Progress in Breast Cancer Prevention

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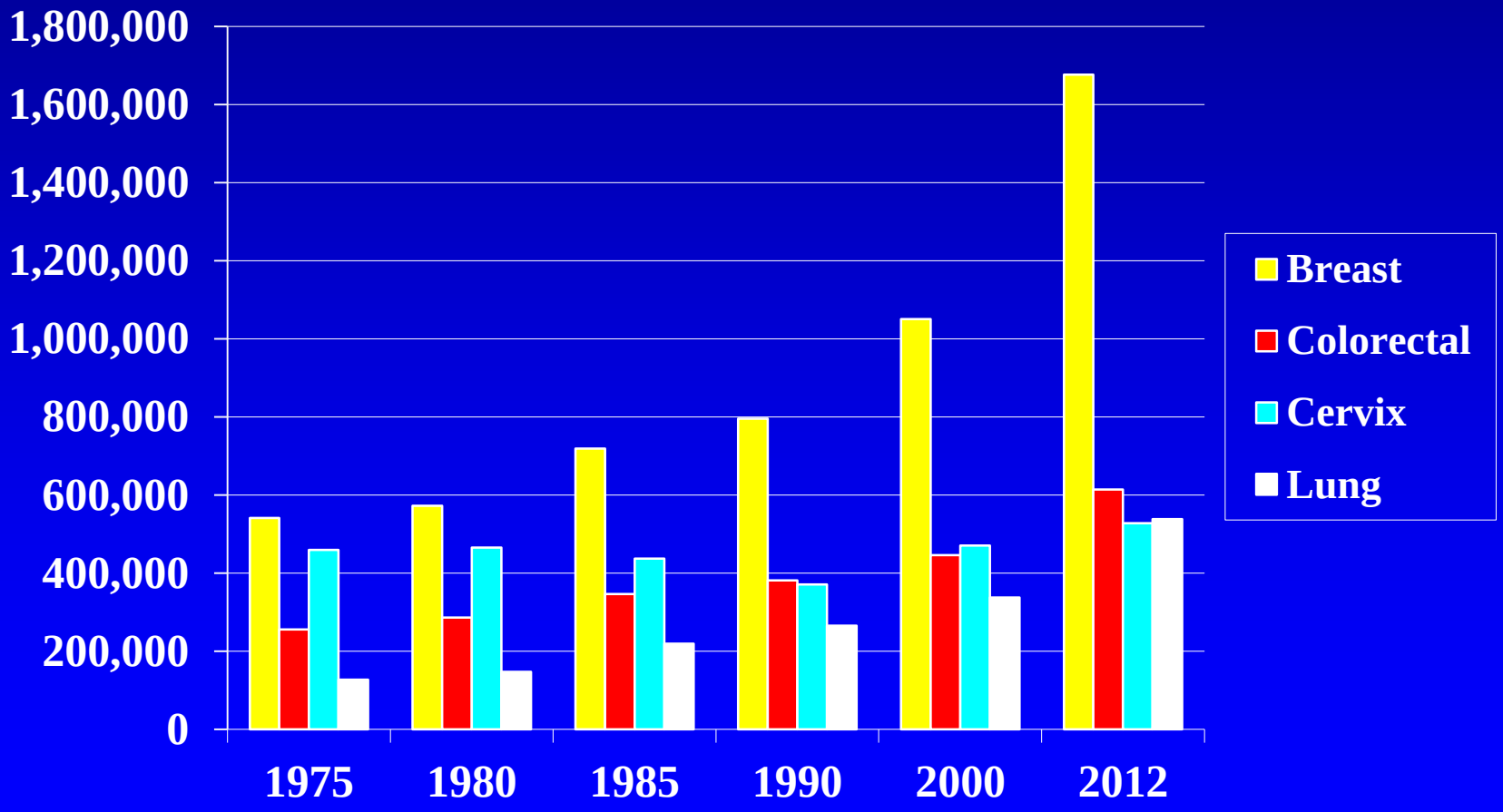
CANCER RESEARCH UK

Global Incidence of Breast, Colorectal, Lung and Cervix Cancer 1975-2012 (Female)



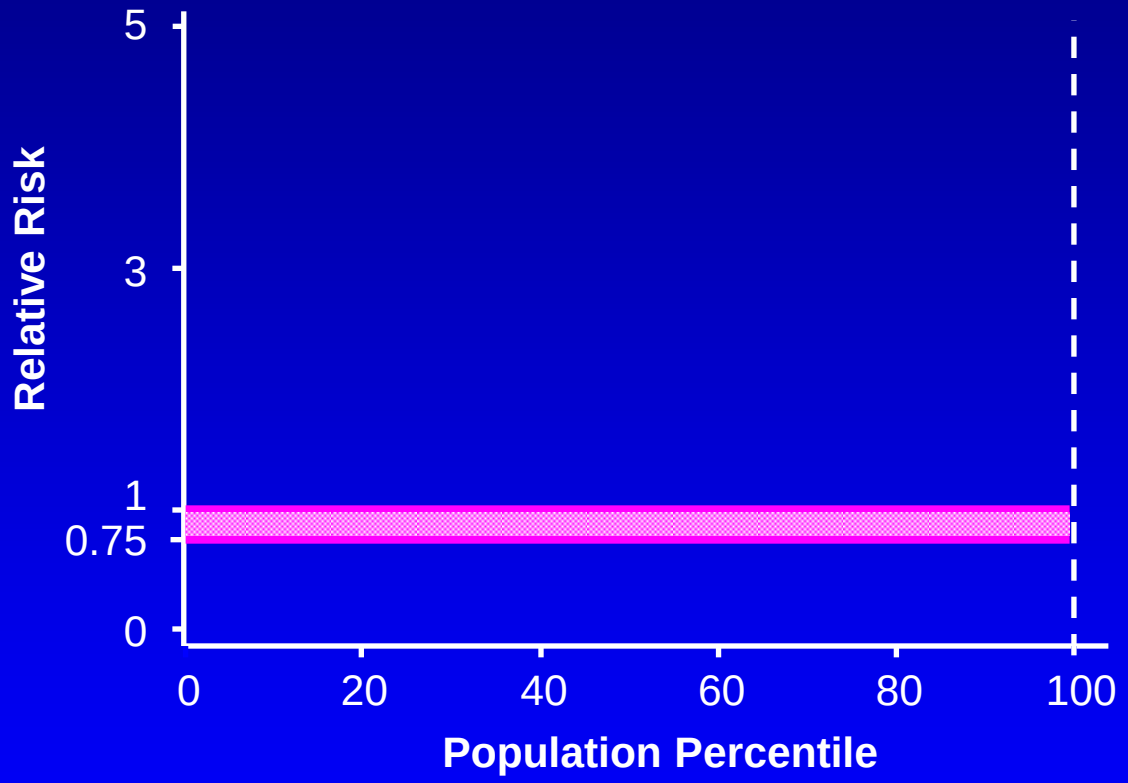
Globocan 2012

Approaches to Prevention

- Lifestyle
  - Diet – Weight
  - Exercise
  - Reproductive
  - Exogenous Hormones

