MANCHESTER 1824

The University of Manchester

NHS National Institute for Health Research

Central Manchester University Hospitals NHS
NHS Foundation Trust

Risk estimation and stratified screening: Is this the way forward?

Predicting Risk Of Cancer At Screening

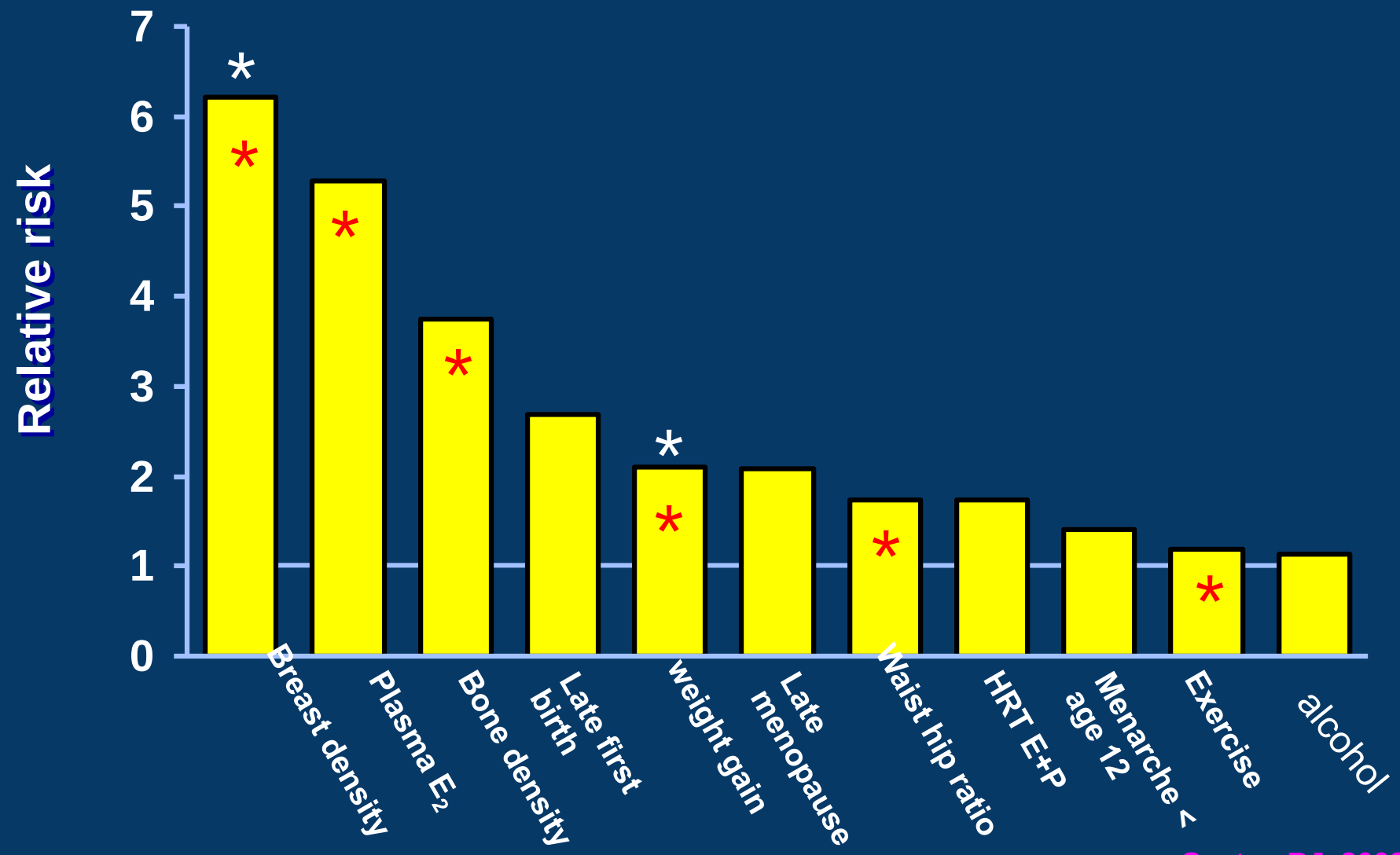
D Gareth Evans

UHSM Your Hospital

genesis preventing breast cancer

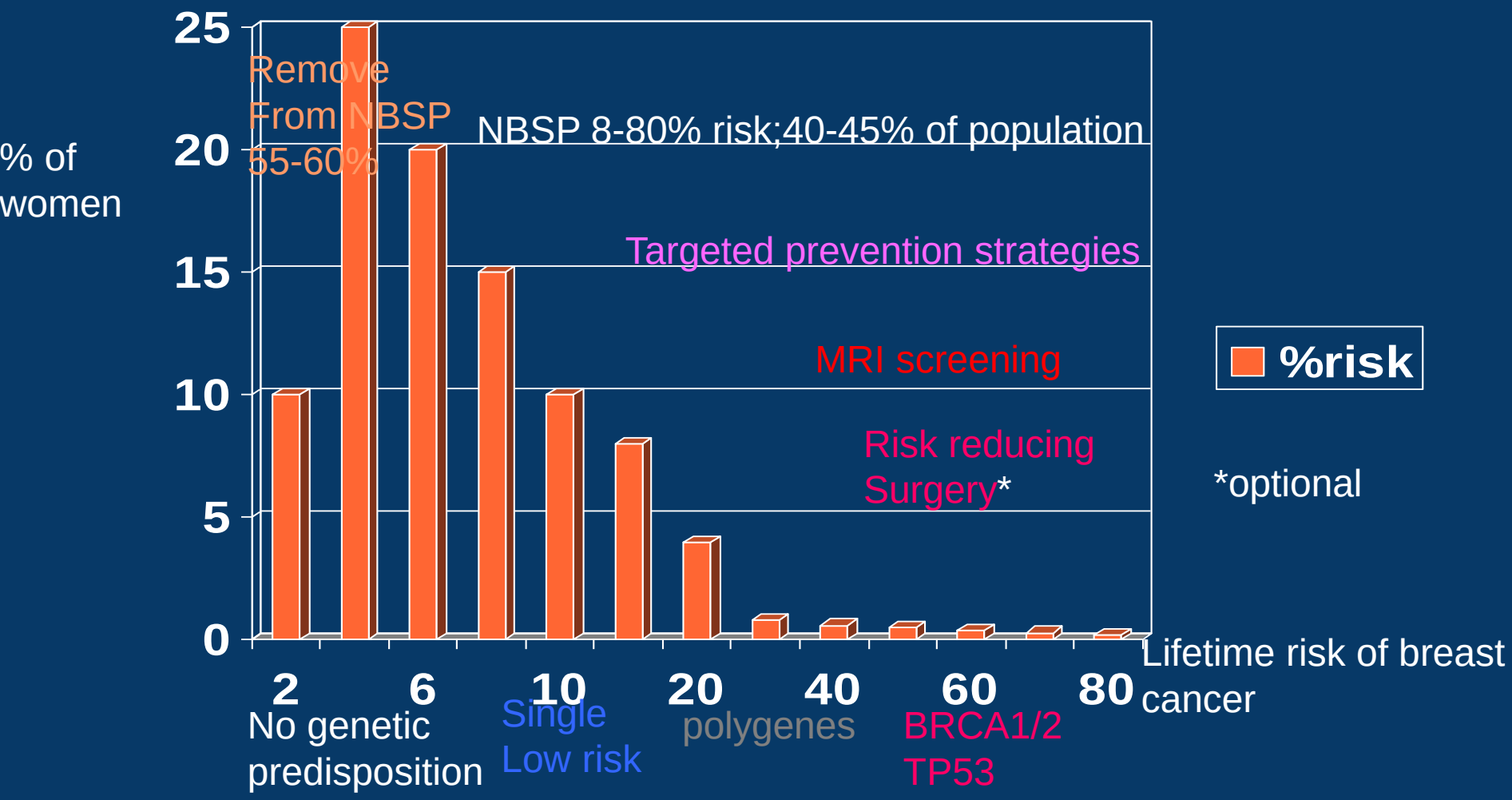
The Christie NHS
NHS Foundation Trust

Potential risk factors* & factors to be investigated* for inclusion in a model



Santen RJ, 2003.

