

# Breast Cancer Risk Assessment Using the Tyrer-Cuzick Model

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# Disclosures

- I receive royalties through Cancer Research UK for commercial use of the Tyrer-Cuzick algorithm.

# Older Models

## GAIL / BCRAT

1st degree relatives (0,1,2+)

Age at menarche

Age at 1st live birth

No. breast biopsies

Atypical hyperplasia

Race/Ethnicity

## CLAUS

No. affected relatives

Degree of relationship

Age of onset

Paternal relatives

Ovarian cancer

BRCA1/2 testing

*Gail et al, JNCI, 1989.*

*Claus et al, Am J Epidemiol, 1990.*

# Breast Cancer Surveillance Consortium Model

Based on SEER mammographic screening database (Breast Cancer Surveillance Consortium)

## Factors included

Age

Race/Ethnicity

Family history

History of Benign Biopsy

Mammographic density by BIRADS

(Tice et al Ann Intern Med, 2008)

# BOADICEA Model

- Developed for high risk families with multiple cases
  - Details of breast and ovarian cancer and dominant gene testing in first and second degree relatives
- Current versions also add some other factors, but not complete
- Validation study not yet reported

# Tyrer – Cuzick Model

Initial version - Variables in Gail and Claus models - plus

Weight

HRT

Bilaterality

(Tyrer, Duffy, Cuzick, Stat in Med (2004))