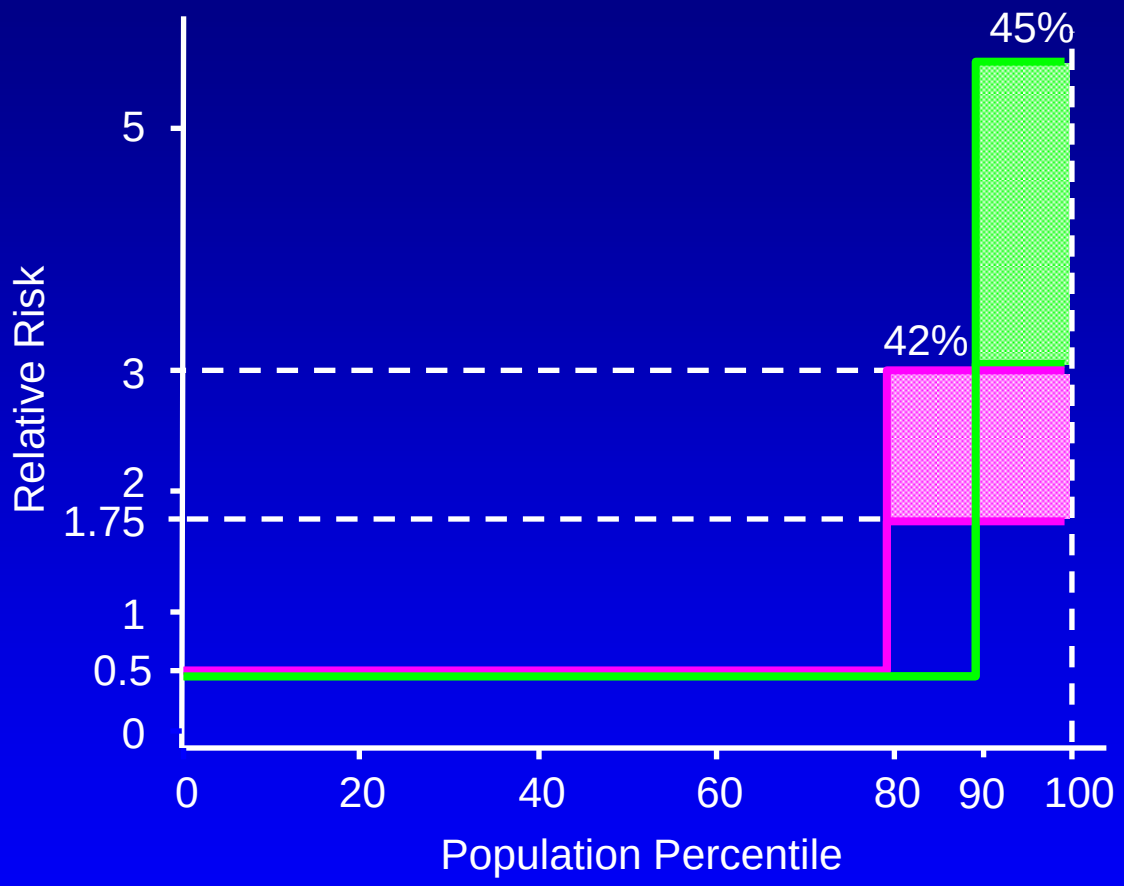
Whole Population

25% reduction in risk



Small Proportion at High Risk

25% reduction in risk



Key Ingredients

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

Major Risk Factors

- Family history
- Reproductive/ Hormonal
- Benign Pathology
- Mammographic Density

- Risk Assessment Model available at:

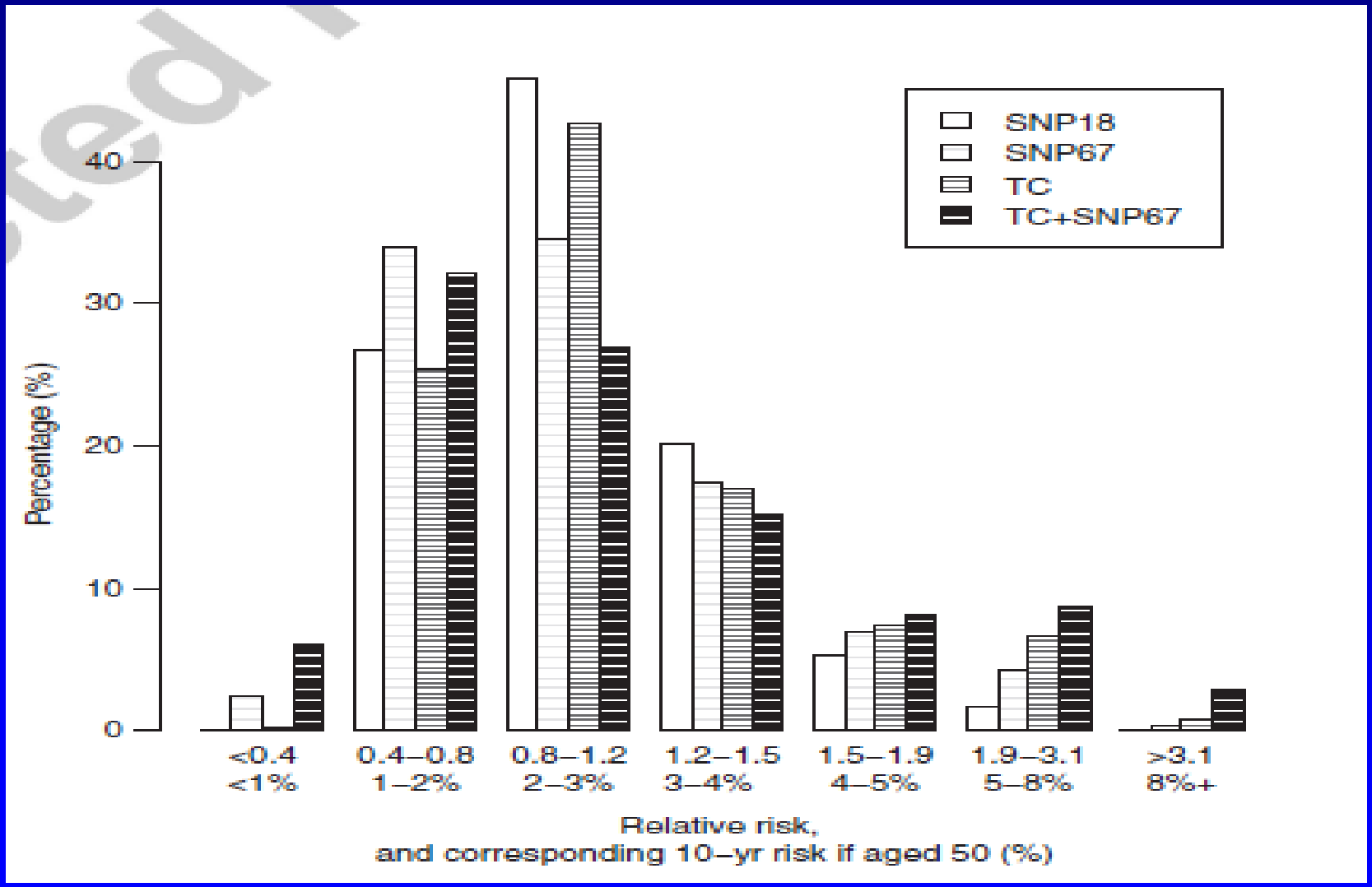
http://www.ems-trials.org/riskevaluator/

