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The University of Manchester

NHS National Institute for Health Research

Central Manchester University Hospitals NHS NHS Foundation Trust

Current application of genetic variants to clinical management

Predicting Risk Of Cancer At Screening

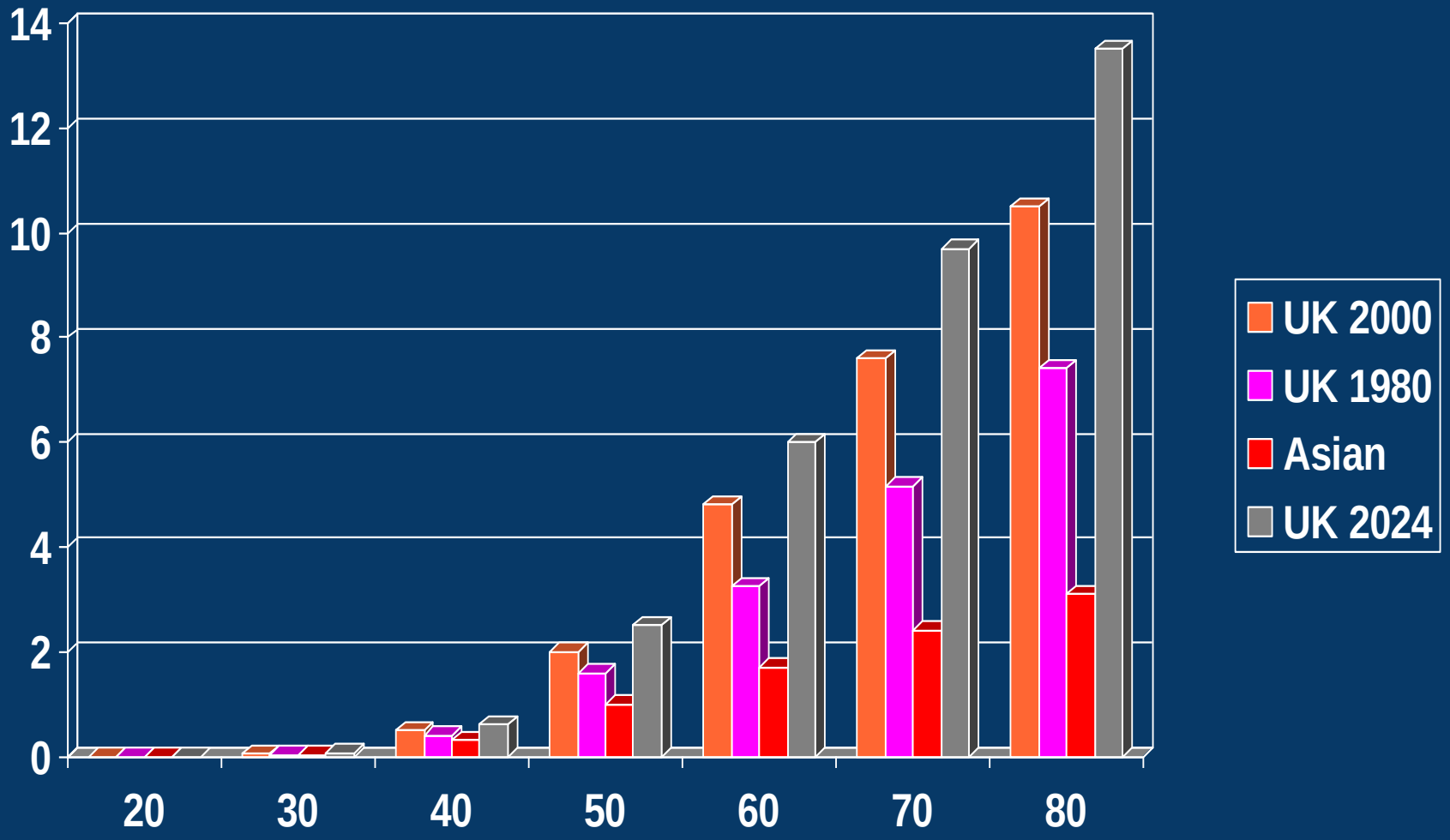
Prof D Gareth Evans

UHSM Your Hospital

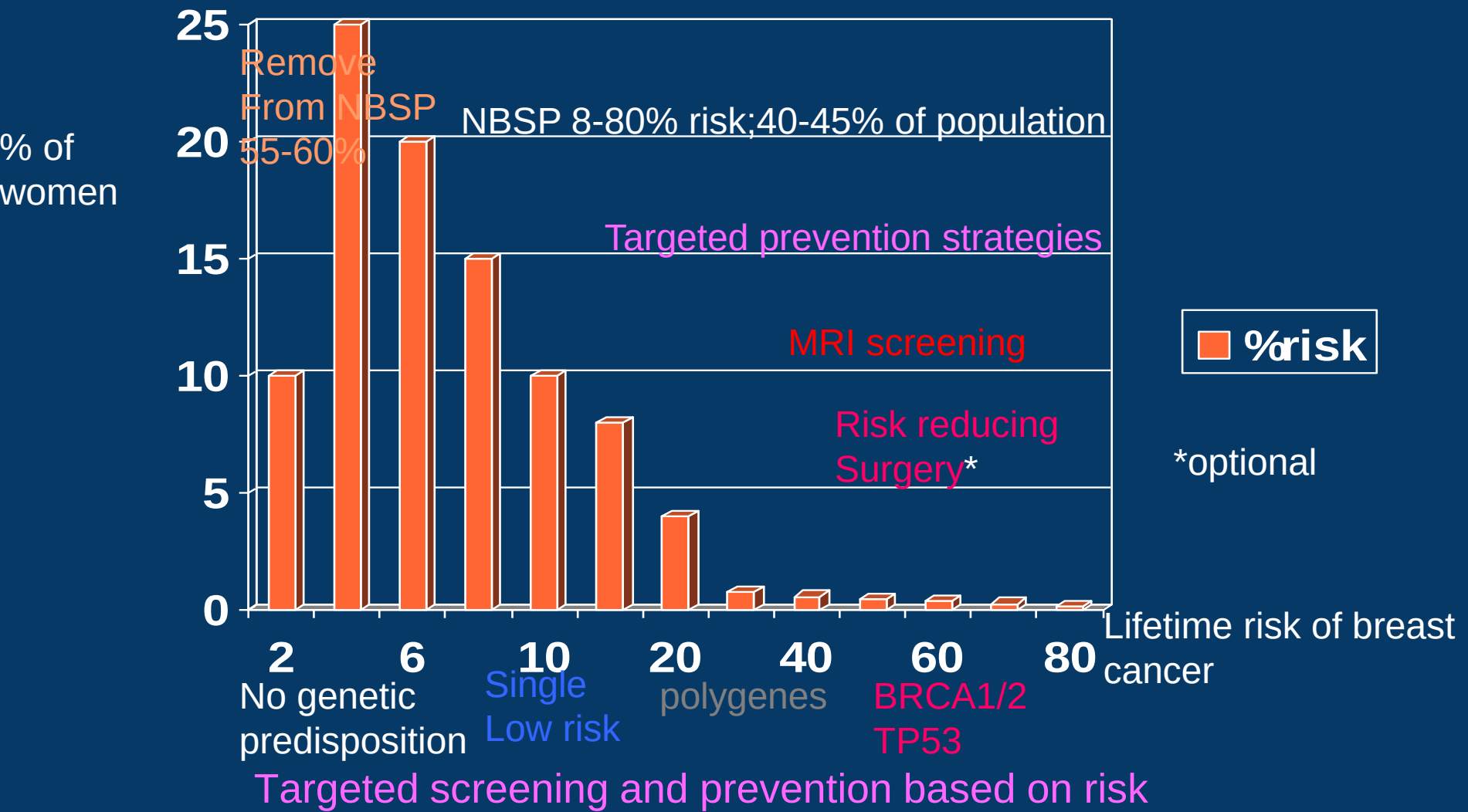
The Christie NHS NHS Foundation Trust

genesis preventing breast cancer