# New developments – 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

# Major Risk Models - Target Populations

Gail Model – normal risk

BC Consortium model – normal risk

Claus / BRCAPRO/BOADICEA – very high risk

Tyrer/Cuzick – moderately increased risk



# Major Factors

Family history

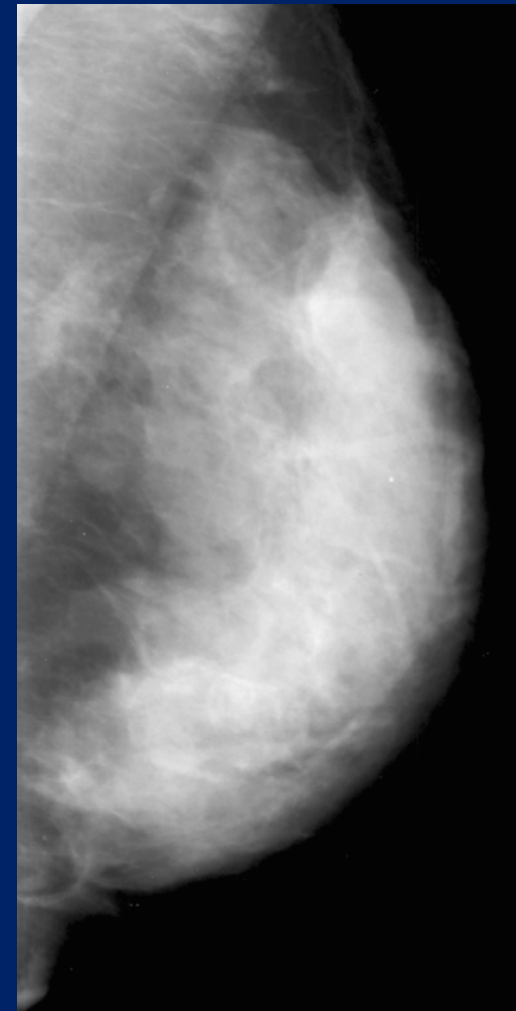
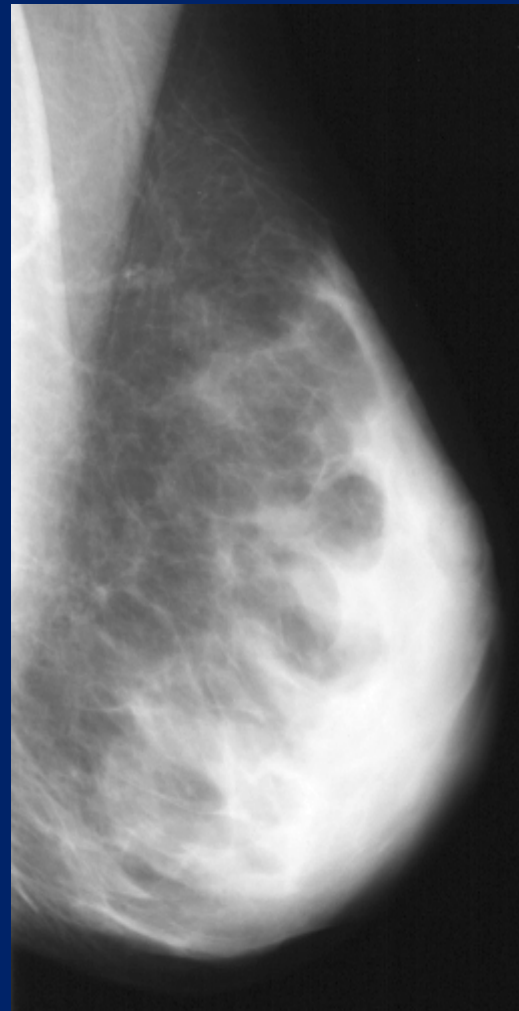
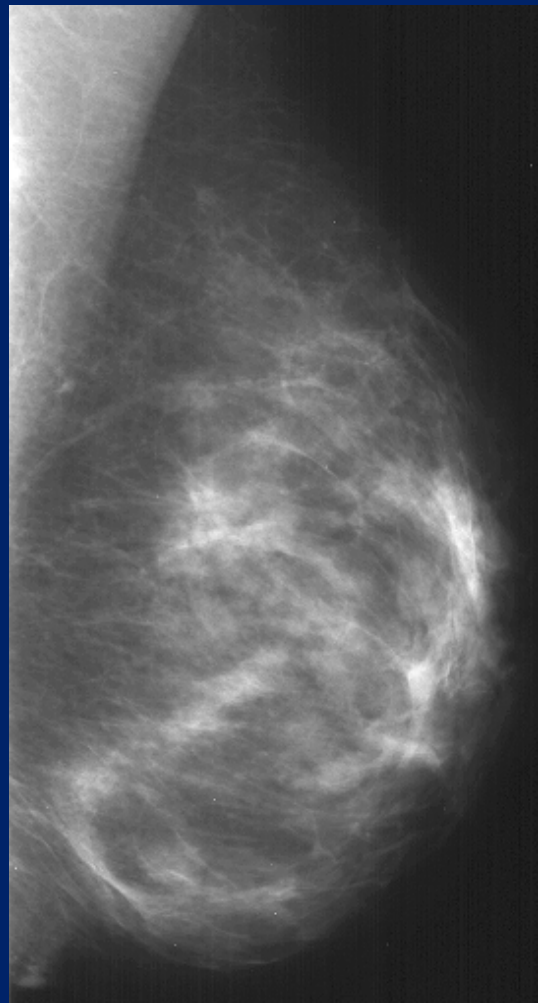
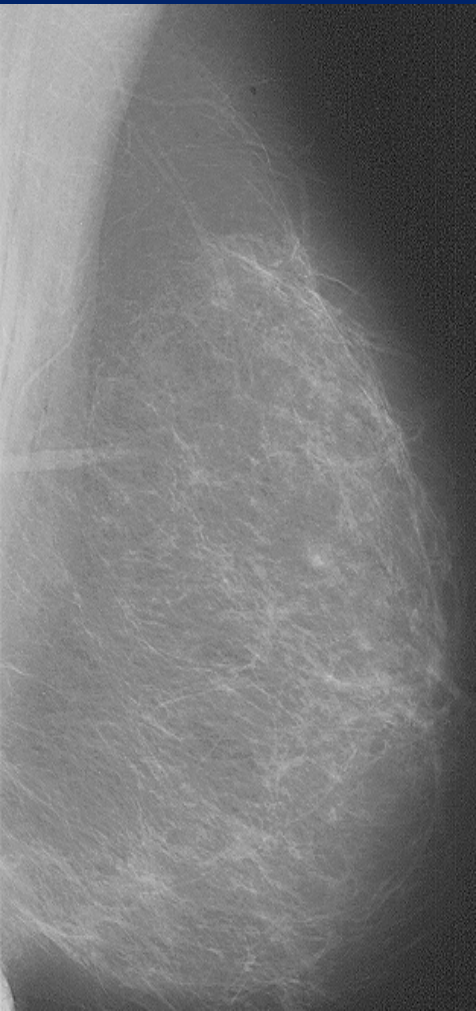
Reproductive/ Hormonal