Breast cancer risk in general population



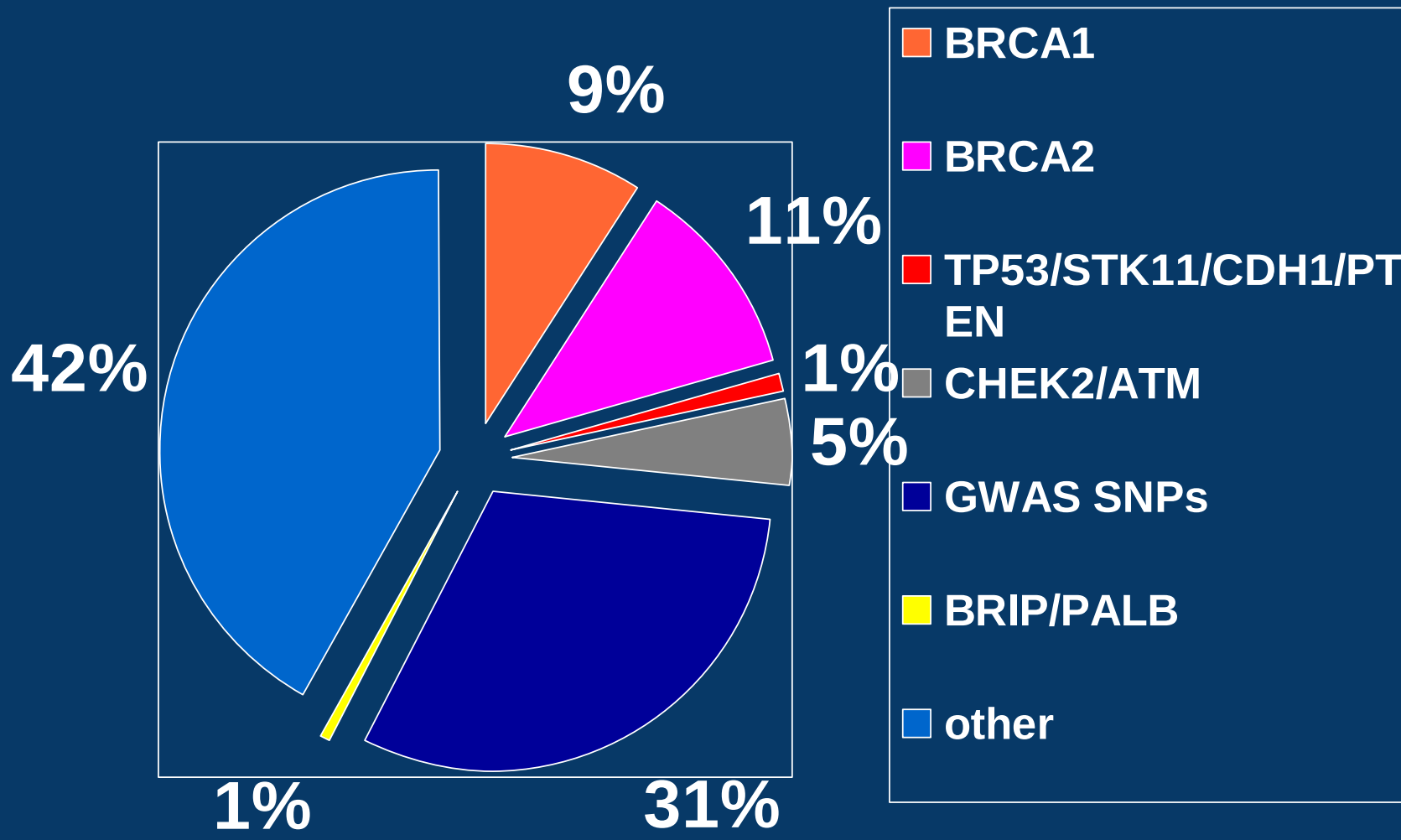
Targeted screening and prevention based on risk

Family History & Genetics

- Number of affected family members, and age of developing breast cancer.
- BRCA1 & BRCA2 gene mutations
- Genetic variants – currently >100 known genetic variants that can increase the risk of breast cancer by between 5-30%

Genesis
creating a future without breast cancer

Proportion of familial breast cancer 2016



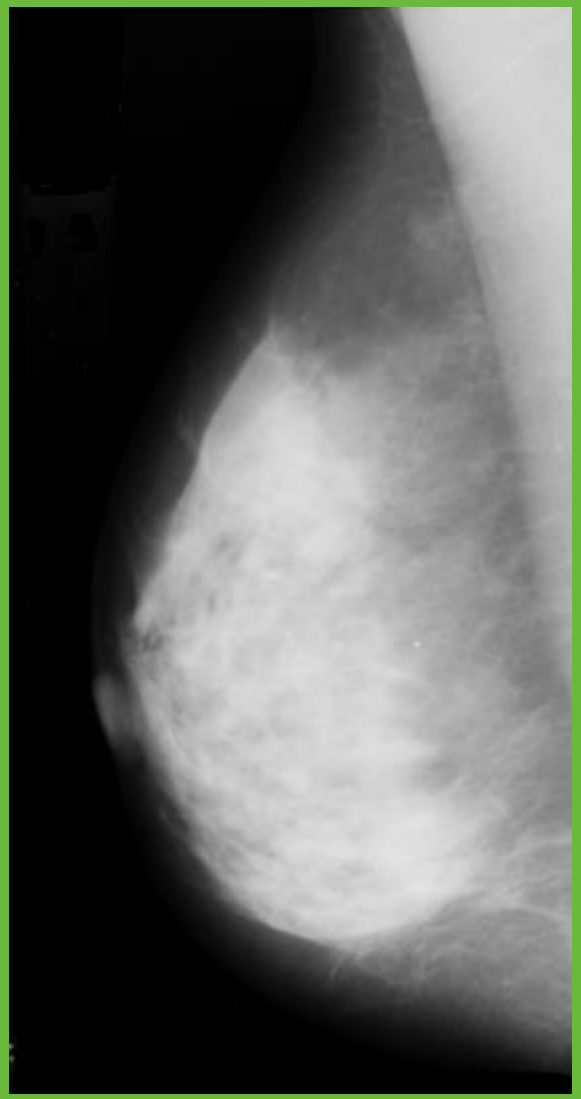
Breast Density

- Increased breast density increases risk of breast cancer.
- After family history and age this is the largest risk factor.
- Breast density is assessed from mammograms.
- There are a number of different methods for assessing breast density, but these methods need validating.

Mammographic Density

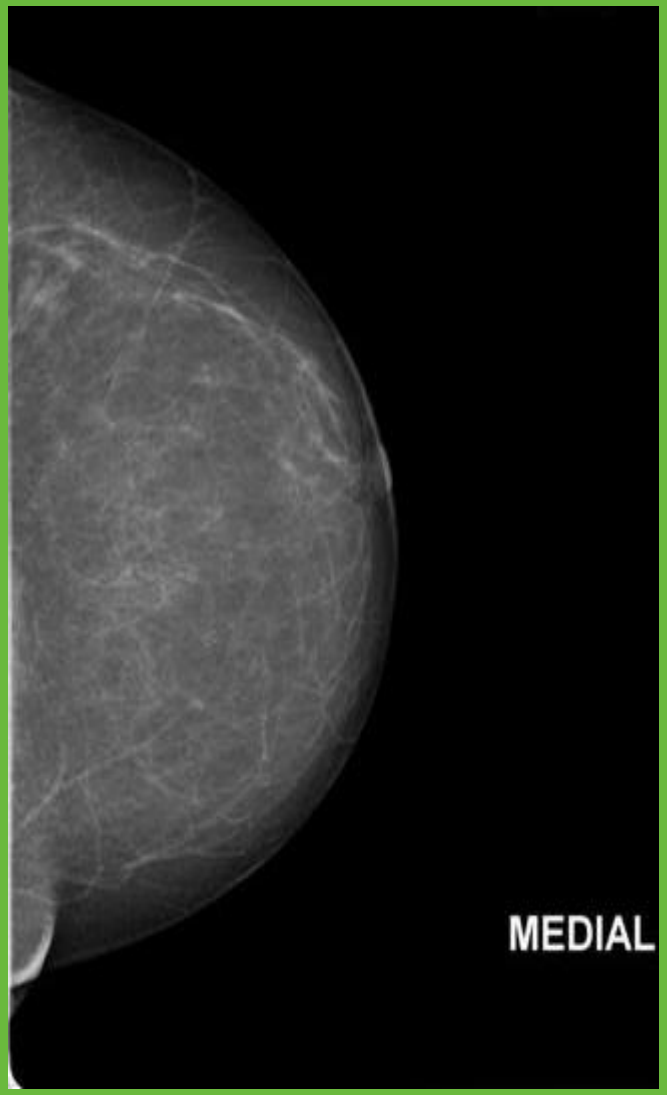
Dense breast

Lifetime risk 25%



Non dense breast

Lifetime risk 4%



Aims of the PROCAS study

- To determine whether it is feasible to incorporate personal breast cancer risk prediction into NHS BSP
- Alter mammographic screening interval based on each woman's personal risk of cancer
- Introduce preventive measures for women who are high risk

Genesis
creating a future without breast cancer

PROCAS Summary

- 60,000 women, who attend NHS BSP in Greater Manchester will take part.
- Information on lifestyle and family history will be collected from a study questionnaire.
- Breast density assessments will be carried out.
- 10,000 of the 60,000 women will have genetic testing.
- This information will be incorporated to predict each woman's individual breast cancer risk

MANCHESTER 1824

The University of Manchester

Breast Density

- Breast density results will be obtained from 2 mammograms (Y1 and Y3) for each woman.
- We will use a number of breast density assessment methods and determine which is best for use within NHS BSP.