Breast cancer cumulative risk UK population and Asia



Breast cancer risk in general population



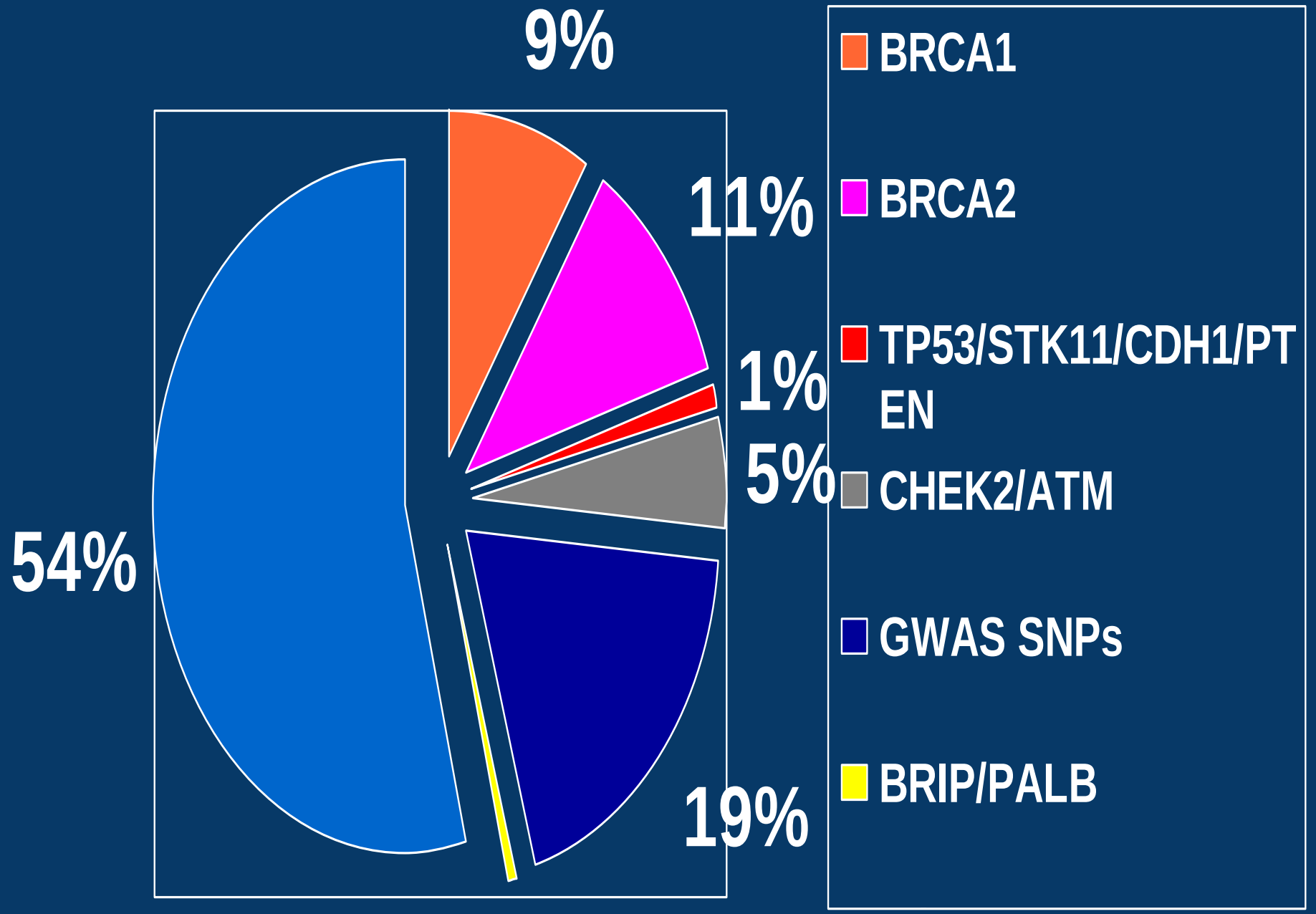
Breast Cancer

- **4-5% due to high risk genes (Claus 1994, Newman 1989)**
- **27% have a hereditary element from twin studies (Peto & Mack)**
- **Only about 13% of breast cancer accounted for.**

Genes predisposing to breast cancer

	>4 BC<60	familial	All BC	Lifetime risk
BRCA1	**50%**	**6%**	**1.7%**	**60-85%**
BRCA2	**30%**	**6%**	**1.5%**	**50-85%**
TP53	**<1%**	**<1%**		**90-100%**
ATM	**?1-5%**	**3%**	**1-5%**	**20%**
CHK2	**0%**	**2%**	**?8%**	**18%**
PTEN	**0%**	**<1%**	**<1%**	**60%**
STK11	**0%**	**<1%**	**<1%**	**40%**

Proportion of familial breast cancer 2014



Combined effects of FGFR2 and TNRC9

Please cite this article in press as: Antoniou et al., Common Breast Cancer-Predisposition Alleles Are Associated with Breast Cancer Risk in *BRCA1* and *BRCA2*..., The American Journal of Human Genetics (2008), doi:10.1016/j.ajhg.2008.02.008