Benign Pathology

Mammographic Density

Polygenic (SNP) risk score

# Mammographic Density



# Mammographic Density and Risk of Breast Cancer

	Case (N = 1112)	Control (%) (N = 1112)	Odds Ratio (95% CI)
< 10%	230	362 (32.6)	1.0
10 to < 25%	272	270 (24.3)	1.8 (1.4-2.2)
25 to < 50%	336	290 (26.1)	2.1 (1.6-2.6)
50 to < 75%	178	144 (12.9)	2.4 (1.8-3.3)
≥ 75%	96	46 (4.1)	4.7 (3.0-7.4)
P value (trend)			< 0.001

# IBIS – 1 - high risk Baseline Density

Variable	Category (%)	OR <sup>†</sup> Breast cancer	95% CI	z (linear trend)	P-value
Breast density at entry	0	Ref	-	3.22	0.001
	1-10	1.69	0.64-4.42		
	11-25	2.24	0.91-5.47		
	26-50	1.58	0.66-3.77		
	51-75	2.67	1.13-6.31		
	76-100	3.93	1.64-9.43		

<sup>†</sup> adjusted for age at entry, bmi(continuous) and treatment

# 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 <sup>2</sup> (heterogeneity) = 8.32, p=0.004			

†Adjusted for age and density at entry, and bmi

# Tyrer – Cuzick Version 8

Untitled - IBIS Risk Evaluator

File Edit View Tools Help

Add Del Risk Sort Find

**Personal factors**

Woman's age:  Menarche:  Height (m):  Weight (kg):  Measurements: Metric:  Imperial:

Nulliparous:  Parous:  Unknown:  Age at Menopause:  Age First Child:

No prior biopsy / no proliferative disease:  Prior biopsy, result unknown:  Hyperplasia (not atypia):  Atypical hyperplasia:  Lobular Carcinoma in Situ (LCIS):

Premenopausal:  Perimenopausal:  Postmenopausal:  No information:

Ovarian cancer:

Patient id:  no.:  **Calculate Risk**

Competing mortality:  **Risk Options**

HRT use Length of use (years):

Never:  5 or more years ago:  Less than 5 years ago:  Current user:

Mammographic density (age 40+):   % Volpara® Volumetric Density\*  % VAS Percentage Density\*  BI-RADS® ATLAS Density\*

Ashkenazi inheritance:  **Show start up screen**

Mother: Ovarian:  Bilateral:  Breast cancer:  Age:

Sisters: Number:  Ovarian:  Bilateral:  Breast cancer:  Age:   

Paternal Gran: Ovarian:  Breast cancer:  Age:

Maternal Gran: Ovarian:  Breast cancer:  Age:

Paternal aunts: Number:  Ovarian:  Bilateral:  Breast cancer:  Age:  

Maternal aunts: Number:  Ovarian:  Bilateral:  Breast cancer:  Age:  

Daughters: Number:  Ovarian:  Bilateral:  Breast cancer:  Age:  