Genesis
creating a future without breast cancer

PROCAS Study Questionnaire

Collects information on:

- Family history
- Age at menarche
- Parity
- Age at first full term pregnancy
- Age menopause
- HRT use
- BMI
- Alcohol intake
- Exercise

Genesis
creating a future without breast cancer

DNA testing

Genesis
creating a future without breast cancer

- Carried out at Withington Community Hospital
- Participants provided with a saliva sample collection kit

- Collect sample (approx 5 min) seal and post to laboratory
- Laboratory extract DNA
- St Mary's Hospital, Manchester carry out analysis to look for genetic variants

MANCHESTER 1824

The University of Manchester

DNA testing

- 10,000 participants will be invited to have DNA testing
- Laboratory extract DNA
- St Mary's Hospital, Manchester
- carry out analysis to look for
- genetic variants
- 10,000 recruited

MANCHESTER 1824

The University of Manchester

Flowchart

Invitation letter sent

↓

Consent taken & questionnaire completed

↓

Mammogram 1 performed

↓

OPTIONAL - DNA sample collected (10,000/60,000)

↓

Initial risk calculation (Tyrer-Cuzick)

↓

High risk & selection of low risk women informed of risk (if opted to receive risk information)

↓

Mammogram 2 performed

↓

Breast density results, questionnaire results & DNA results (if applicable) combined to give re-adjusted risk score

MANCHESTER 1824

The University of Manchester

Recruitment

Number recruited 01/03/2015 – 57,432

- Uptake year 1: 35%
- Uptake year 2: 43%
- Uptake year 3: 37%
- Uptake year 4 47%

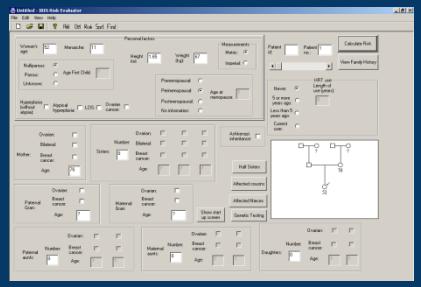
- Year 2 uptake amongst first attendees aged

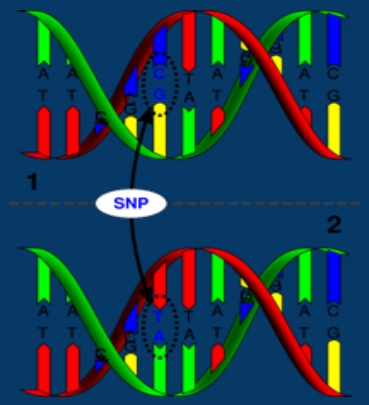
47-52- 52%

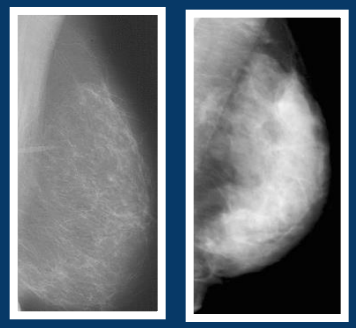
- Uptake when study staff present 60%

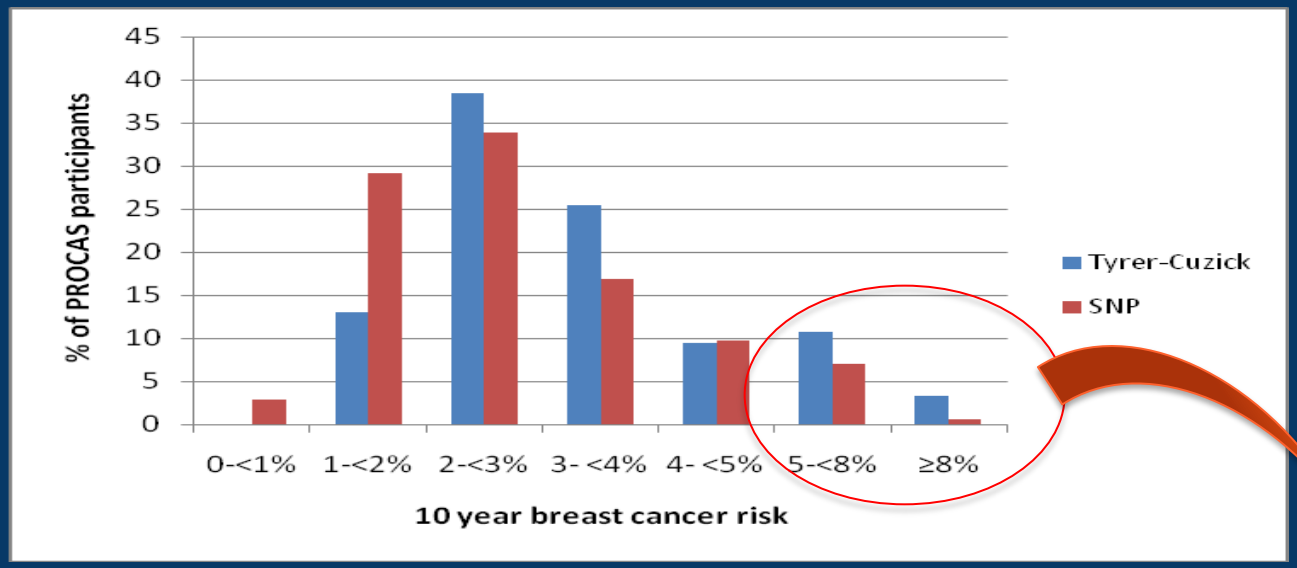
PRediction Of Cancer At Screening (PROCAS)

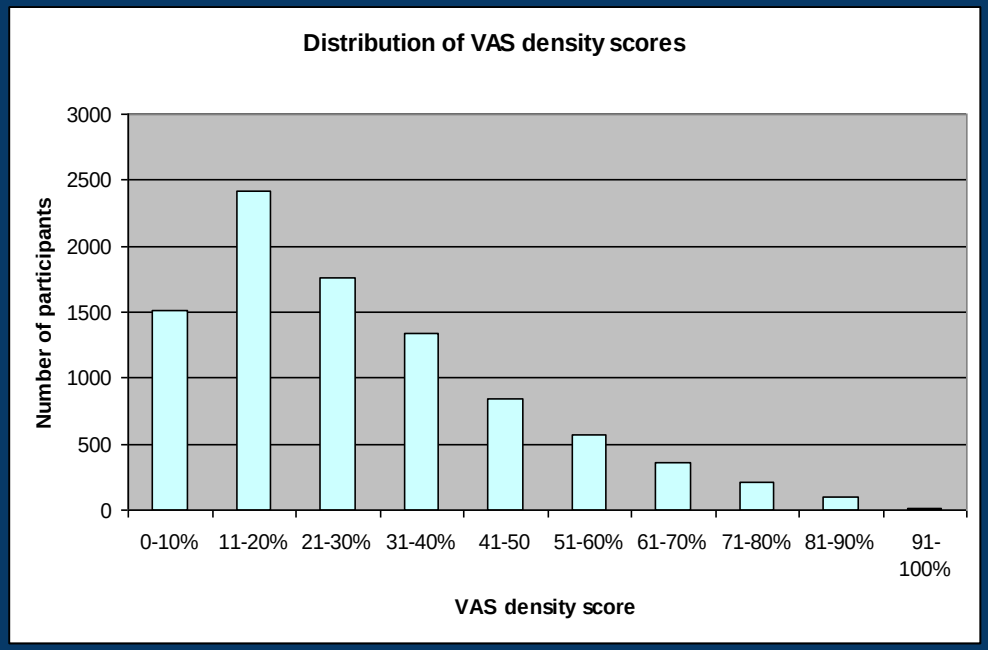
NHS
National Institute for Health Research







