621

Approaches to Prevention

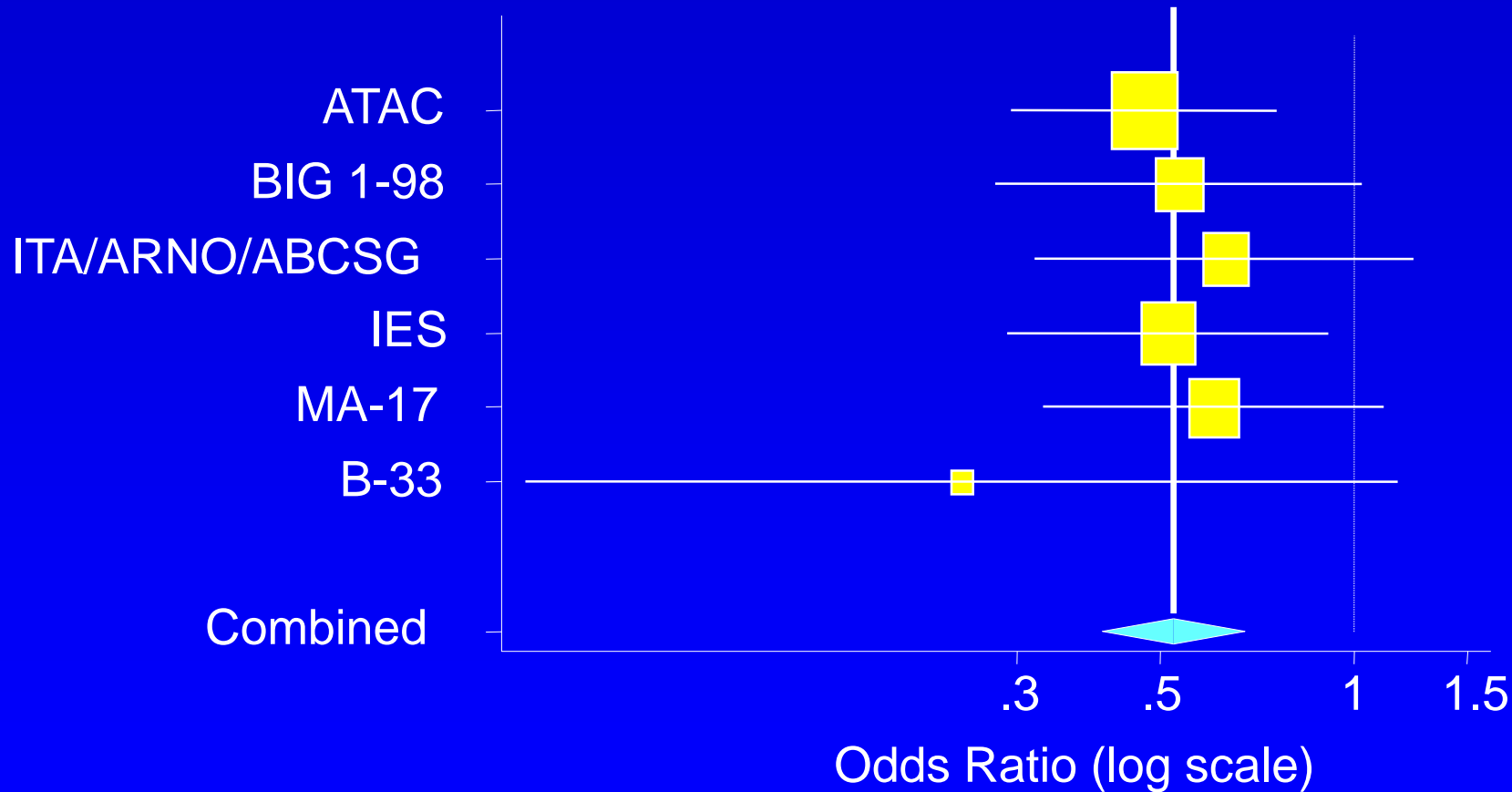
- SERMS
 - Tamoxifen
 - Raloxifene
- Aromatase Inhibitors
 - Anastrozole
 - Letrozole
 - Exemestane

ATAC - Incidence of contralateral breast cancer (HR-positive population)