Genetic Testing

Male relatives

Half Sisters

Affected cousins

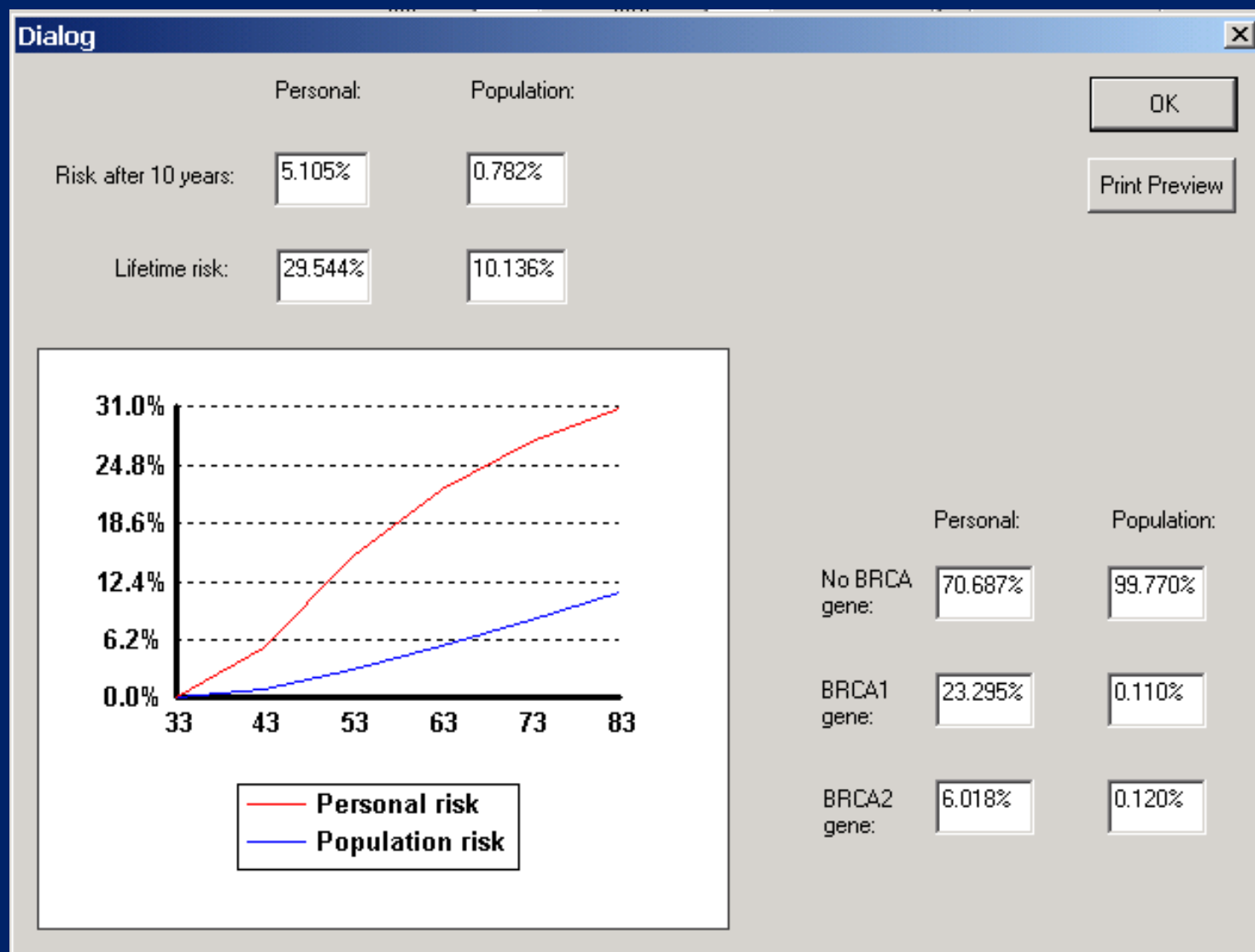
Affected Nieces

**View Family History**

IBIS Risk Evaluator v8.0b

Ready

# Displaying the predictions



# Model review

## Age-specific incidence

First invasive breast cancer (England cancer registries)

More country specific baseline hazards (and potentially ethnic)

## Family history

*BRCA1/2* penetrance (based on Antoniou *et al* Br J Cancer 2008)

`Unknown' dominant gene (modelled to fit data)

## Other risk factors

Relative hazards, independent except for atypia/LCIS

From literature, preference for large overview studies that adjust for other risk factors



# Incorporating density into risk models

- All density measures strongly correlated with age, body mass index (BMI)
- Use a density residual
  - observed minus expected density given age and BMI
  - BI-RADS groups treated as integers

# Manchester cohort - VAS (PROCAS)

Principle Investigator: Gareth Evans

- 50,628 women attending three-yearly screening aged 47–73y from Manchester UK, recruited 2009-13
- Risk assessment questionnaire
- Density from various methods, primary was visual % dense from 2 readers

# KARMA cohort

Principle Investigator: Per Hall

- 70,877 women attending bi-annual screening aged 40-74y in four Swedish hospitals, entry 2011-13
- Self-reported risk questionnaire, Volumetric density (Volpara) at entry

# U Virginia (UVa) case-control study

Principle Investigator: Jennifer Harvey

- 480 cases and 2299 controls aged 40-79 years attending screening in Virginia
- Self-reported classical risk factors from women 2012-13
- Mammogram closest to questionnaire

# BCSC Washington cohort

Principal Investigators Erin Bowles, Diana Buist

- 105,558 women aged 40-73y in Kaiser Permanente Washington registry (formerly Group Health) with 2+ screens
- First risk questionnaire and BI-RADS density 1996-2013, updated each screening episode
- 2,877 invasive cancers to 2014 (median follow up 7.4y)

# 3 Volumetric Density Studies

Study	Visual Assessment Score	Volumetric density (Volpara)	BI-RADS density
<b>1. PROCAS</b> UK cohort	✓	✓	
<b>2. KARMA</b> Swedish cohort		✓	
<b>3. UVa</b> US case-control		✓	✓
<b>4. BCSC Washn</b> US cohort			✓