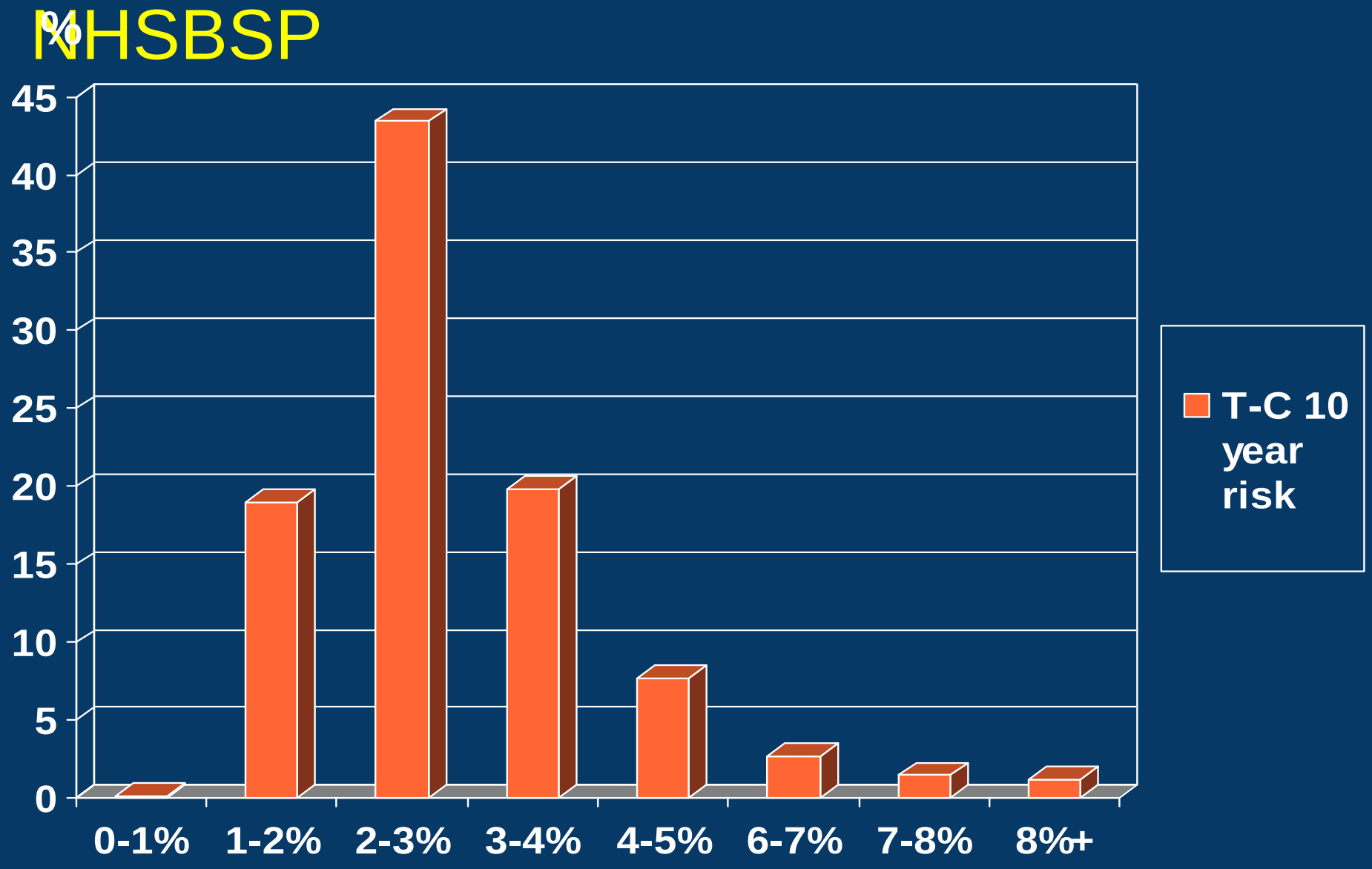




Offer interventions

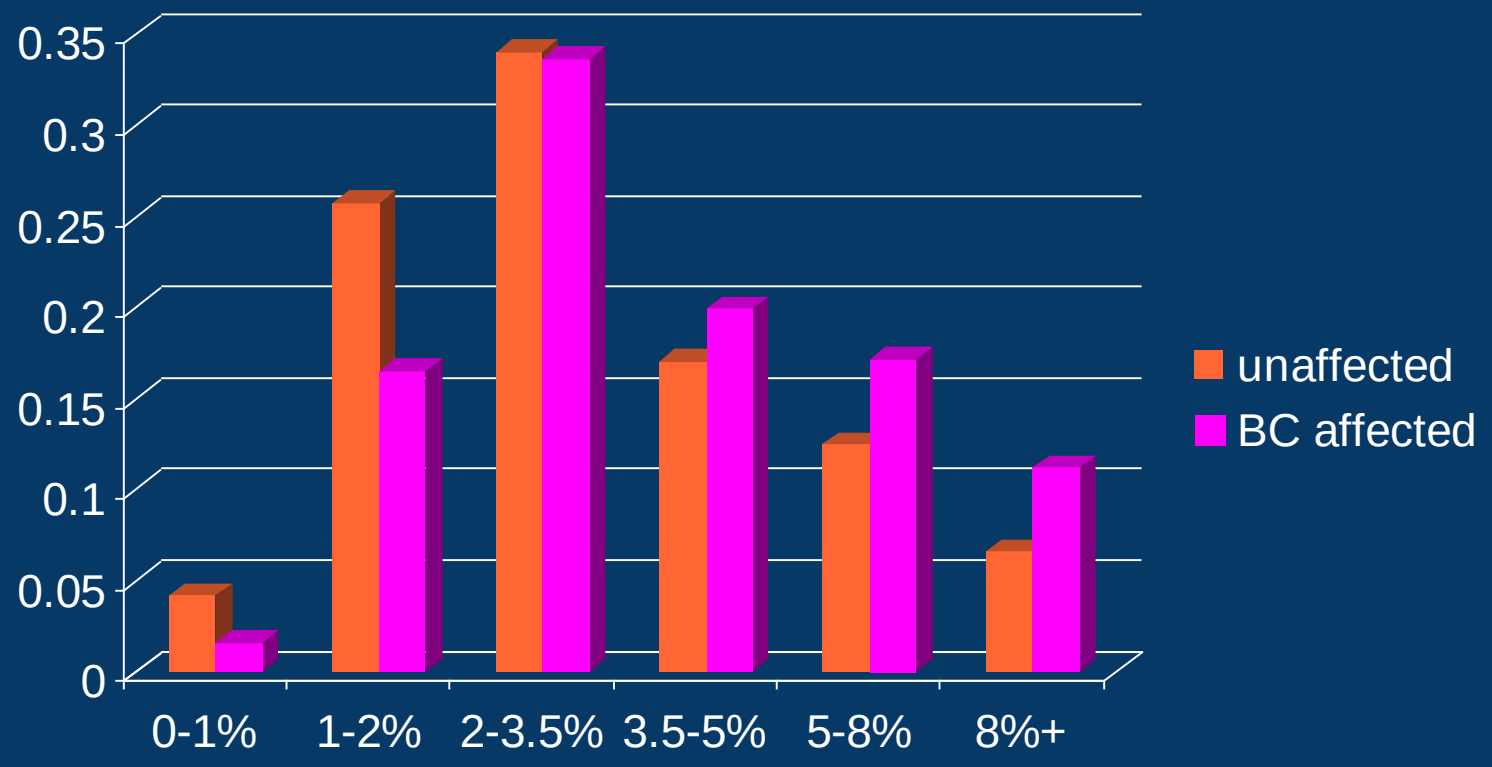
Cuzick et al Lancet 2014
Harvie et al BJN 2013