Genes Predisposing to Breast Cancer

76 SNPs now identified

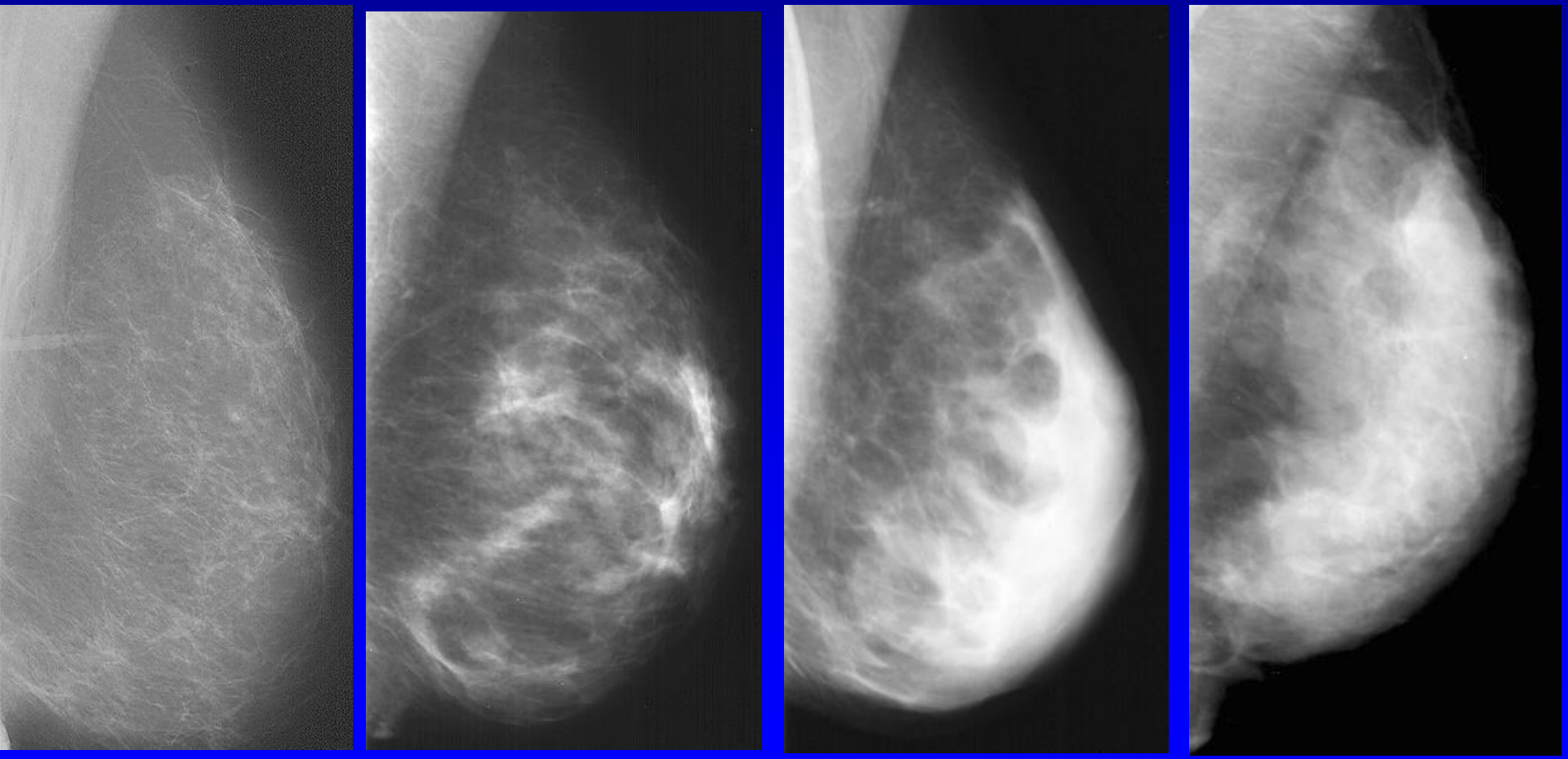
Gene	Allele Frequency (%)	OR per allele	Evidence for differential treatment effect
BRCA1	~ 0.1	~ 10	Often triple negative
BRCA2	~ 0.1	~10	Usually ER+
CHEK2	0.7	2.34	Young age at onset
ATM	0.4	2.37	
FGFR2	38	1.26	Interaction with HRT?*
TNRC9	46	1.11	
MAP3KI	28	1.13	
LSP1	30	1.07	
H19	31	0.96 (protective)	
8q	40	1.08	