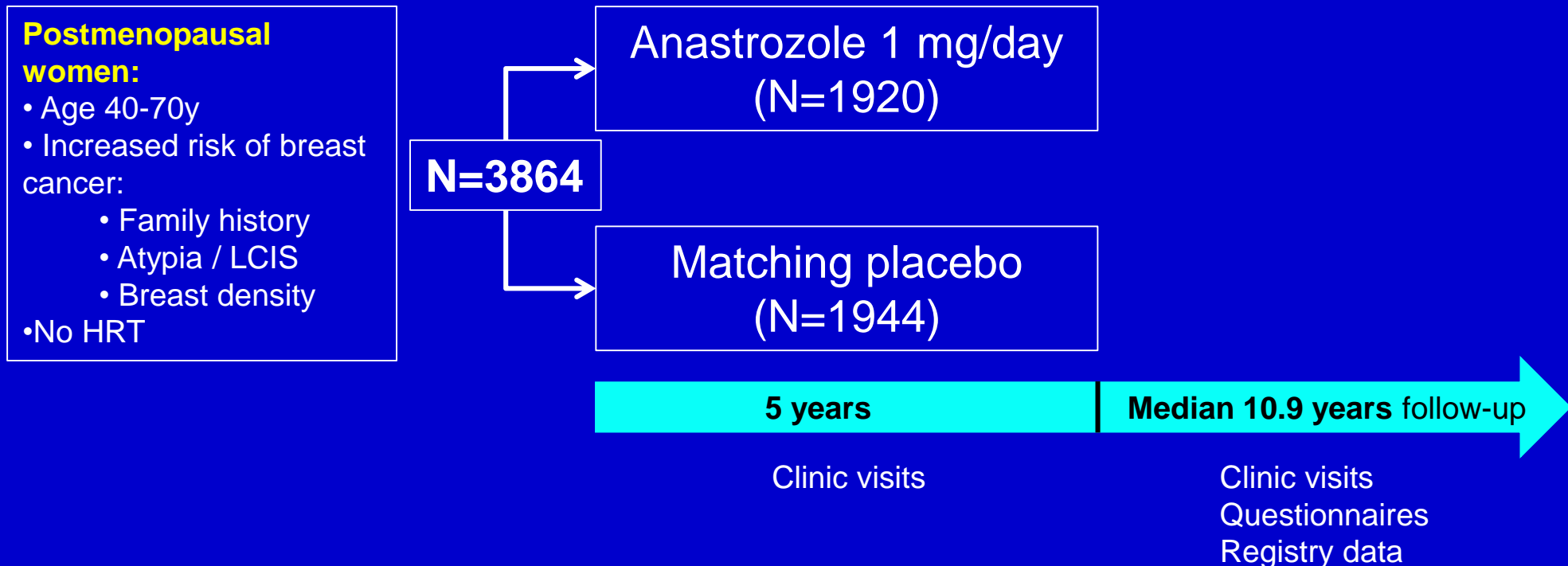
	HR	95% CI	p-value
HR+	0.47	(0.29–0.75)	0.001
ITT	0.58	(0.38–0.88)	0.01