Tyrer-Cuzick risk in 53594 women in NHSBSP

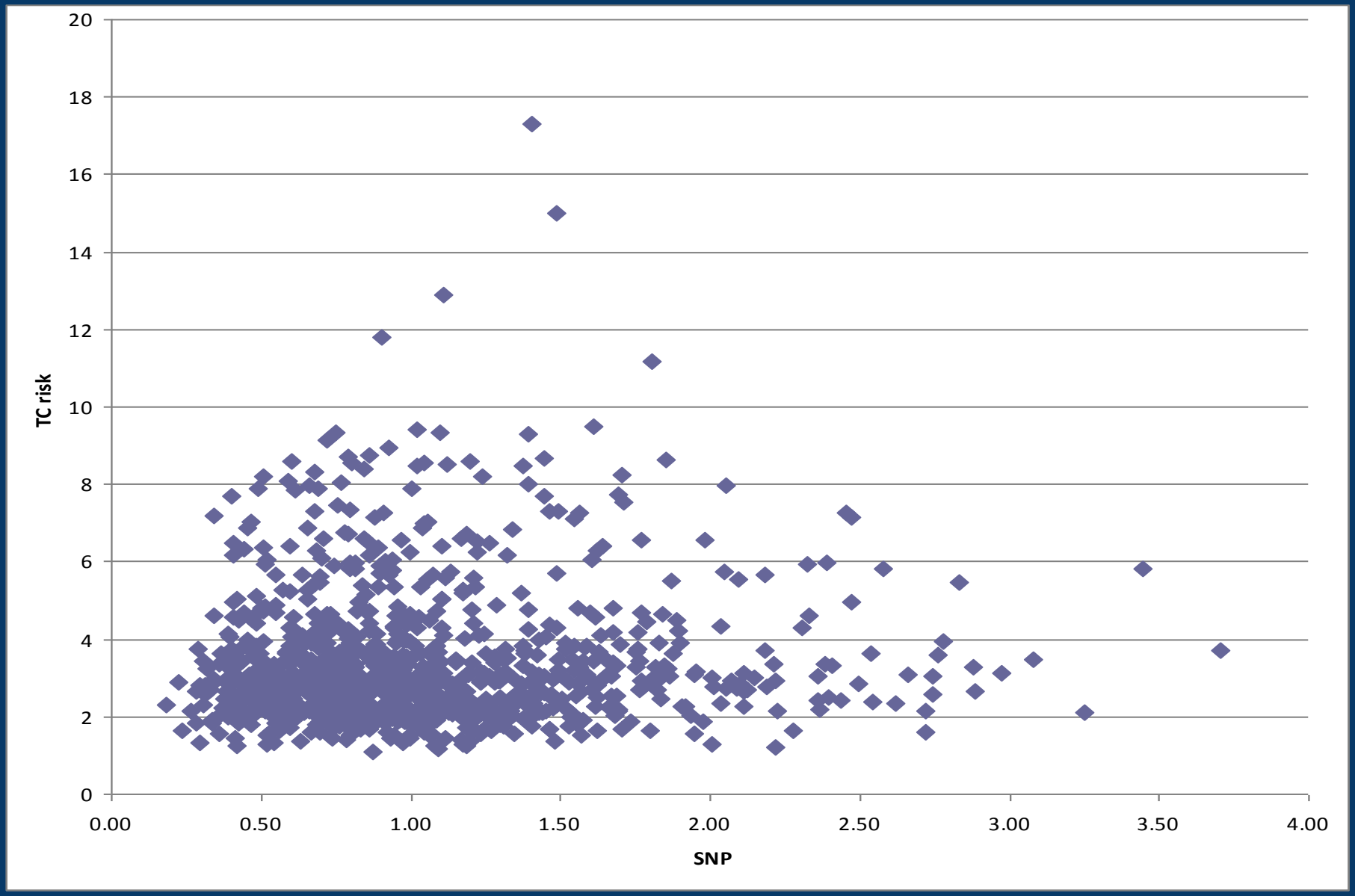


SNP	gene	risk e	RA F	weight 0	weight 1	weight 2	0 freq	1 freq	2 freq	RR	W*F
rs2981579	FGFR2	T	42	0.72	1.03	1.47	34	49	17	1.43	100
rs10931936	CASP8	C	74	1.20	1.06	0.93	7	38	55	0.88	100
rs3803662	TOX3	T	26	0.86	1.12	1.45	55	38	7	1.3	100
rs889312	MAP3K	C	28	0.89	1.08	1.32	52	40	8	1.22	100
rs13387042	2q	A	49	0.82	0.99	1.20	26	50	24	1.21	100
rs1011970	cdkn2a	T	16	0.94	1.12	1.35	70	27	3	1.2	100
rs704010	10q22	A	39	0.89	1.03	1.18	37	48	15	1.15	100
rs6504950	cox11	G	73	0.87	0.96	1.05	7	40	53	1.1	100
rs11249433	notch	C	42	0.94	1.01	1.09	34	48.5	17.5	1.08	100
rs614367	11q13	T	15	0.92	1.19	1.55	72	26	2	1.3	100
rs10995190	10q21	G	86	0.61	0.81	1.07	2	24	74	1.32	100
rs4973768	3p24 SLC	*T*	47	0.87	1.00	1.16	28	50	22	1.16	100
rs3757318	*ESR1*	A	7	0.96	1.25	1.62	86.5	13	0.5	1.3	100
rs1562430	8q24	G	42	1.14	0.97	0.82	33.5	49	17.5	0.85	100
rs8009944	*RAD51L 1*	A	75	1.21	1.06	0.94	6	38	56	0.88	100
rs909116	*LSP1*	T	53	0.84	0.98	1.15	22	50	28	1.17	100
rs9790879	*5p12*	C	40	0.92	1.02	1.12	36	48	16	1.1	100
rs1156287	*COX11*	A	71	0.87	0.96	1.05	8.5	41	50.5	1.1	100
rs713588	*10q*	A	60	1.19	1.02	0.88	16	48	36	0.86	100

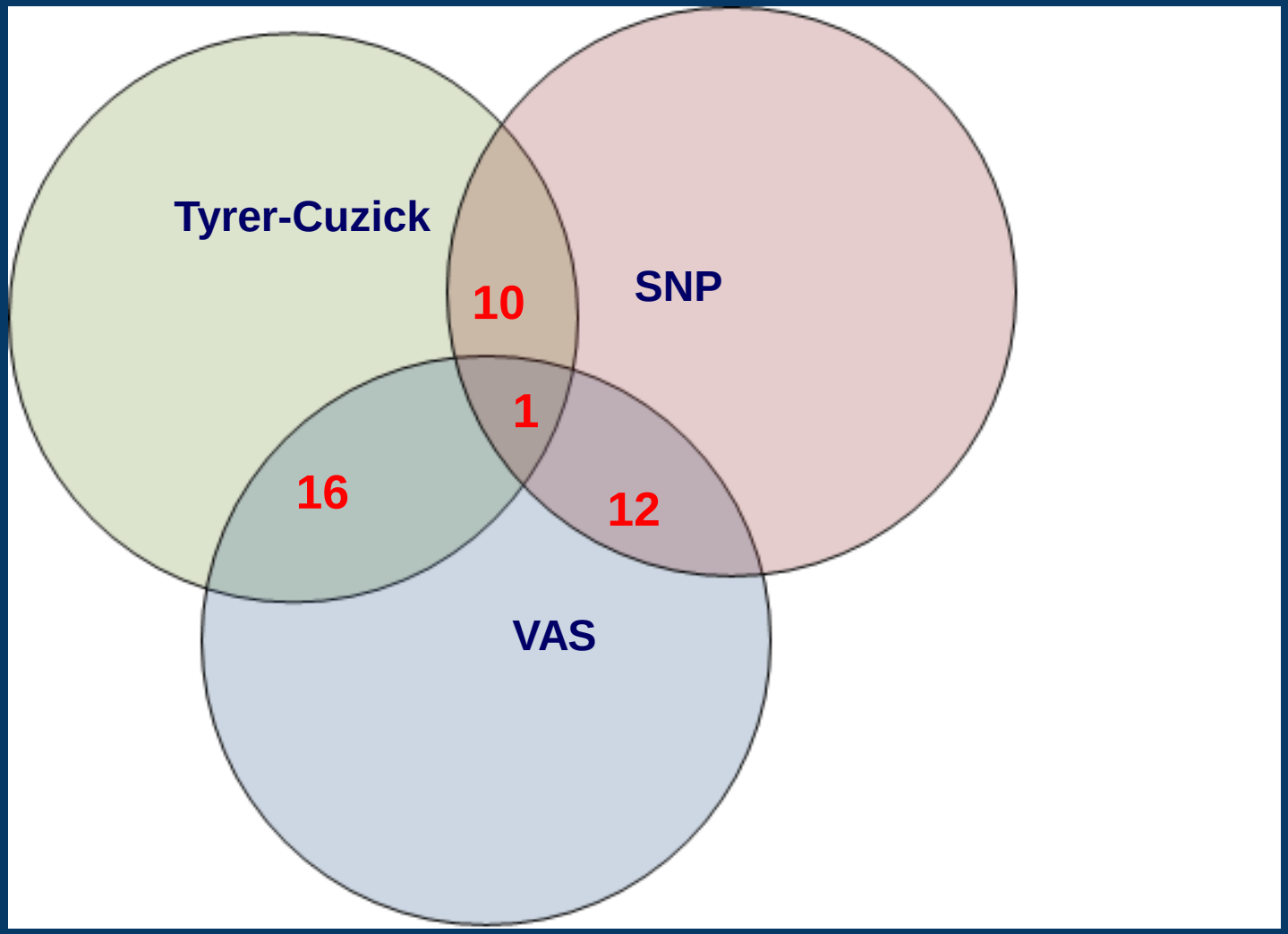
10 year 18 SNP risks with MD adjusted TC in 9346 women



Correlation SNPs to T-C RR



Venn diagram of overlap of highest 10% risk from 1000 women with SNP, Tyrer-Cuzick score and VAS density



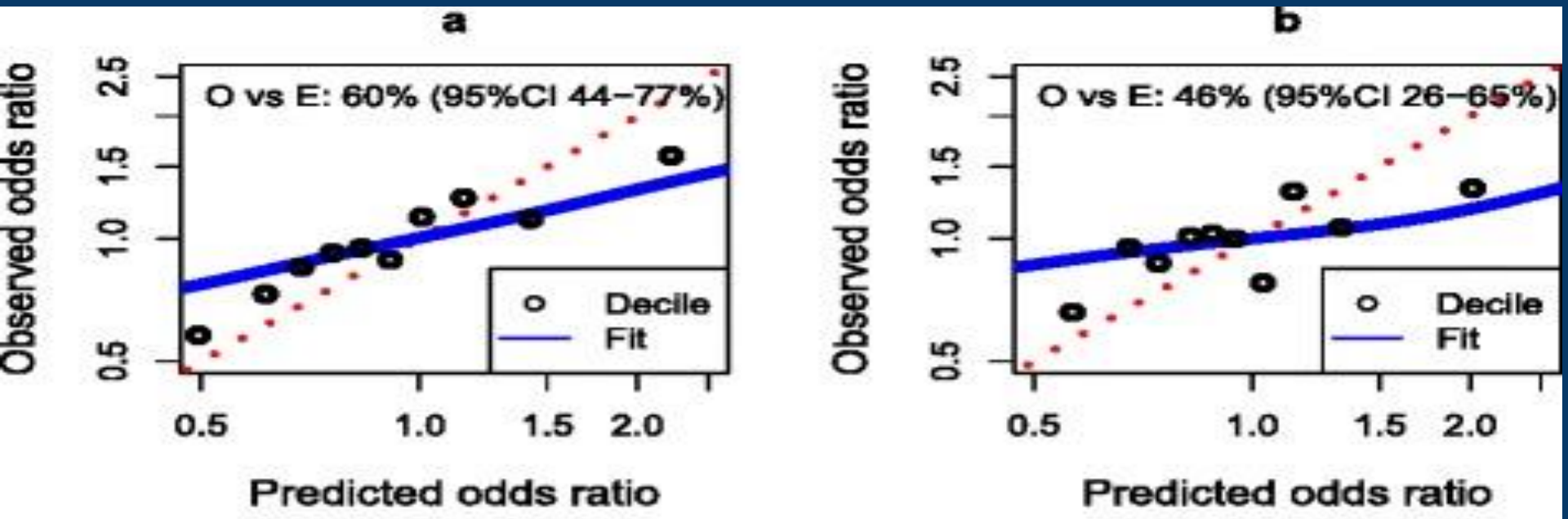
Stage of cancer by MD adjusted risk category
Age and BMI adjusted MD -1015 Breast cancers

	Number	% of popul	BCs	% with BC	LN+ve	High Stage 2/3
High >8%	1314	**2.6%**	52	4.0%	9/38 (24%)	18/47 (38%)
Mod 5-7.9%	4654	**9.1%**	160	3.4%	21/121 (17.3%)	42/144 (29%)
Above ave 3.5-4.9%	8339	16.3%	222	2.7%	39/165 (23.6%)	54/197 (27.5%)
Average 2-3.5%	22001	42.9%	402	1.8%	64/312 (20.5%)	98/363 (27%)
Below average 1-2%	14272	27.8%	176	1.2%	22/133 (16.5%)	35/155 (22.5%)
Low <1%	684	1.3%	3	0.4%	1/3 (33%)	1/3 (33%)
Above vs below average-		11.7% 29%	3.6% 1.2%	P<0.0001	19% v 17% p=0.18	31.5%v23% p=0.09