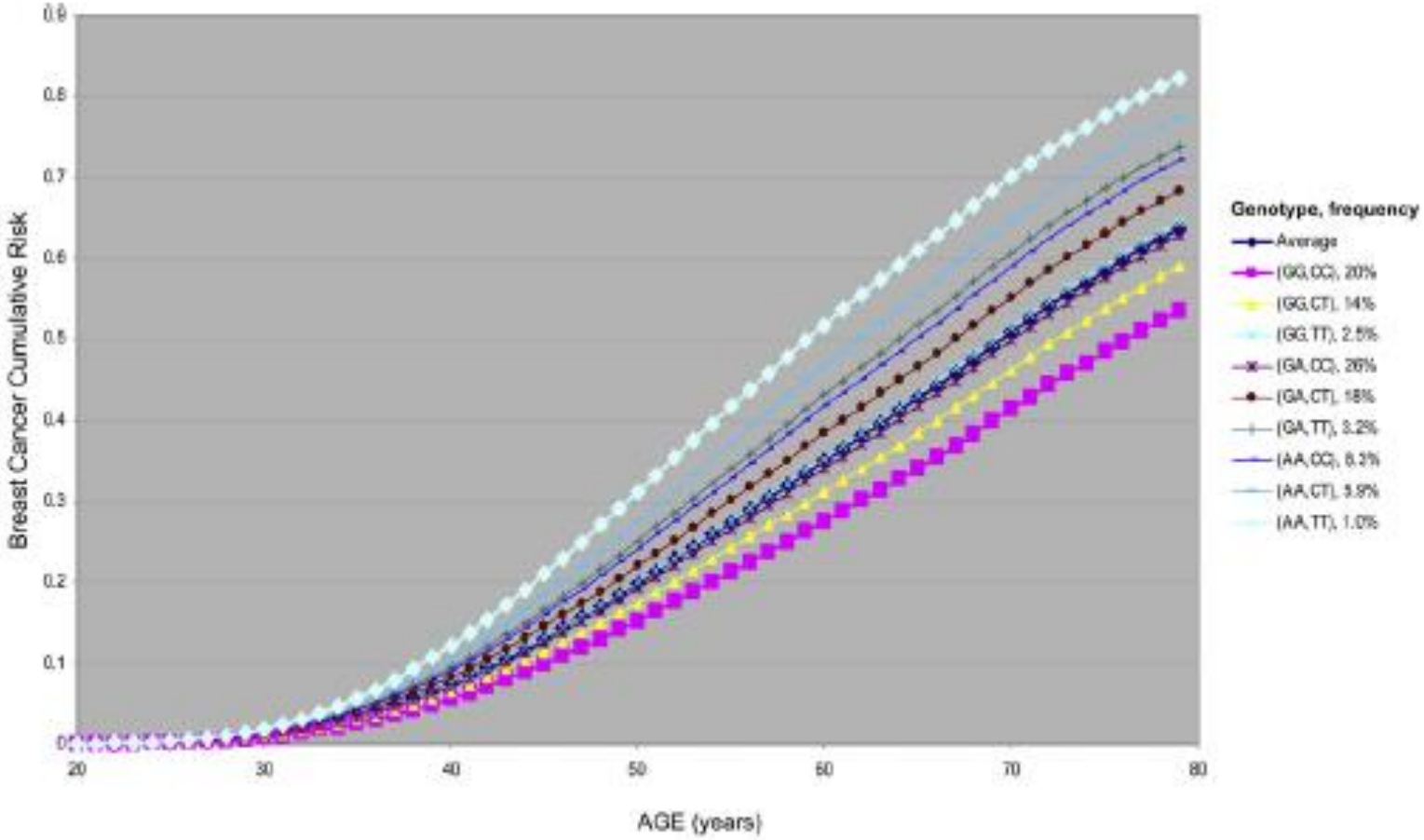
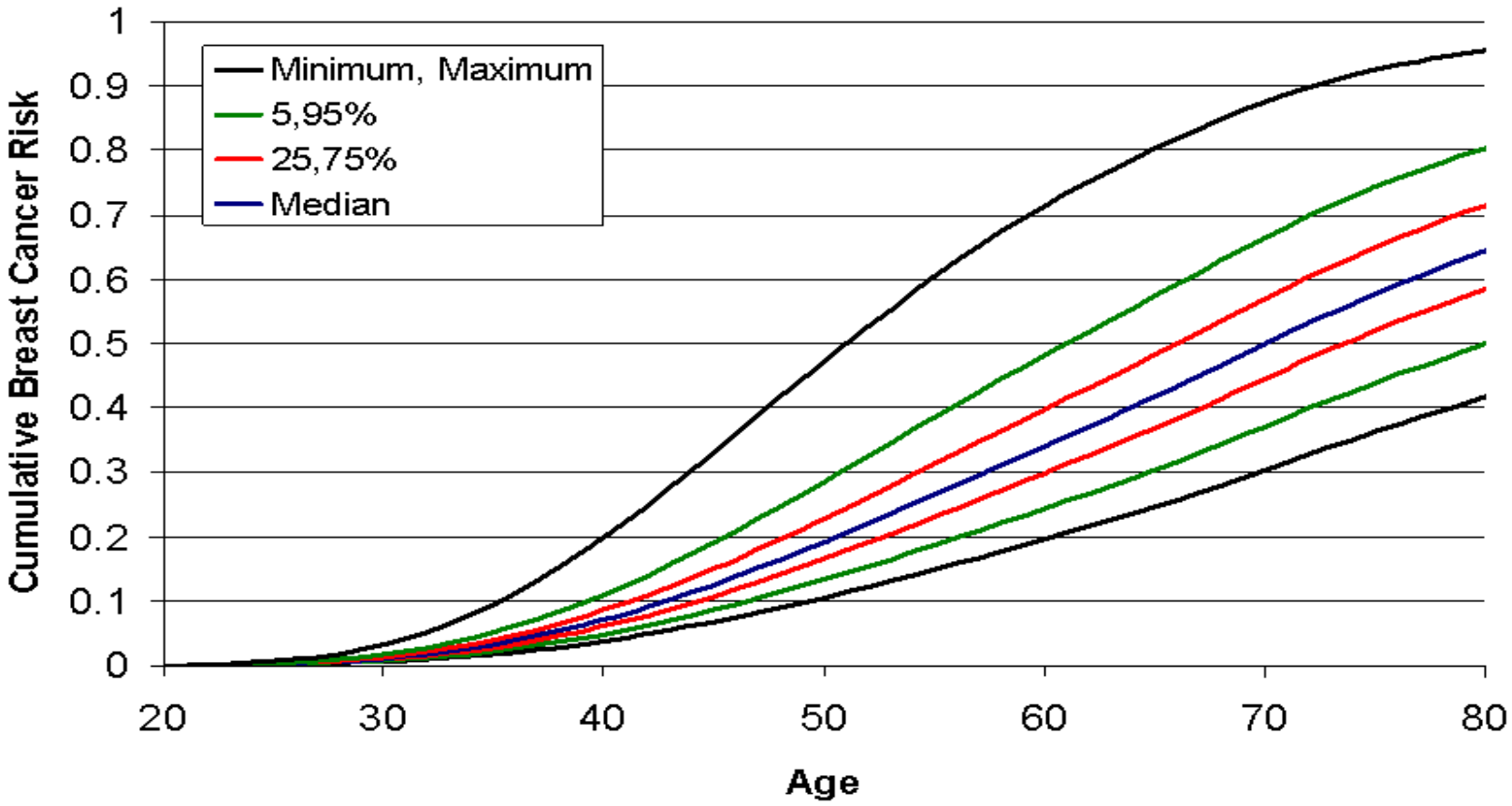