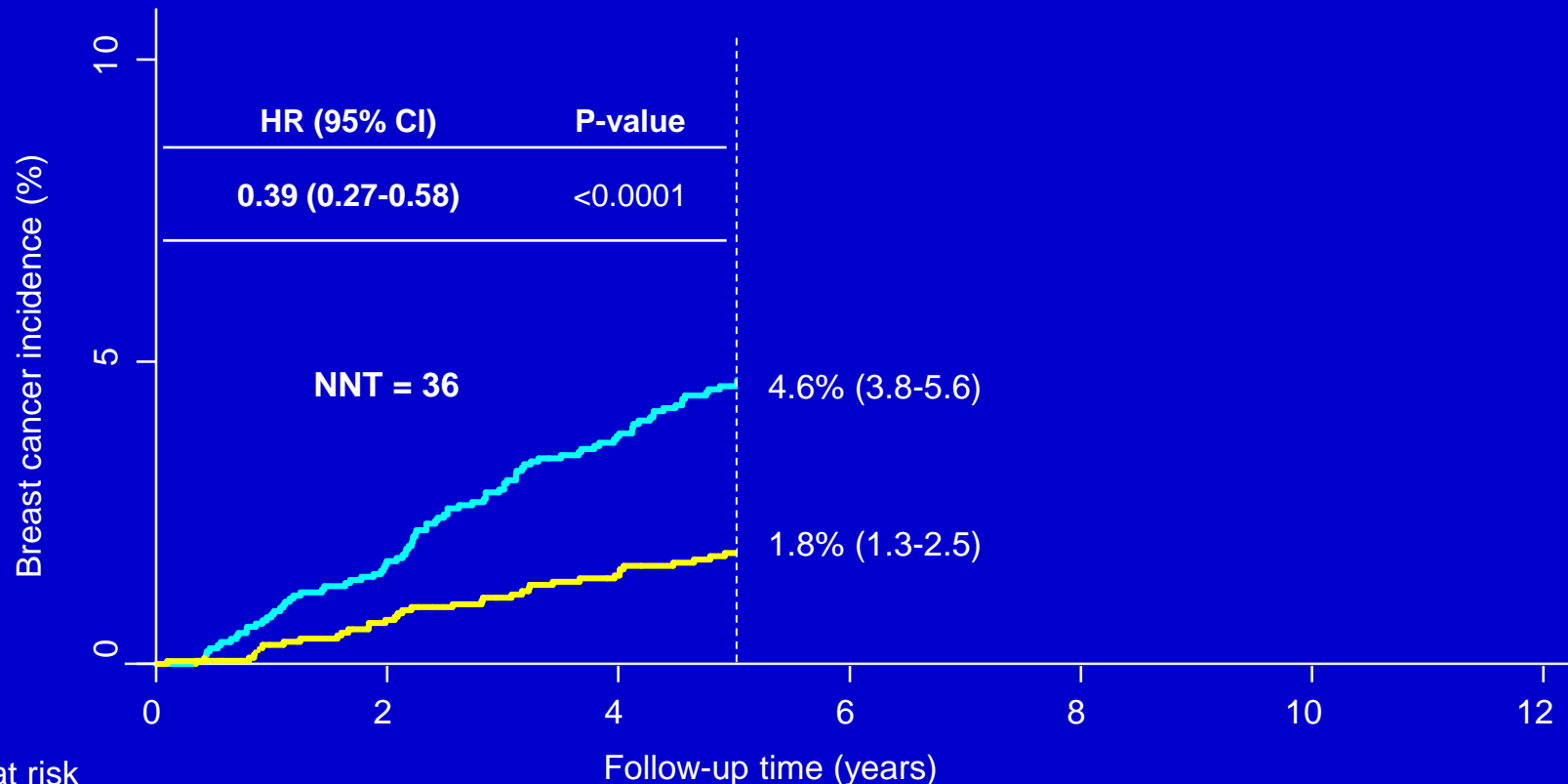
Contralateral Tumours in Aromatase Inhibitor Trials