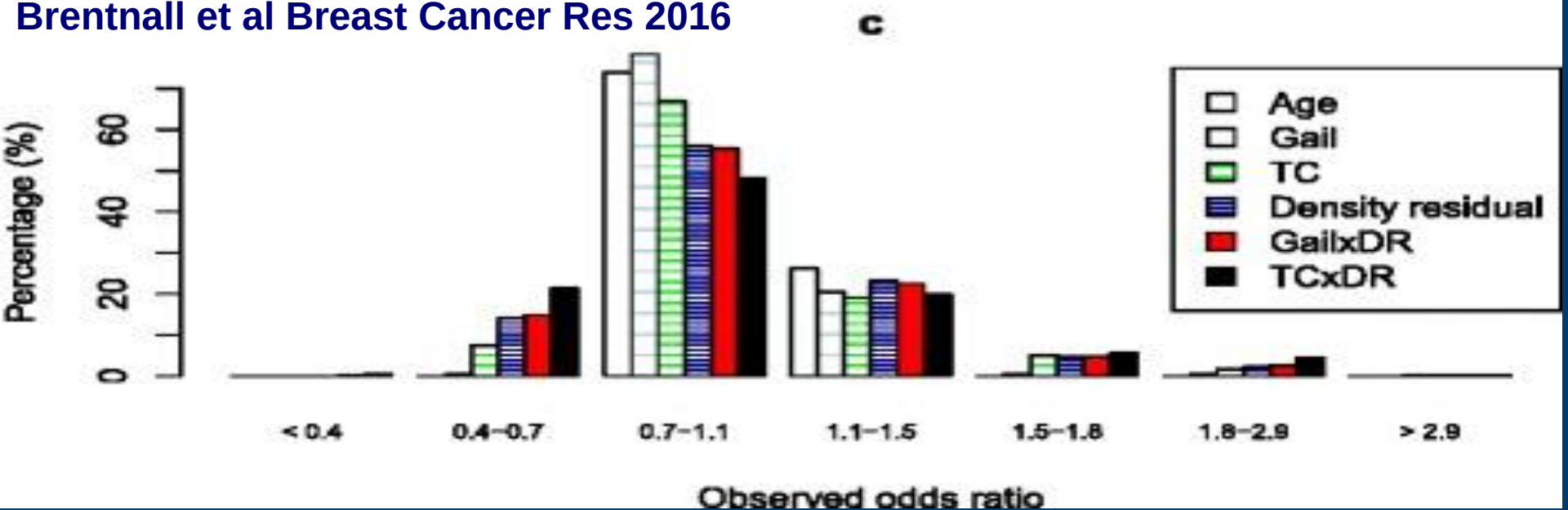
Effects of risk on stage

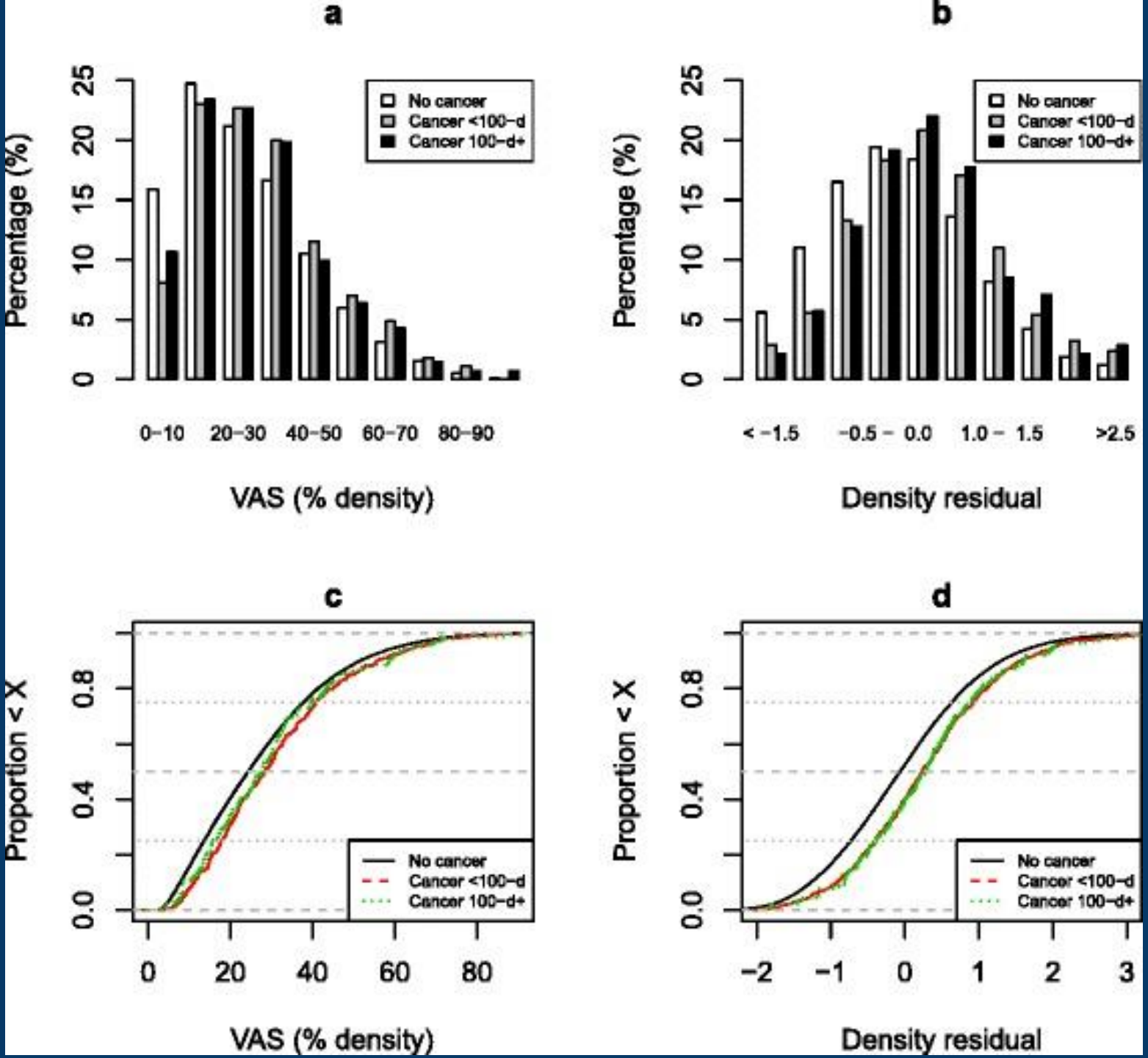
- 60/191 (31.5%) >mod/high risk stage 2a-3;
- 36/158(23%) below average stage 2a-3; p=0.09
- 59/5968 = 10 per 1000 stage 2a-3 >average risk
- 36/14956 = 2.4 per 1000 stage 2a-3 average or lower risk p<0.0001 -<0.6 per 1000 p.a
- 36957/50627 (71%) at average or below