Figure 4. Cumulative Risk of Breast Cancer among *BRCA2* Mutation Carriers by Combined *FGFR2* and *TNRC9* Genotype under a Multiplicative Model for the Joint Effects of the Loci

The combined *FGFR2* and *TNRC9* genotypes are as follows: *FGFR2* = GG, GA, or AA; *TNRC9* = CC, CT, or TT. "Average" represents the cumulative breast cancer risk over all possible modifying effects among *BRCA2* mutation carriers born after 1950. The minor allele frequencies for the *FGFR2* and *TNRC9* SNPs were assumed to be 0.39 and 0.26, respectively.

Cumulative breast cancer risks for *BRCA2* by combined genotype distribution at SNPs rs2981582 in *FGFR2*, rs3803661 in *TOX3/TNRC9*, rs889312 in *MAP3K1*, rs3817198 in *LSP1*, rs13387042 in 2q35 region, rs4773768 rs10941679



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

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

- 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

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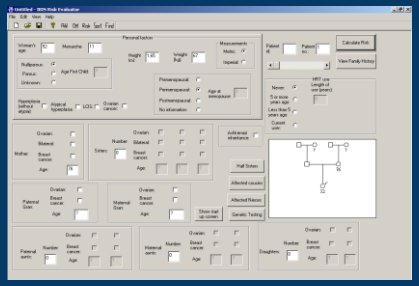
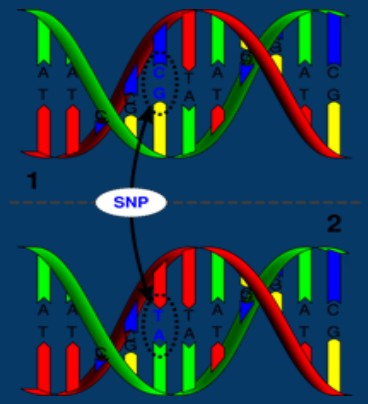
DNA testing