# Visual assessment score

## Inter-quartile range odds ratio (IQ-OR)

### PROCAS

697 breast cancers with median 3.2y follow-up

- Tyrer-Cuzick model  
**1.36** 95%CI (1.25–1.48)
- Density residual  
**1.48** 95%CI (1.34–1.63)
- Density residual adjusted for Tyrer-Cuzick  
**1.47** 95%CI (1.33–1.62)

# Volumetric density residual risk: IQ-OR (adjusted for TC)

## Cohorts

PROCAS: **1.48** (95%CI 1.30 - 1.69)

KARMA: **1.82** (95%CI 1.65 - 2.00)

## Case-control

UVa: **1.40** (95%CI 1.22 – 1.61)



# Volumetric vs BI-RADS Density measures

Study	Visual Assessment Score	Volumetric density (Volpara)	BI-RADS density
1. <i>PROCAS</i> UK cohort	✓	✓	
2. <i>KARMA</i> Swedish cohort		✓	
3. <i>UVa</i> US case-control		✓	✓
4. <i>BCSC Washn</i> US cohort			✓

# BI-RADS density risk (IQ-RR) (after adjustment age, BMI, TC)

UVa (IQ-OR):

**1.51** (95%CI 1.30 – 1.77)

BCSC Washington (IQ-HR)