Relative risk and 10 yr Absolute risk for 50yr old women attending screeningv



Brentnall et al , Br J Cancer 2014

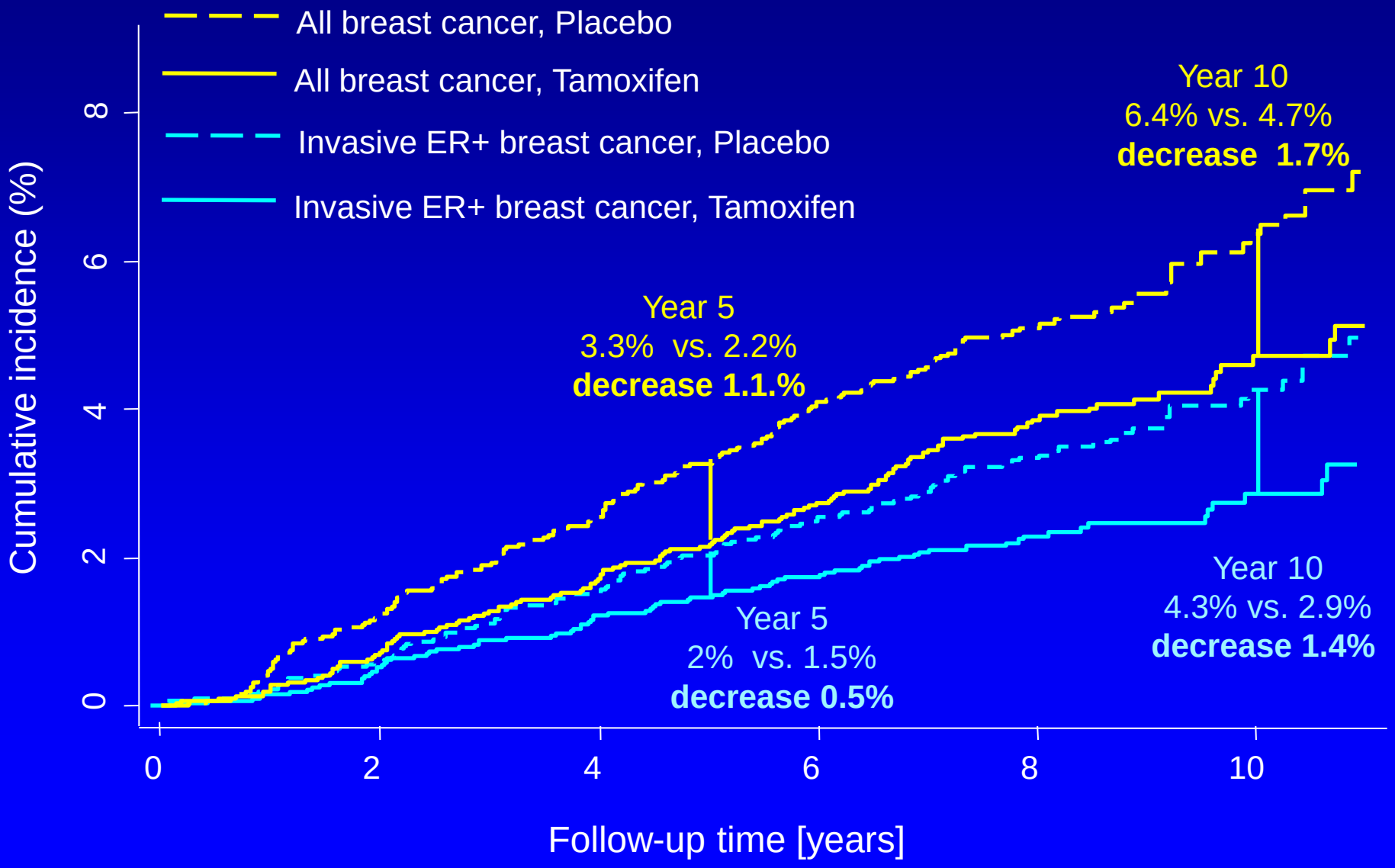
Mammographic Density



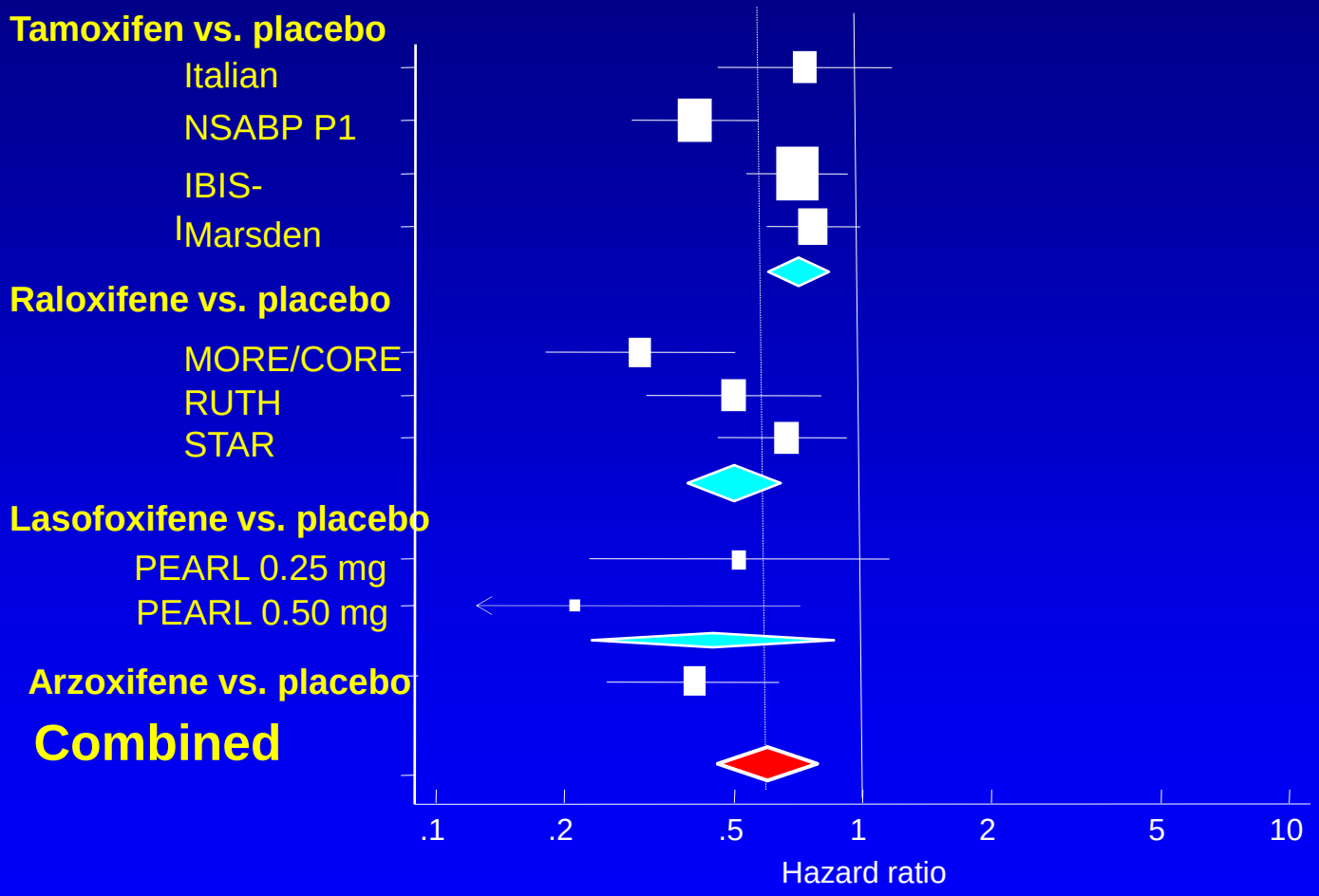
Breast Cancer Prevention Trials using Tamoxifen

Trial (Entry Dates)	Population	Number Randomised	Agents (vs Placebo) and daily dose	Intended Duration of Treatment
Royal Marsden (1986-1996)	High Risk Family History	2471	Tamoxifen 20mg	5-8y
NSABP-P1 (1992-1997)	High risk women >1.6% 5y risk	13 388	Tamoxifen 20mg	5y
Italian (1992-1997)	Normal Risk Hysterectomy	5408	Tamoxifen 20mg	5y
IBIS-I (1992-2001)	>2-fold relative risk	7139	Tamoxifen 20mg	5y
Adjuvant Overview (1976-1995)	Women with ER+ operable breast cancer in 11 trials	~15000	Tamoxifen 20-40mg with or without chemotherapy in both arms.	3 years or more (average ~5 yrs)