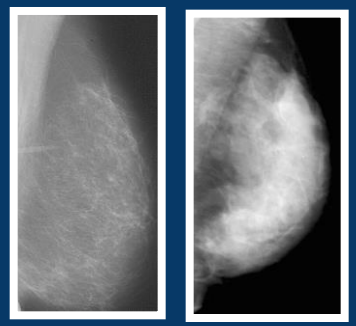
- 10,000 participants will be invited to have DNA testing
- Laboratory extract DNA
- St Mary's Hospital, Manchester
- carry out analysis to look for
- genetic variants
- 10,000 recruited

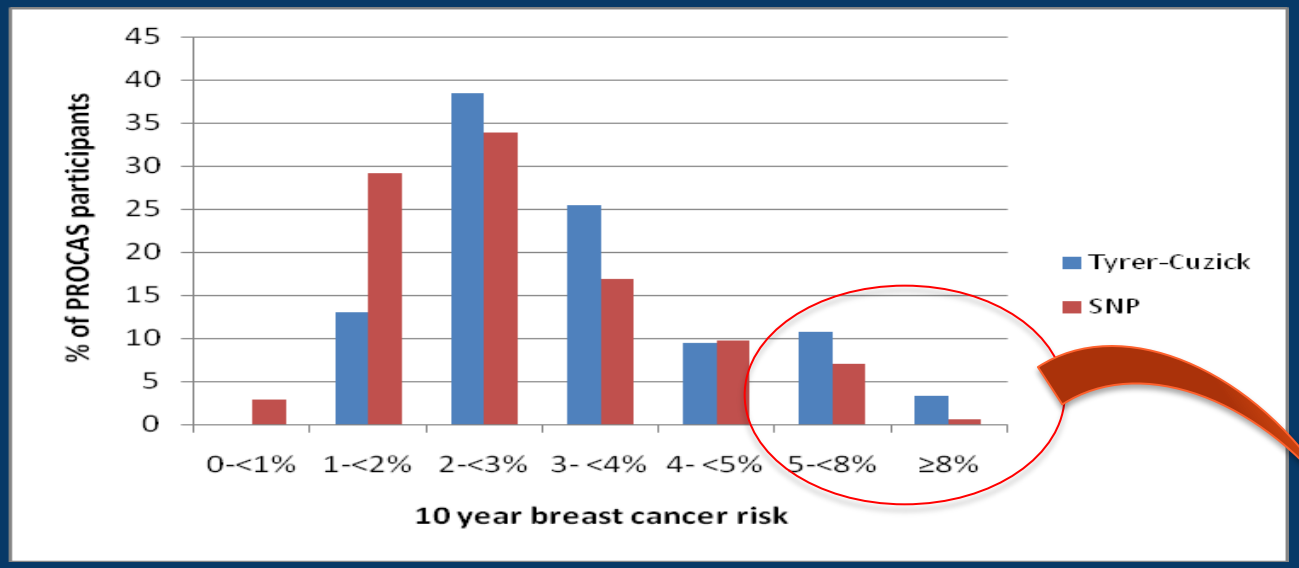
PRediction Of Cancer At Screening (PROCAS)

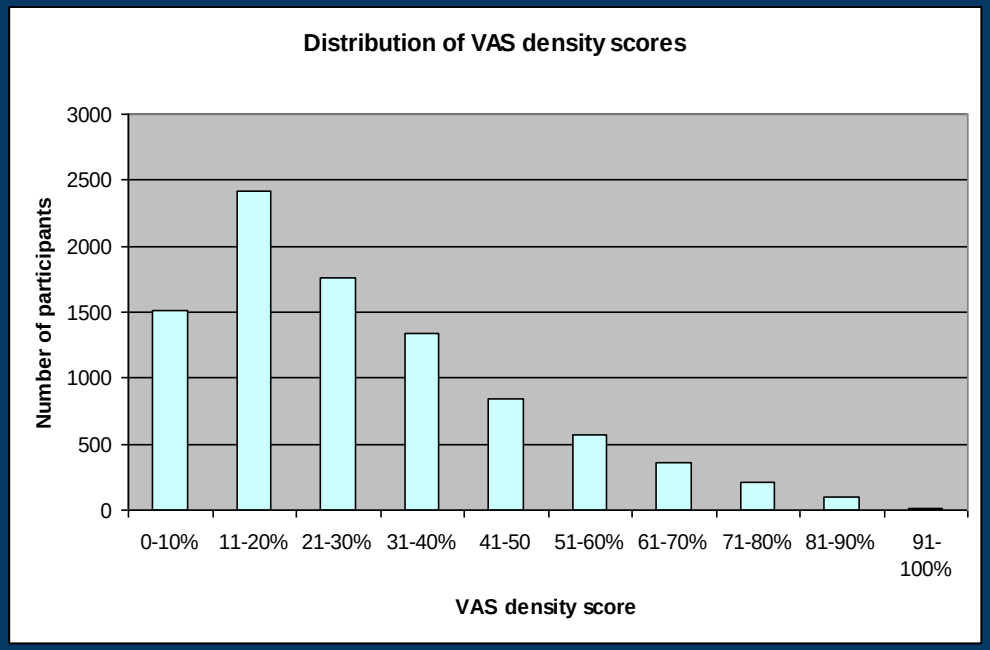
NHS National Institute for Health Research