**1.51** (95%CI 1.44 – 1.59)

# Volumetric vs BI-RADS density risk (IQ-OR)

U Virginia - Adjusted for age, BMI, TC

Volumetric density

**1.40** (95%CI 1.22 – 1.61)

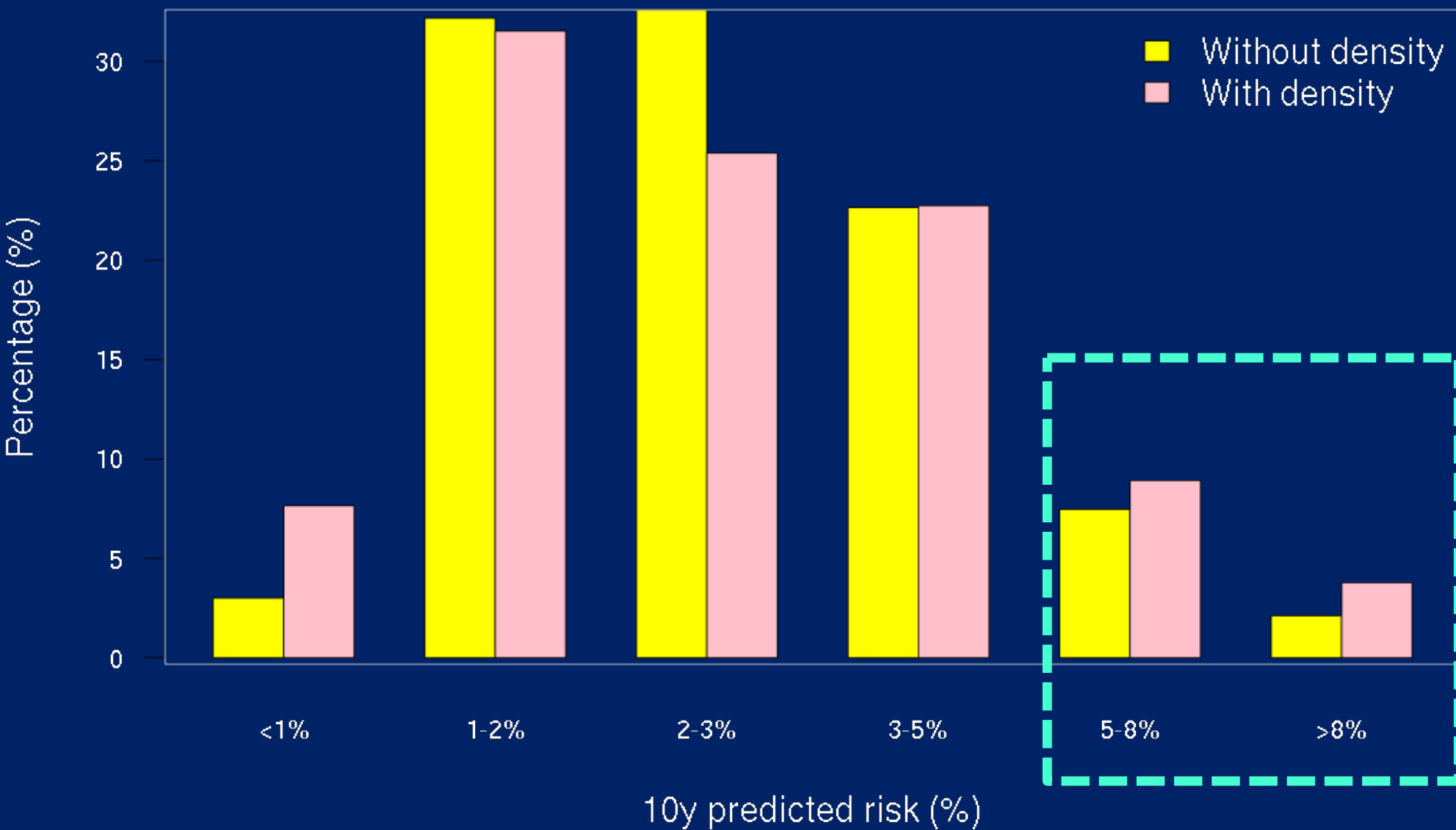
BI-RADS density

**1.51** (95%CI 1.30 – 1.77)

$P_{\text{diff}} = 0.21$

# BCSC Washington cohort

## BiRads



# BCSC Washington cohort

- Incorporating breast density **improved predictive power by 50%** (LR- $\chi^2$  496 to 754)
- **Accurately identified more high-risk women (>8% 10y risk)**
  - without density**  $n=2228$ , **2.1%** of women, 159 cancers, O/E 0.96 (95%CI 0.82-1.12), 10y incidence rate 9.7%
  - with density**  $n=3986$ , **3.8%** of women, 291 cancers, O/E 0.93 (0.83-1.05), 10y incidence rate 10.0%

# Density and SNPs Combined

# Single nucleotide polymorphism (SNP) risk scores

- ~150 independent single nucleotide polymorphisms associated weakly with risk
- Common, with small risks individually
- Risk panels have good potential to stratify risk

# Density and SNPs combined

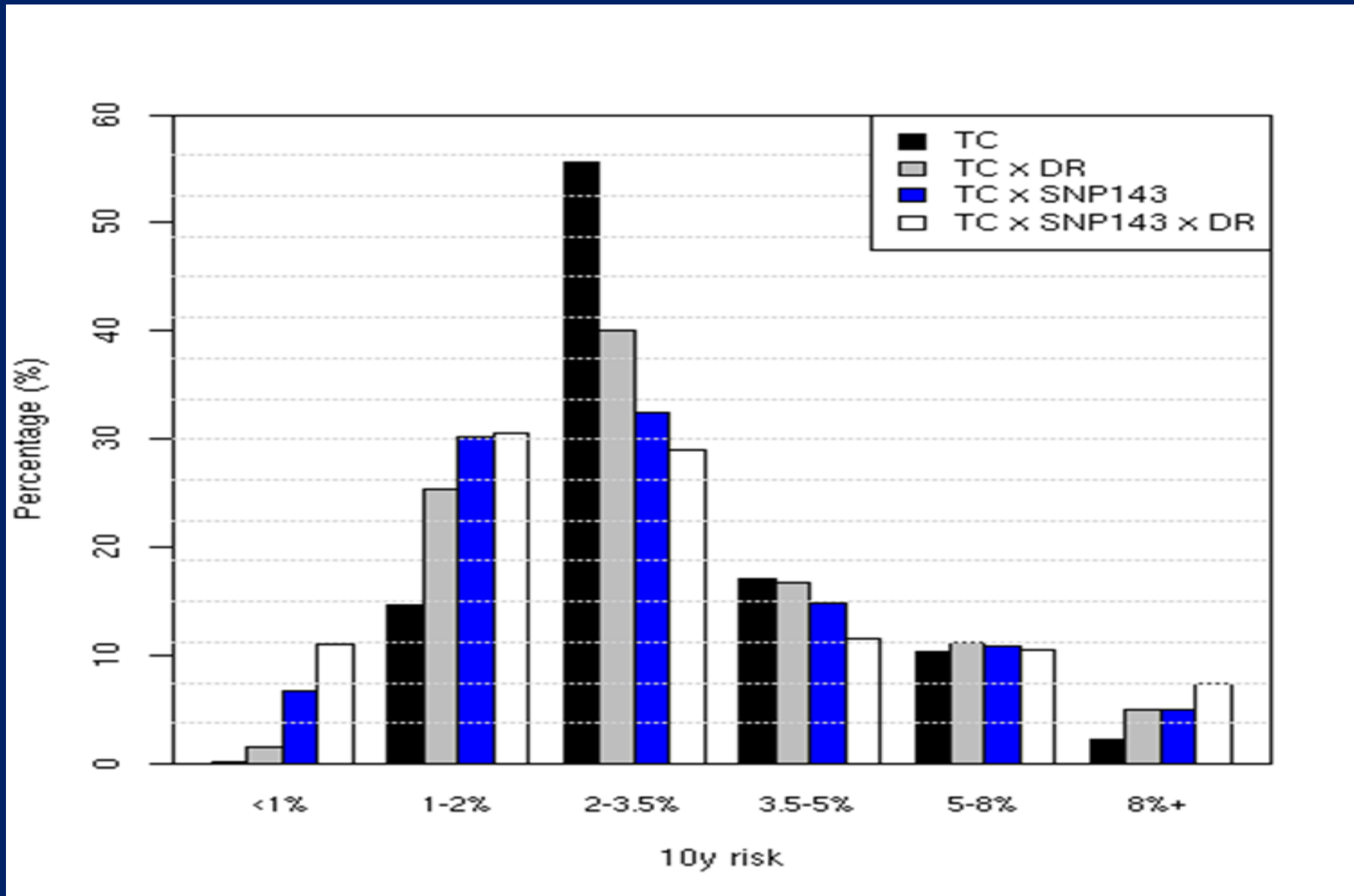
- Case-control study in nested in PROCAS screening cohort, Manchester UK
- 466 cases diagnosed after questionnaire; 8896 controls
- SNP18 : first 18 SNPs discovered (strongest)
- Density: Visual Assessment