IBIS-1 Cumulative Incidence of Breast Cancer



ALL INVASIVE BREAST CANCERS, 0-10y
SERM vs. placebo



Fixed-effect model: -36.2% [-43.0%;-28.7%], p<0.001
Random-effect model: -39.8% [-51.6%;-25.0%], p<0.001
Test for heterogeneity: Q(9df) = 29.73, p<0.001

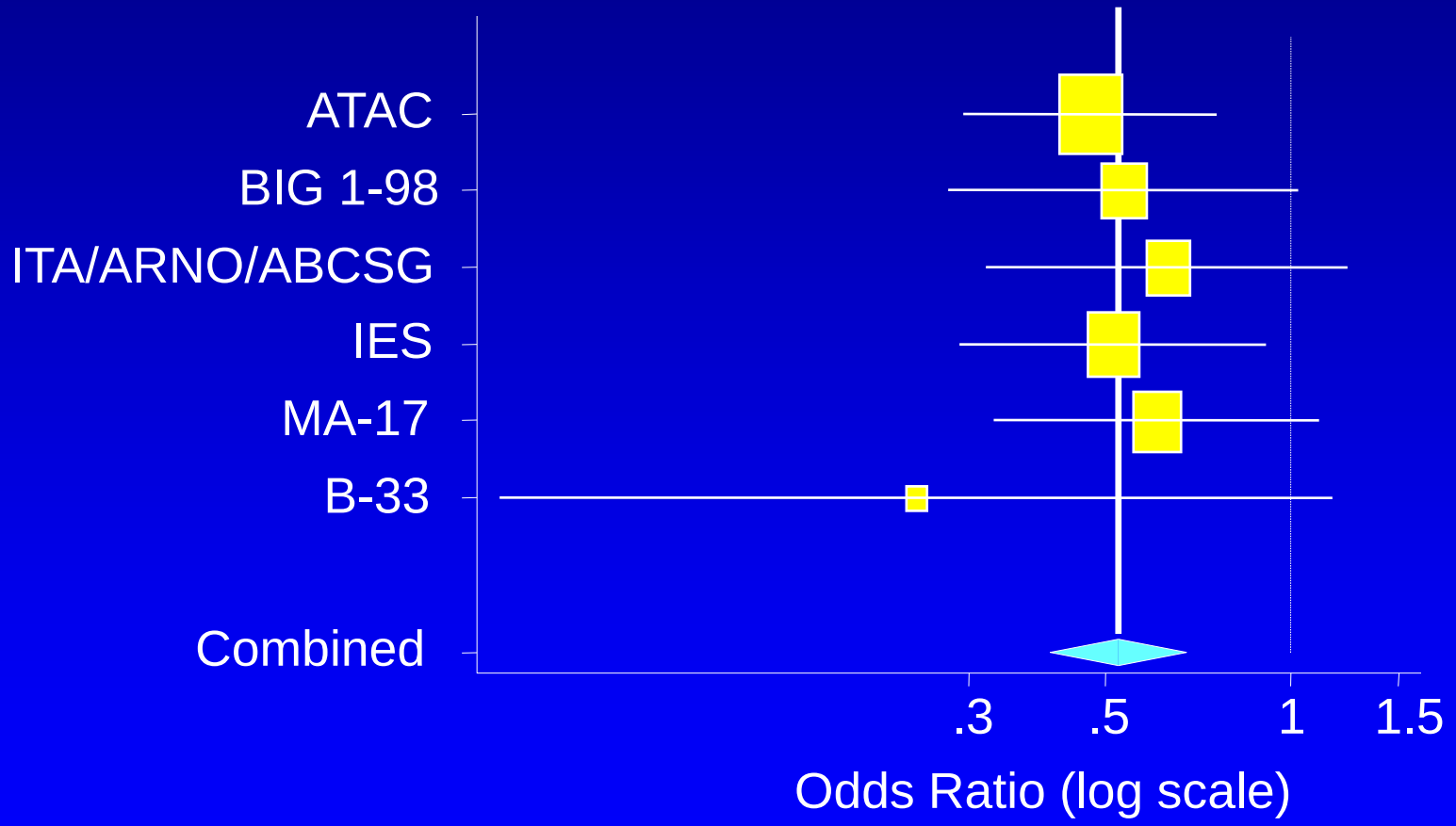
Effect of tamoxifen on breast cancer risk

according to reduction in density at 12-18 months

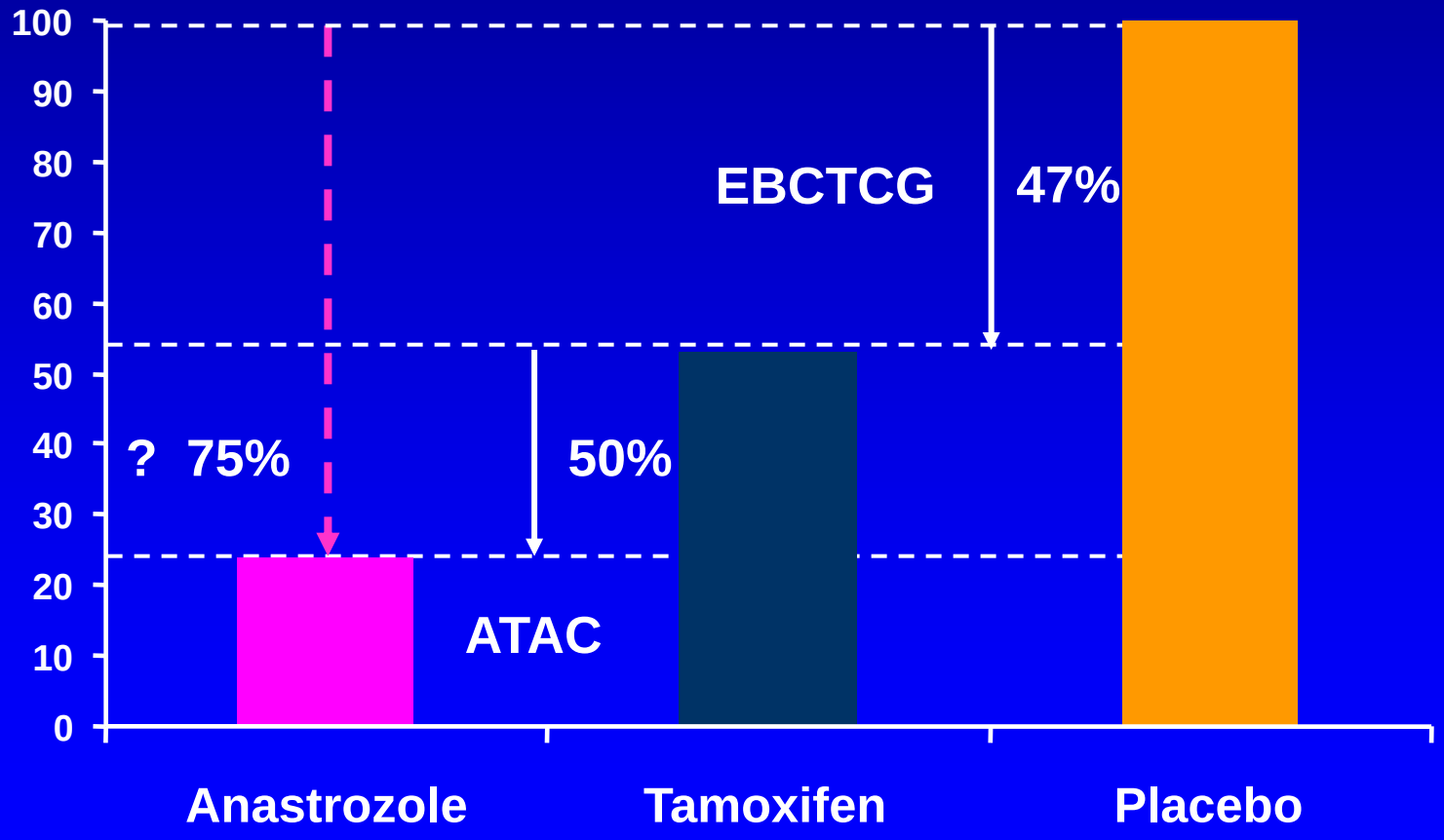
Group	OR	95% CI†	P-value
Placebo	**Ref**	**-**	**-**
Tamoxifen, Reduction < 10%	**1.03**	**(0.66-1.61)**	**0.89**
Tamoxifen, Reduction ≥ 10%	**0.37**	**(0.20-0.69)**	**0.002**
X^2(heterogeneity) = 8.32, p=0.004			