Calibration T-C and Gail model



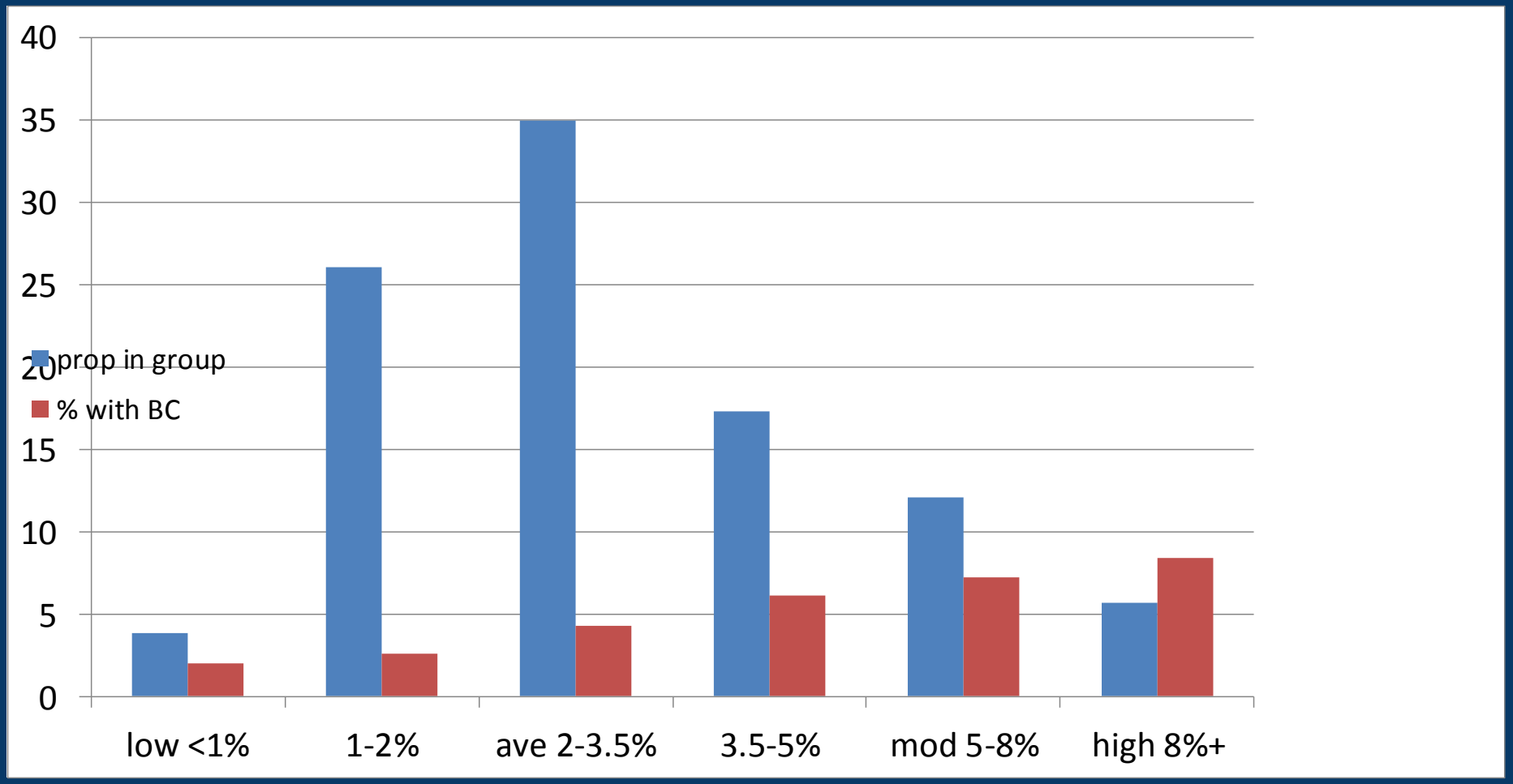
Brentnall et al Breast Cancer Res 2016



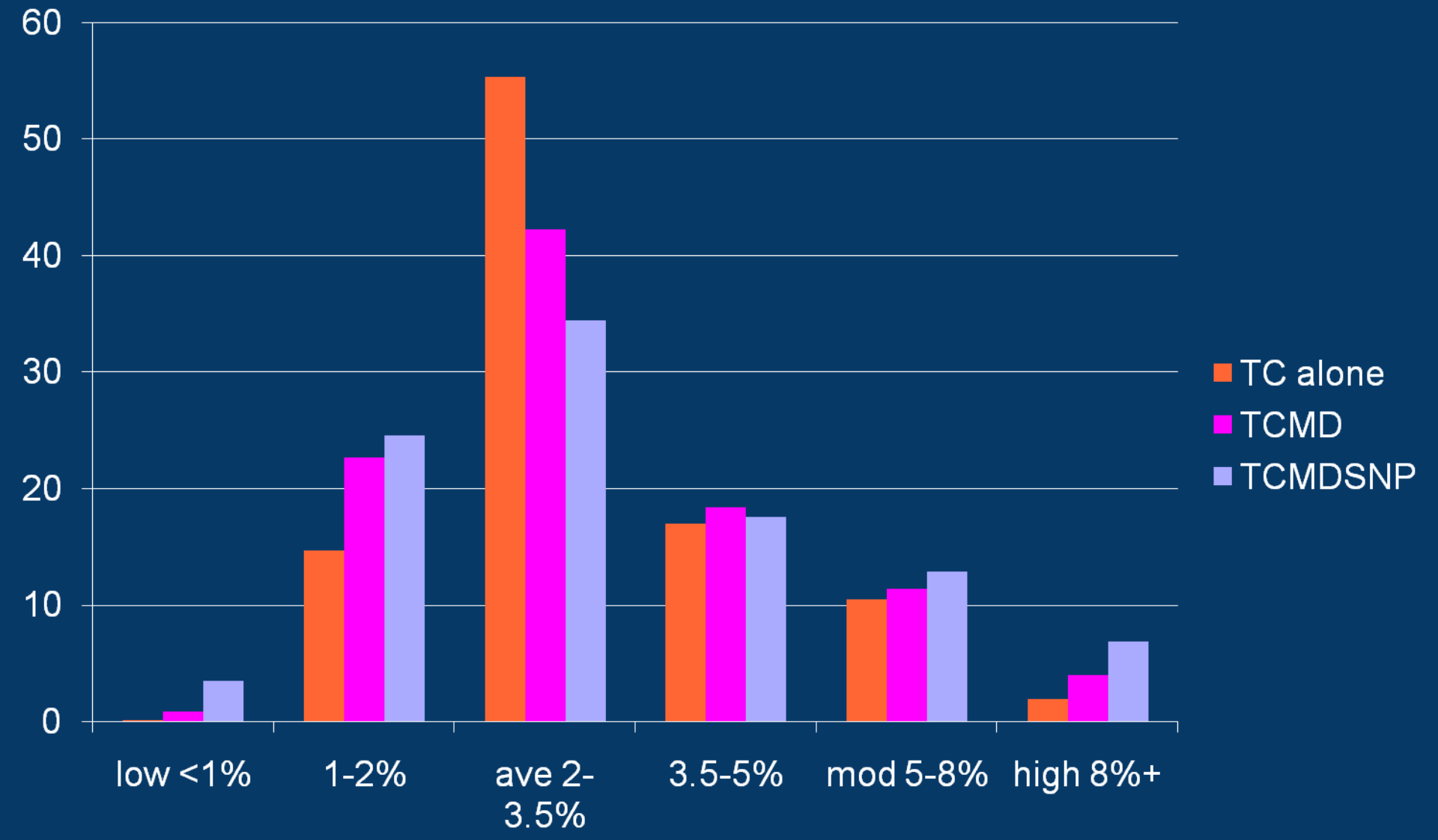


Breast density and residual by time of diagnosis since enrolment

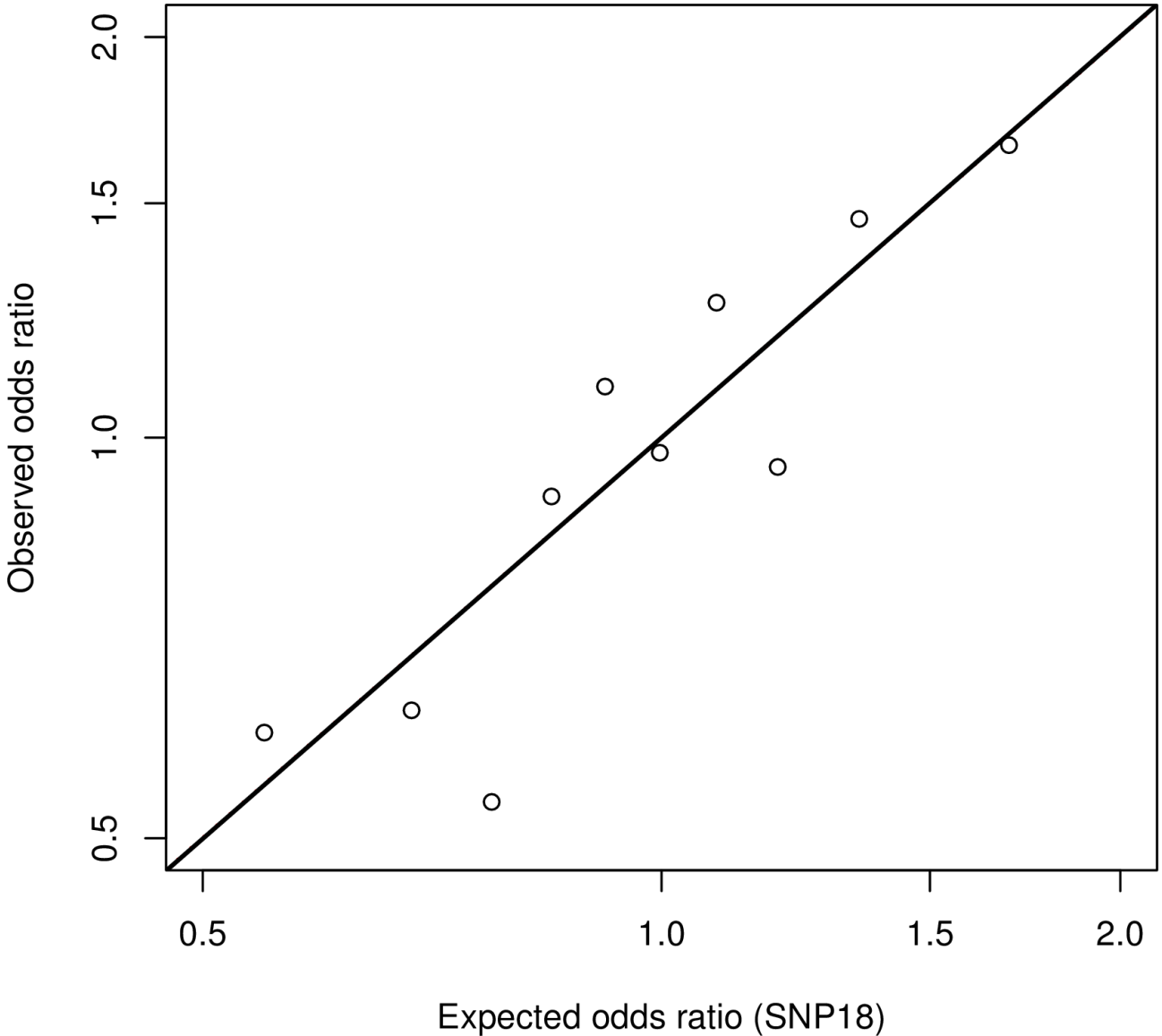
T-C Density and SNPs in PROCAS 9346 women 439 cancers