IBIS-II Trial schema



IBIS - II - Breast cancer incidence

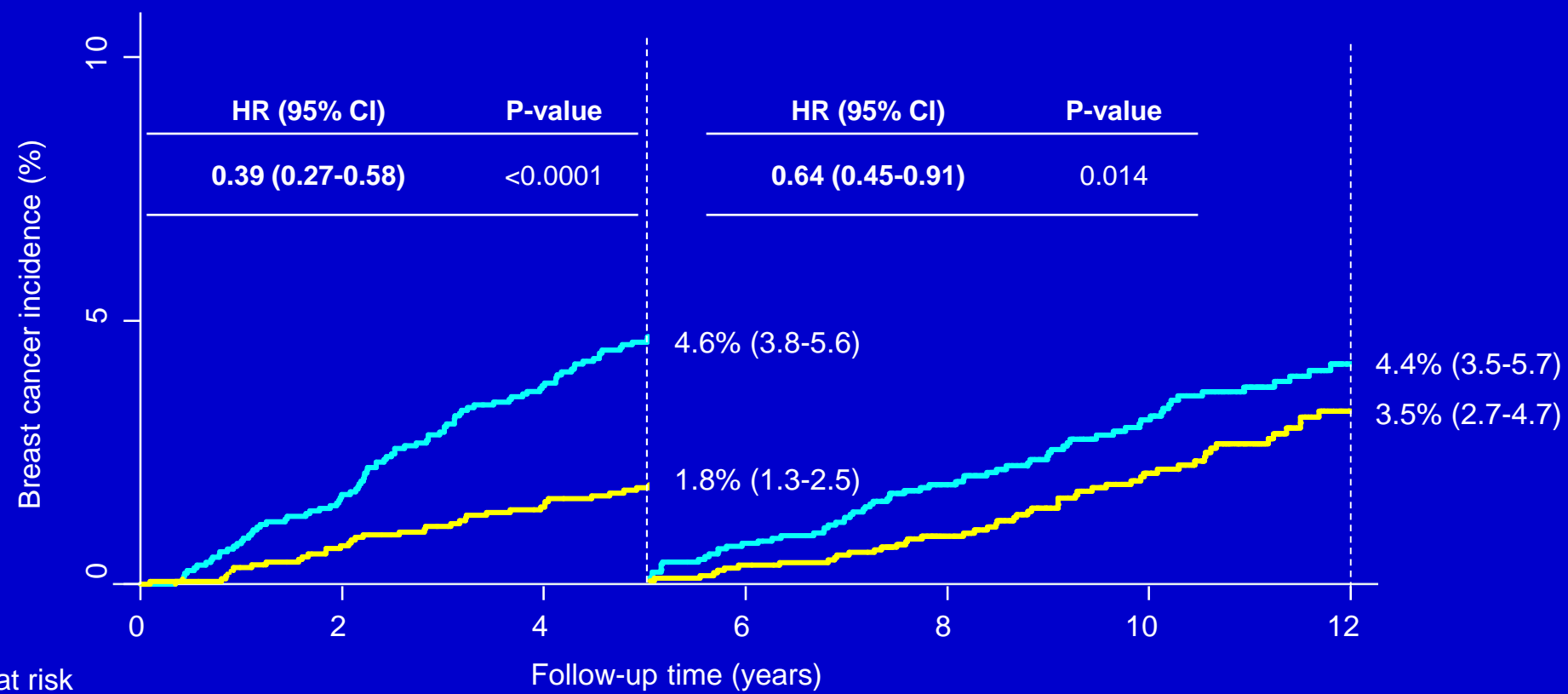


Number at risk

	0	2	4	6	8	10	12
Anastrozole	1920	1898	1874	1856	1611	1221	698
Placebo	1944	1907	1857	1818	1561	1172	681