†Adjusted for age and density at entry, and bmi

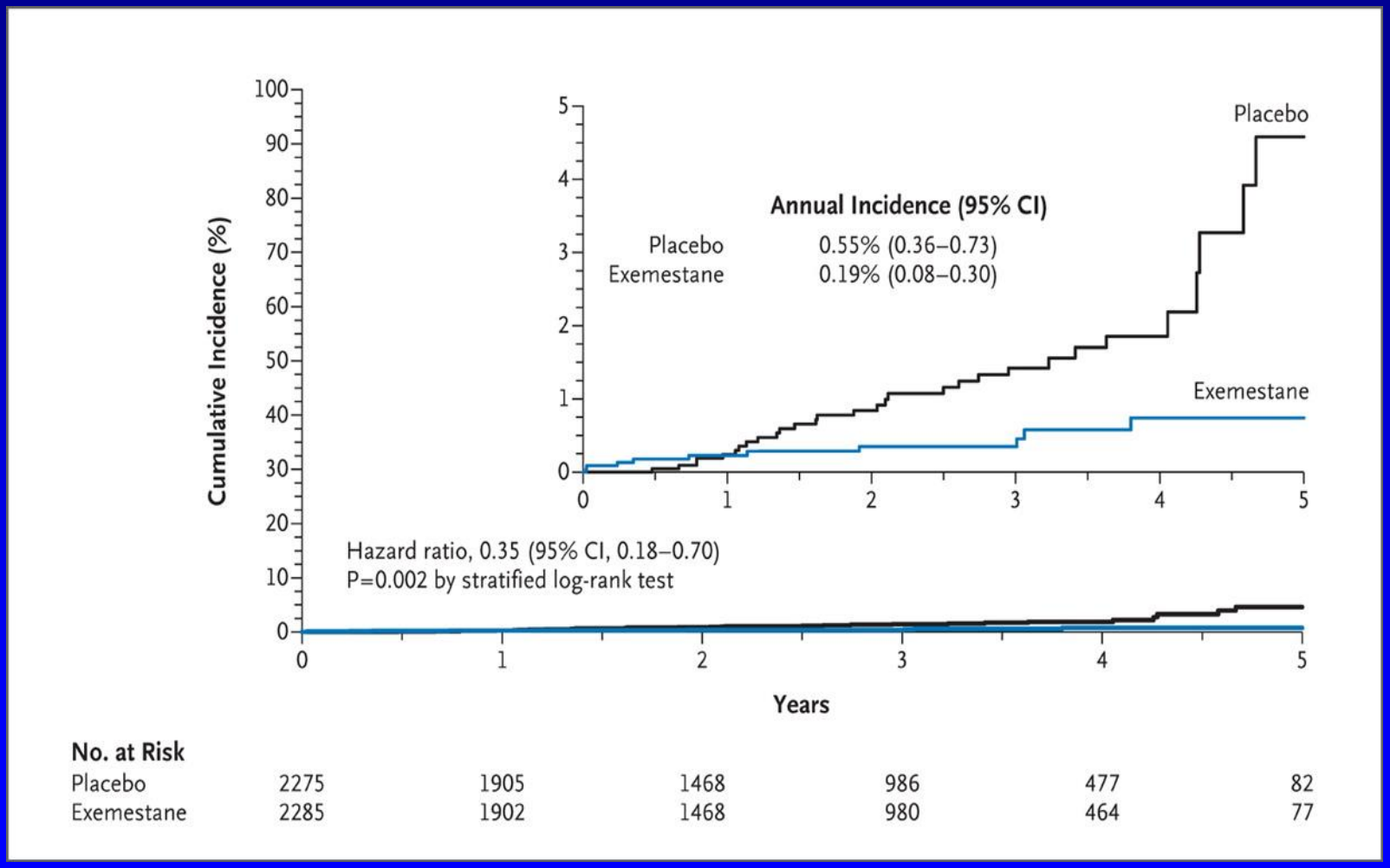
Contralateral Tumours in Aromatase Inhibitor Trials