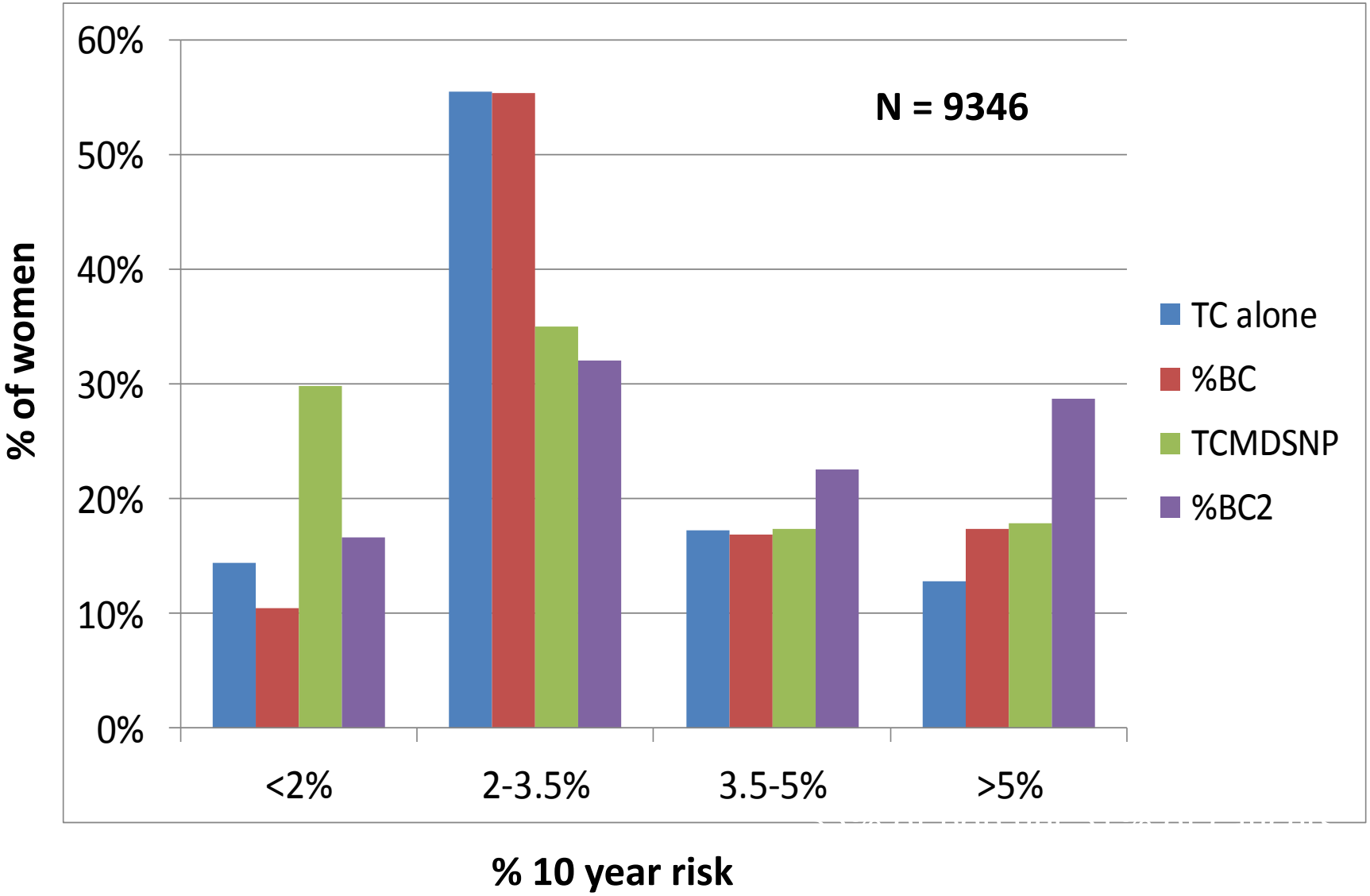
T-C + Density + SNPs in PROCAS Risks 9346 women



Calibration of SNP18



Distribution of 10 year breast cancer and 439 incident breast cancers in PROCAS



Effects of risk on stage

- 33/116 (28.5%) >mod/high risk stage 2a-3;
- 36/158(23%) below average stage 2a-3; p=0.09
- 33/1668 = 20 per 1000 stage 2a-3 >average risk
- 13/2796 = 4.6 per 1000 stage 2a-3 average or lower risk p<0.0001 -1 per 1000 p.a c.f 4 per 1000

Cancers found on interval screen in high risk

Age	Histology	Invasive/CIS	CIS	Size	Stage	Grade	LN
51	IDC	invasive	no	15mm	1	II	0/9
63	IDC	invasive	no	28mm	2a	III	1/2
55	IDC	invasive	no	11mm	1	III	0
56	ILC	invasive	no	25mm	2a	II	0/1
54	IDC	invasive	yes	7mm	1	I	0/2

PROCAS Risk Assessment

- First 50,000 women recruited
- 94.7% wished to know risk
- 0.5% indicated no preference
- 4.8% did NOT want to know

Intervention in those at high risk

- Women with a lifetime risk of 30%+ or
- 8% risk in 10 years
- are classified high risk by NICE
- All high risk women will be invited for a clinic visit

a. If found after initial T-C assessment without MD/DNA
b. If found after adding extra factors

- An equal number of low risk women will be invited
- Women can opt out of knowing risk on 2 occasions

1. At consent
2. When they receive a clinic appt

Risk appointments

High risk (8%+ 10 yr risk or 5%+ and >60% MD)

- Participants who are high risk: **815**
- Participants who want to know their risk: **784**
- Participants who have been invited for an appointment: **784**
- Participants who have attended their risk appointment:**582 -74%**
- Participants who DNA'd their appointment: **10**
- Participants who did not respond after two reminders: **132**
- Participants who declined an appointment: **60**

- **12/60 (20%) women entered IBIS2 and**
- **5/25 (20%) in dietary studies**
- **327/345 (95%) attended next mammogram p<0.001 compared to usual re-attendance of 84%**

Risk appointments update

Low risk (<1.5% 10 year risk <10% MD)

- Participants who are low risk: **171**
- Participants who want to know their risk: **150**
- Participants who have been invited for an appointment: **192**
- Participants who have attended their risk appointment: **105**
- Participants who DNA'd their appointment: **6**
- Participants who did not respond after two reminders: **56**
- Participants who declined an appointment: **25**

Reattendance at next invited NHSBSP visit -84% (64/76)

Evans et al Brit J Cancer 2016

MANCHESTER 1824

The University of Manchester

Conclusions

- Breast cancer risk assessment is feasible in NHSBSP
- As many as 12-17% of the female population are at least moderate risk and entitled to consideration for:
- Chemoprevention with tamoxifen
- Annual mammography – 2.5%
- The great majority of women at moderate risk are unaware and/or that they are eligible for extra interventions
- 3 yearly mammography appears adequate 71% women at <3.5% MD adjusted 10-years risks

MANCHESTER 1824

The University of Manchester

Conclusions

- SNPs are able to significantly add to breast cancer risk discrimination
- Can be used in a population and family history setting
- To risk stratify for screening and chemoprevention

MANCHESTER 1824

The University of Manchester

Contacts

- Chief Investigator: Prof. Gareth Evans
- Project Co-ordinator: Paula Stavrinos
- Data Manager: Sarah Sampson

- Email: PROCAS.Study@uhsm.nhs.uk

The PROCAS team

Eileen and Chris who will be on the vans, and Stella and Julie who have been assisting us in the office

everyone counts
staff awards

Thank you

University Hospital of South Manchester NHS
NHS Foundation Trust

CONTACT US: Phone: 0161 291 4408
Email: PROCAS.study@uhsm.nhs.uk

Genesis
creating a future without breast cancer

MANCHESTER 1824

The University of Manchester

Acknowledgements

Nightingale Centre UHSM

- Prof Anthony Howell
- Dr Andrew Maurice
- Jenny Affen
- Rosemary Greenhalgh
- Dr Michelle Harvie
- Barbara Eckersley
- Miriam Griffiths
- Sue Berry

NIHR Group

- Paula Stavrinos
- Sarah Sahin
- Sarah Ingham
- Sarah Dawe
- Jill Fox
- Louise Donnelly
- Elaine Harkness

University of Manchester

- Prof Iain Buchan
- Dr Sue Astley
- Dr Katherine Royne

Radiology UHSM

- Dr Mary Wilson
- Prof Caroline Boggis
- Dr Emma Hurley
- Prof Anil Jain
- Dr Ursula Beetles
- Dr YY Lim
- Dr N Barr

Christie Hospital

- Dr Alan Hufton
- Dr Jenny Diffey

Surgery UHSM/Christie

- Mr Lester Barr
- Mr Andrew Baildam
- Mrs Ann Brain
- Mr Gary Ross
- Ms Victoria Rose
- Mr Stuart Wilson
- Prof N Bundred

Genetic Service CMFT

- Prof Gareth Evans
- Dr Bill Newman
- Dr Fiona Lalloo
- Helen Byers
- Dr Bronwyn Kerr
- Tara Clancy

Cancer register NWCIS

- Dr Tony Moran

Others

- Prof Jack Cuzick
- Dr Adam Brentnall
- Dr Ruth Warren
- Prof Jane Wardle
- Helen Middleton-Price
- Wendy Watson

Genesis creating a future without breast cancer

Central Manchester University Hospitals NHS Foundation Trust

NHS National Institute for Health Research