— Anastrozole — Placebo

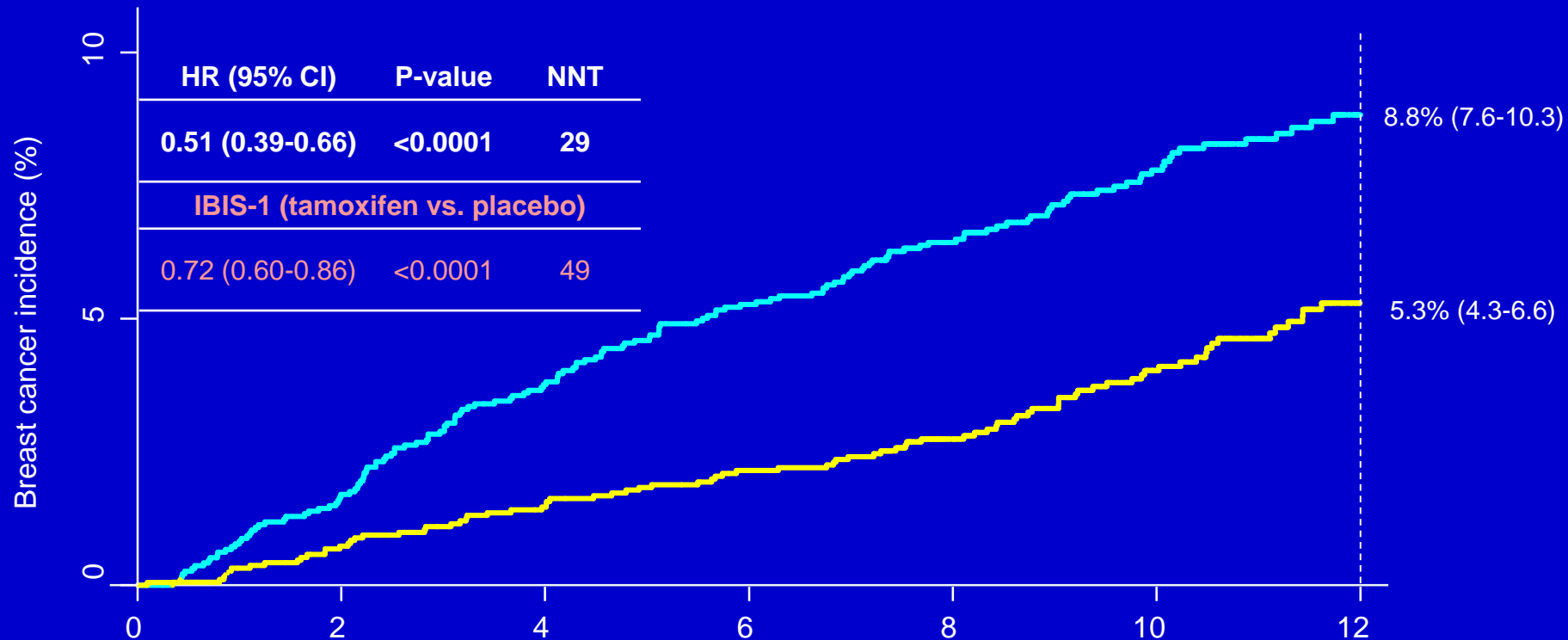
IBIS – II Breast cancer incidence



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IBIS-II Breast cancer incidence



Number at risk

Follow-up time (years)

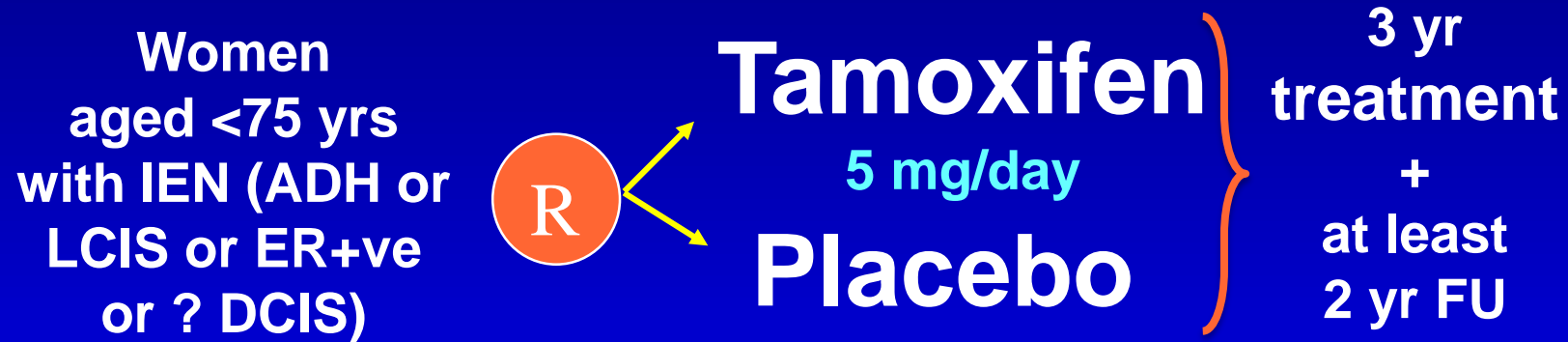
Anastrozole	1920	1898	1874	1856	1611	1221	698
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— Anastrozole — Placebo