New (Contralateral) Breast Primaries - AI adjuvant trials



MAP3 - Cumulative Incidence of Invasive Breast Cancer

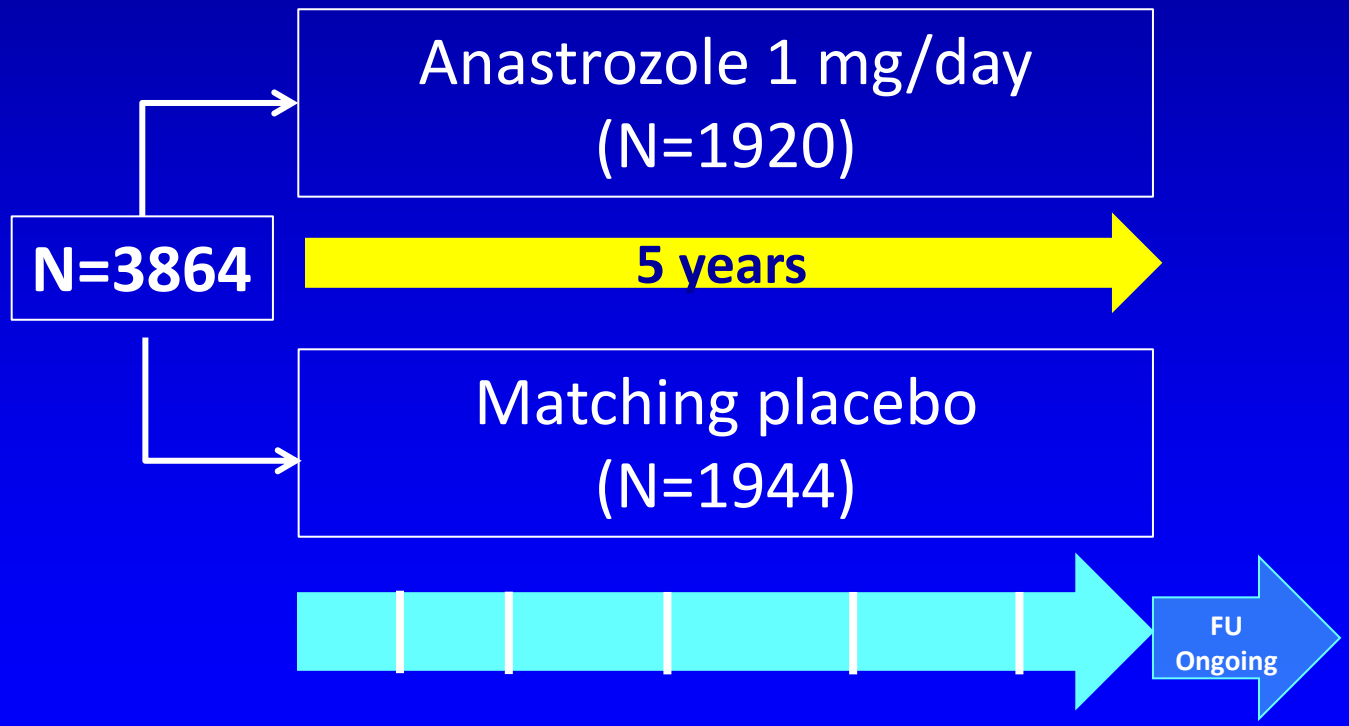


Goss et al NEJM, 2011

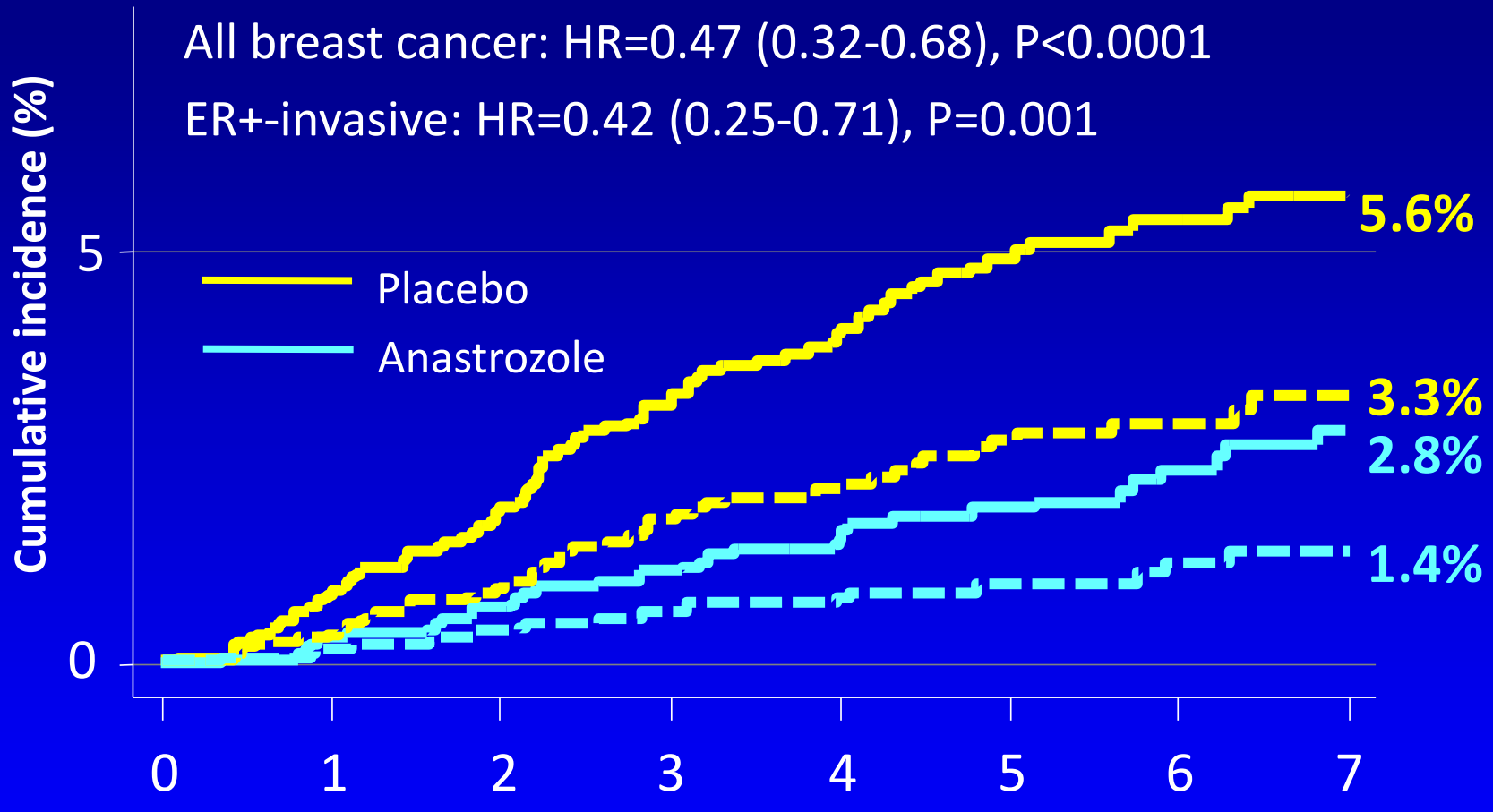
IBIS 2 - Trial schema

Postmenopausal women:

- Ages 40-70
- Increased risk of Breast cancer:
  - Family history
  - Atypia / LCIS
  - Breast density
- No HRT