# Density and SNPs combined

- Adj Density residual **1.47** 95%CI (1.33–1.62)
- SNP18, IQ-OR
  - Unadjusted **1.56** (95%CI 1.38 - 1.77)
  - Adjusted (TC+D) **1.53** (95%CI 1.38 - 1.77)
- calibration SNP18
  - Adjusted OR slope = **0.98** (95%CI 0.69 - 1.28)

# 10-year risk of breast cancer in a screening population using questionnaire factors only (TC), and with a mammographic breast density residual (DR) and/or a 143 gene SNP panel



# SNP88 in Prevention Trials

- Overall

**IQ-OR**      **1.37**    (95%CI 1.14 - 1.66)

**Calibration - Slope**    **0.46** (95%CI 0.19- 0.74)

- No interaction by treatment arm ( $P_{\text{het}} = 0.5$ )

- Tamoxifen IQ-OR      1.25

- Placebo IQ-OR        1.46

# IBIS-1 & Marsden

## Re-classification of cases

by 8% 10y risk groups from TC alone

and when combined with a re-calibrated SNP88 score

	TC x SNP88 risk		
TC risk	<8%	>8%	Total
<8%	225/702 (32%)	40/85 (47%)	265/787 (34%)
>8%	11/44 (25%)	83/164 (51%)	94/208 (45%)
Total	236/746 (32%)	123/249 (49%)	359/995 (36%)

# Better Measures than Density

Wang C, Brentnall AR, Cuzick J, Harkness EF, Evans DG, Astley S.

A novel and fully automated mammographic texture analysis for risk prediction: results from two case-control studies

Breast Cancer Res. 2017 Oct 18;19(1):114

Gray level Co-occurrence Matrix (GLCM) - local texture features

Sum average of square of neighbouring pixels

RESULTS. The strongest features identified in the training set were "sum average" based on the grey-level co-occurrence matrix at low image resolutions (original resolution 10.628 pixels per mm; downsized by factors of 16, 32 and 64), which had a better deviance and mC than volumetric PD. In the validation study, the risk score combining the three sum average features achieved a better deviance than volumetric PD ( $\Delta\chi^2 = 10.55$  or  $6.95$  if logarithm PD) and a similar mC to volumetric PD (0.58 and 0.57, respectively). The risk score added independent information to volumetric PD ( $\Delta\chi^2 = 14.38$ ,  $p = 0.0008$ ).