Newer Developments

Italian DCIS Trial

Decensi et al. JCO 2019

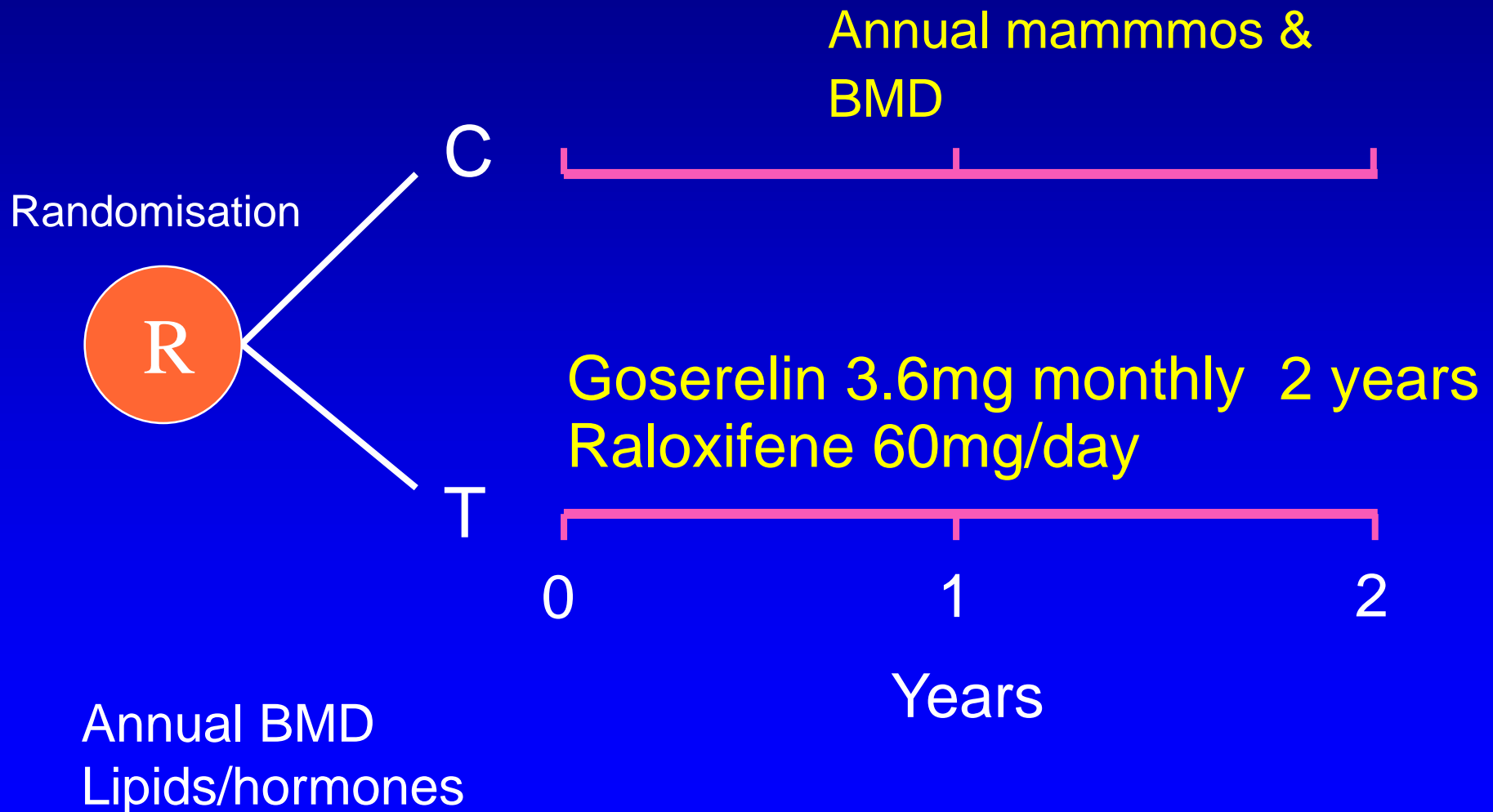


Primary endpoint: Incidence of breast cancer or DCIS

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

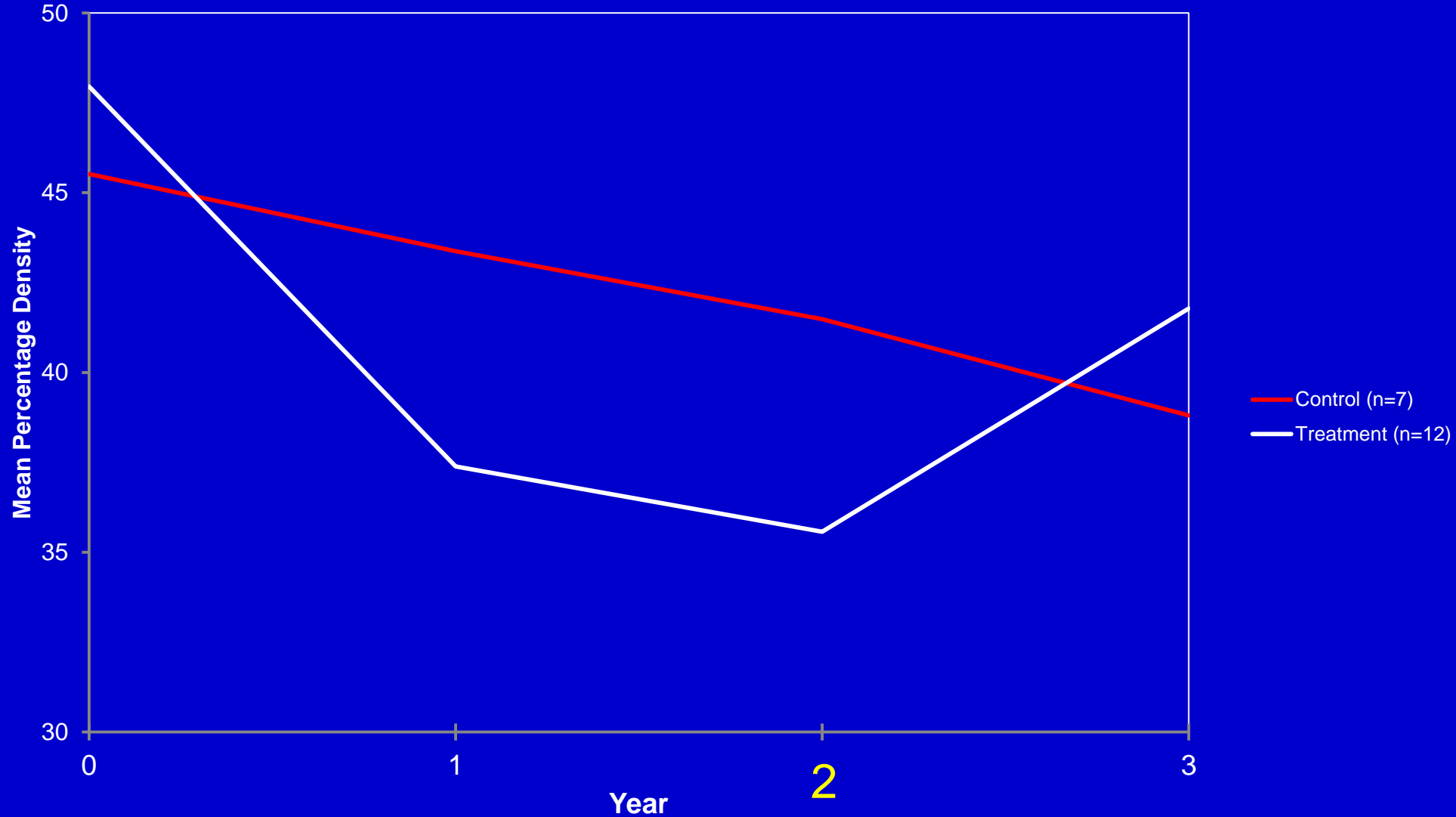
High Risk Premenopausal Women

Raloxifene and Zoladex Research Study (RAZOR)



Mammographic Density Visual Analogue Scale

Consecutive VAS Measurements from 19 Women



Endoxifen Gel

- **Endoxifen is most active common metabolite of tamoxifen**
- Topical preparation developed for applying directly onto the breast
- Anticipated high dose to breast but low systemic dose
 - Effective breast dose to block oestrogen receptor
 - Low side effect profile

Conclusions

- 5 years of tamoxifen produces a very long term 30% reduction of breast cancer
 - Lower dose or topical endoxifen may reduce side effects
- Aromatase inhibitors are more effective
 - (>50% reduction) and less toxic (no endometrial cancer or thromboembolic complications), but suitable only for postmenopausal women
- Further work needed to manage side effect perceptions and explore new treatments with better side effect profile