Breast Cancer Incidence

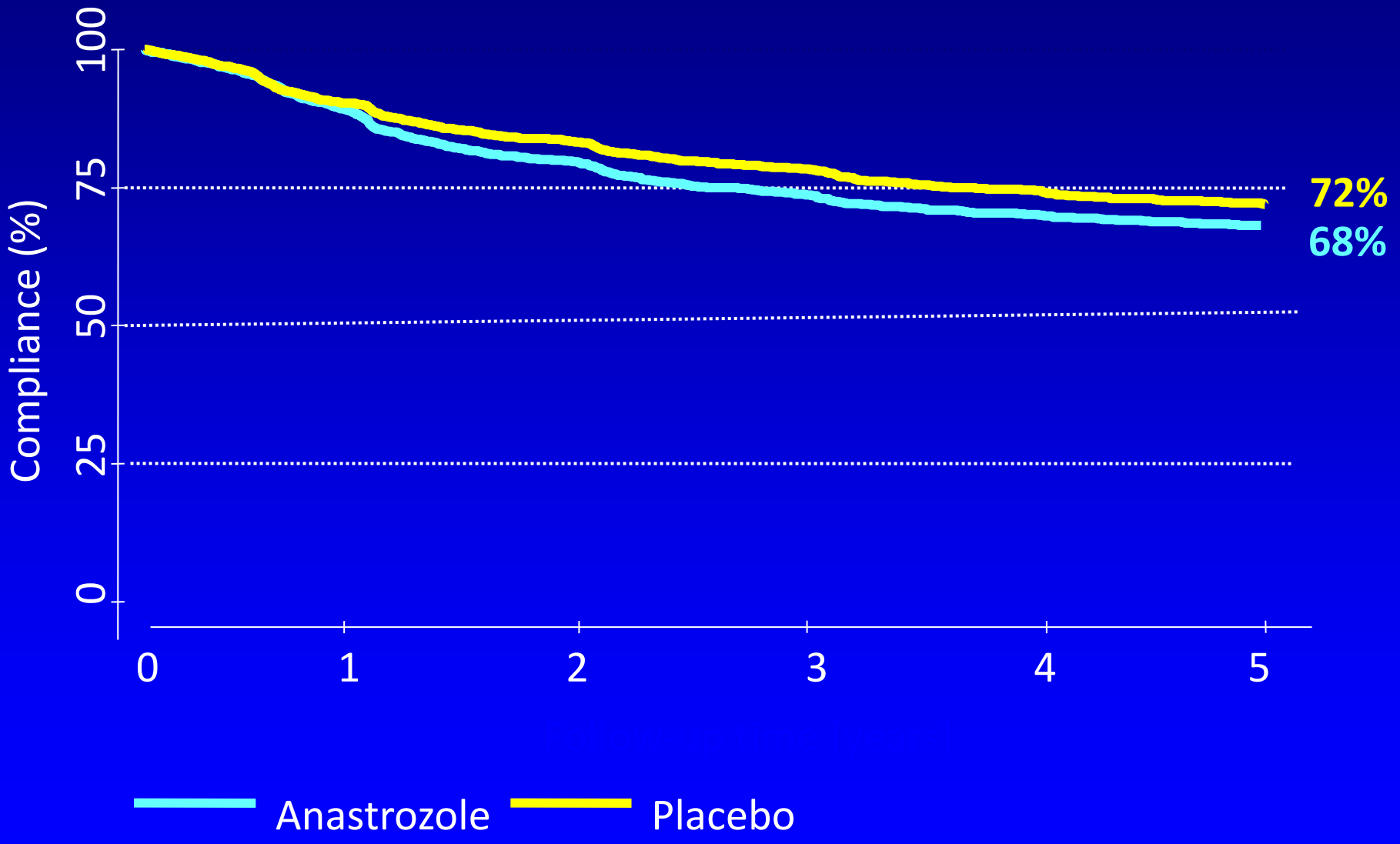


Number at risk

1944	1927	1645	1445	1241	975	706	506
1920	1909	1654	1463	1264	978	720	516

Cuzick *et al* Lancet 2014

Compliance



Fractures/Musculoskeletal

	Anastrozole vs Placebo (Patients (%))	RR (95% CI)
Fractures	164 (8.5%) vs 149 (7.7%)	1.11 (0.90-1.38)

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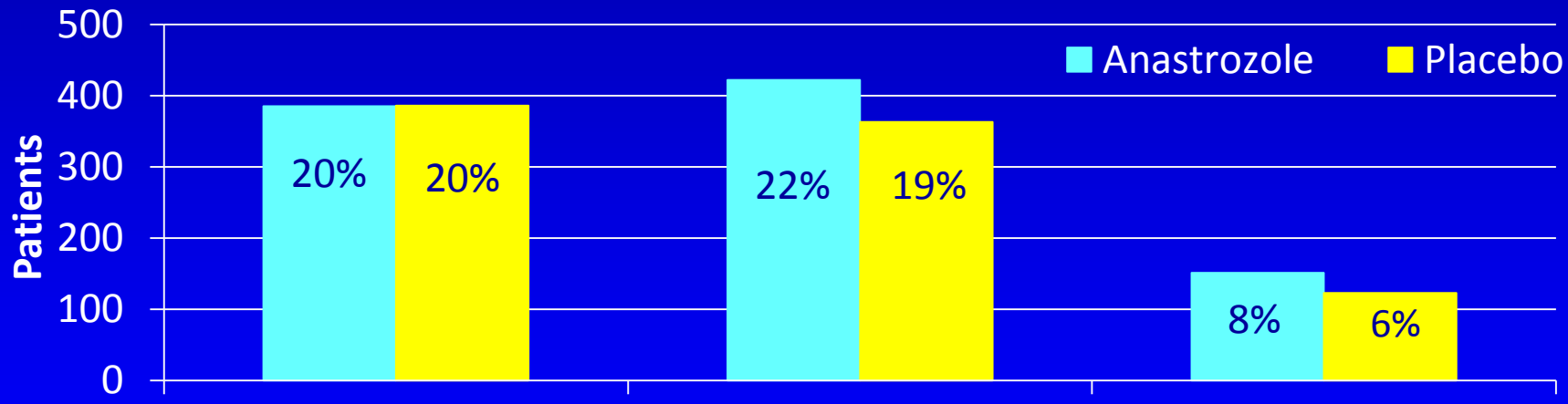
Musculoskeletal	1226 (63.9%) vs 1124 (57.8%)	1.10 (1.05-1.16)
Arthralgia	972 vs 894	1.10 (1.03-1.18)



Summary & Conclusions

- Substantial 53% reduction provides convincing evidence for effectiveness of anastrozole
- Small increase in fractures
  8.5% vs 7.7% (not significant)
- Significant increase (10%) in musculoskeletal adverse events with anastrozole
  High rate also seen with placebo (57.8%)
- Unexpected reduction in other cancers
- Results provide strong support for the use of anastrozole in high risk postmenopausal women
- Long-term follow-up essential to determine full risk and