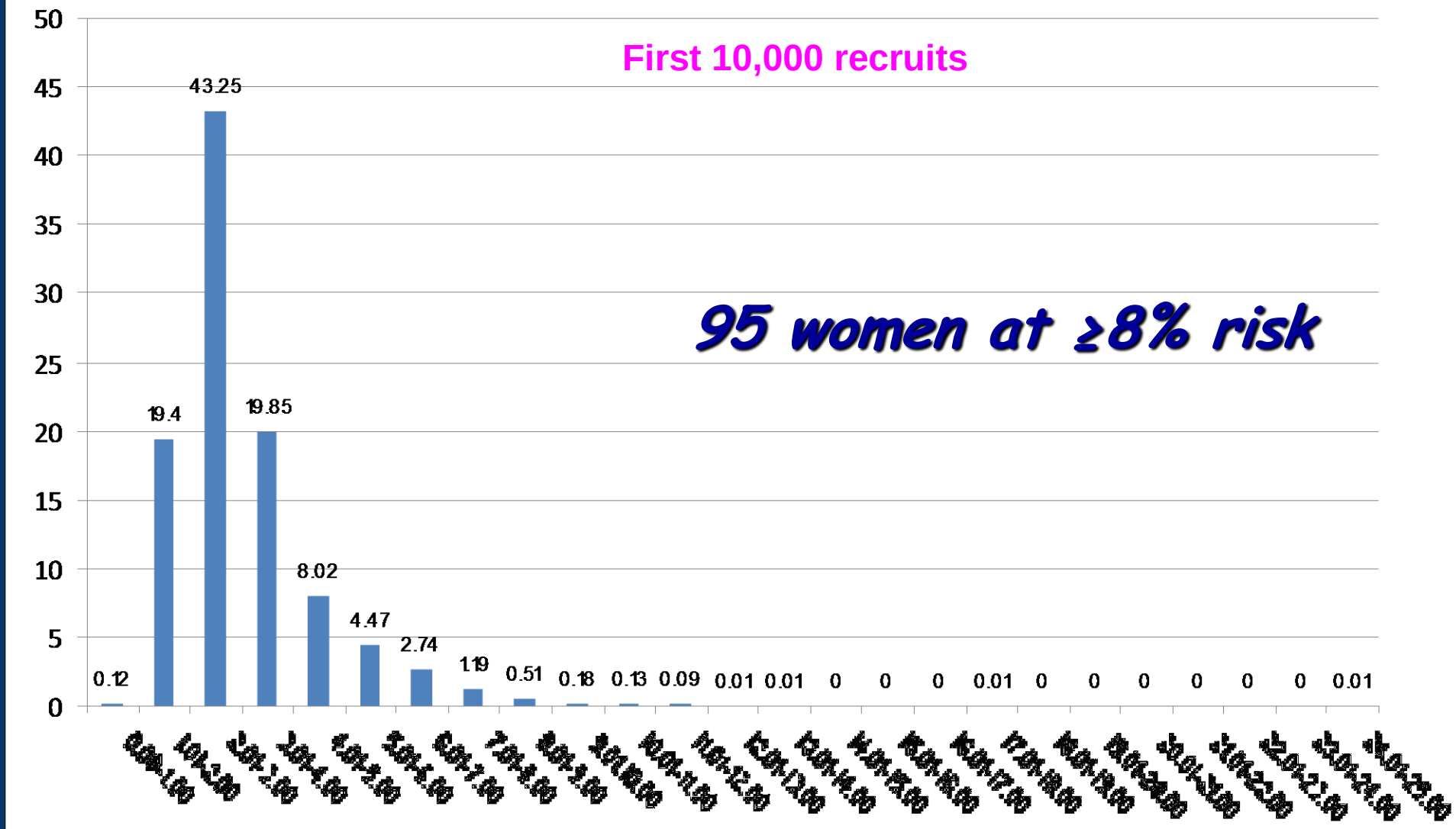




Offer interventions

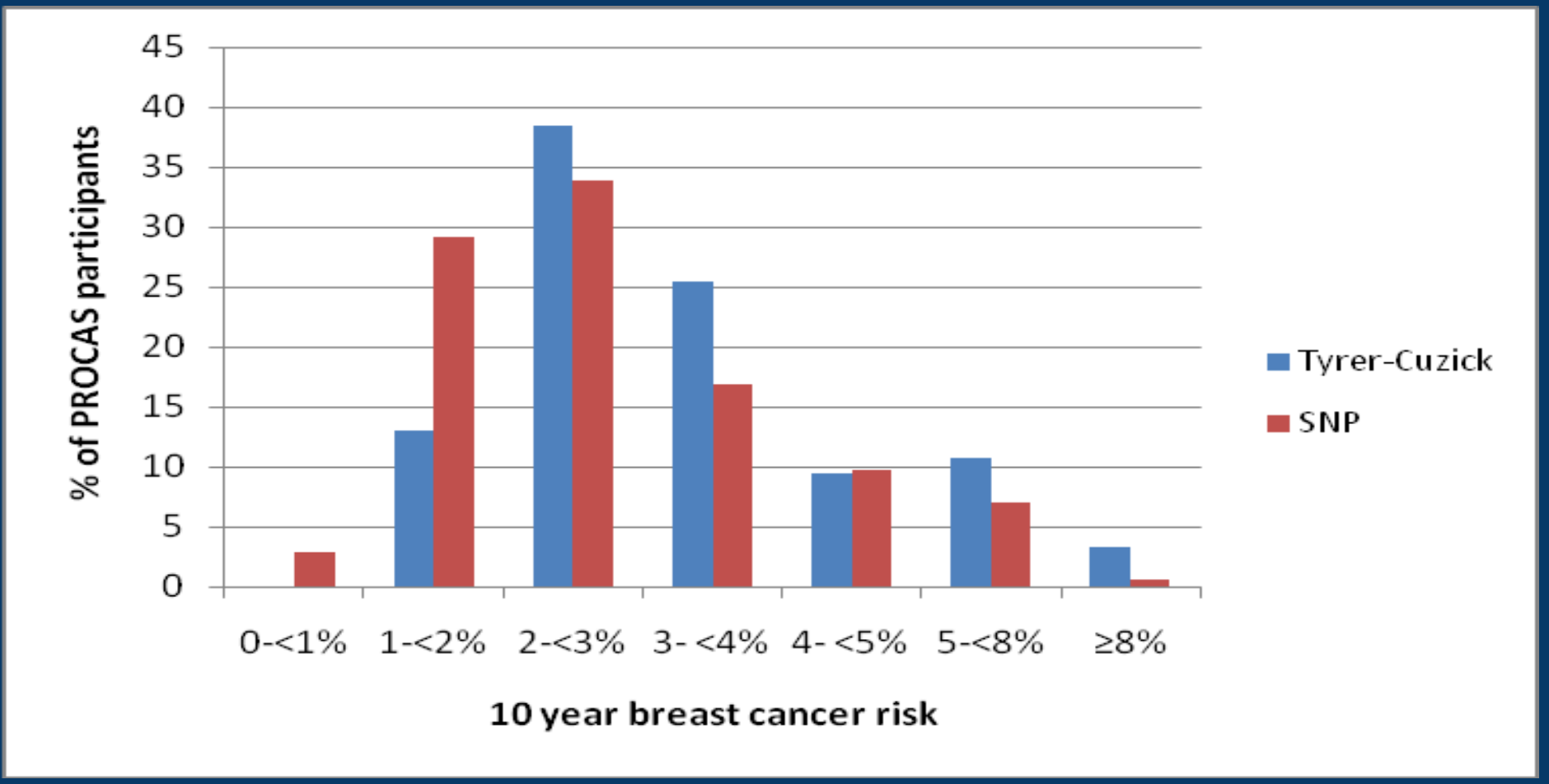
Cuzick et al Lancet 2014
Harvie et al BJN 2013

Distribution of 10 year risk scores (%)



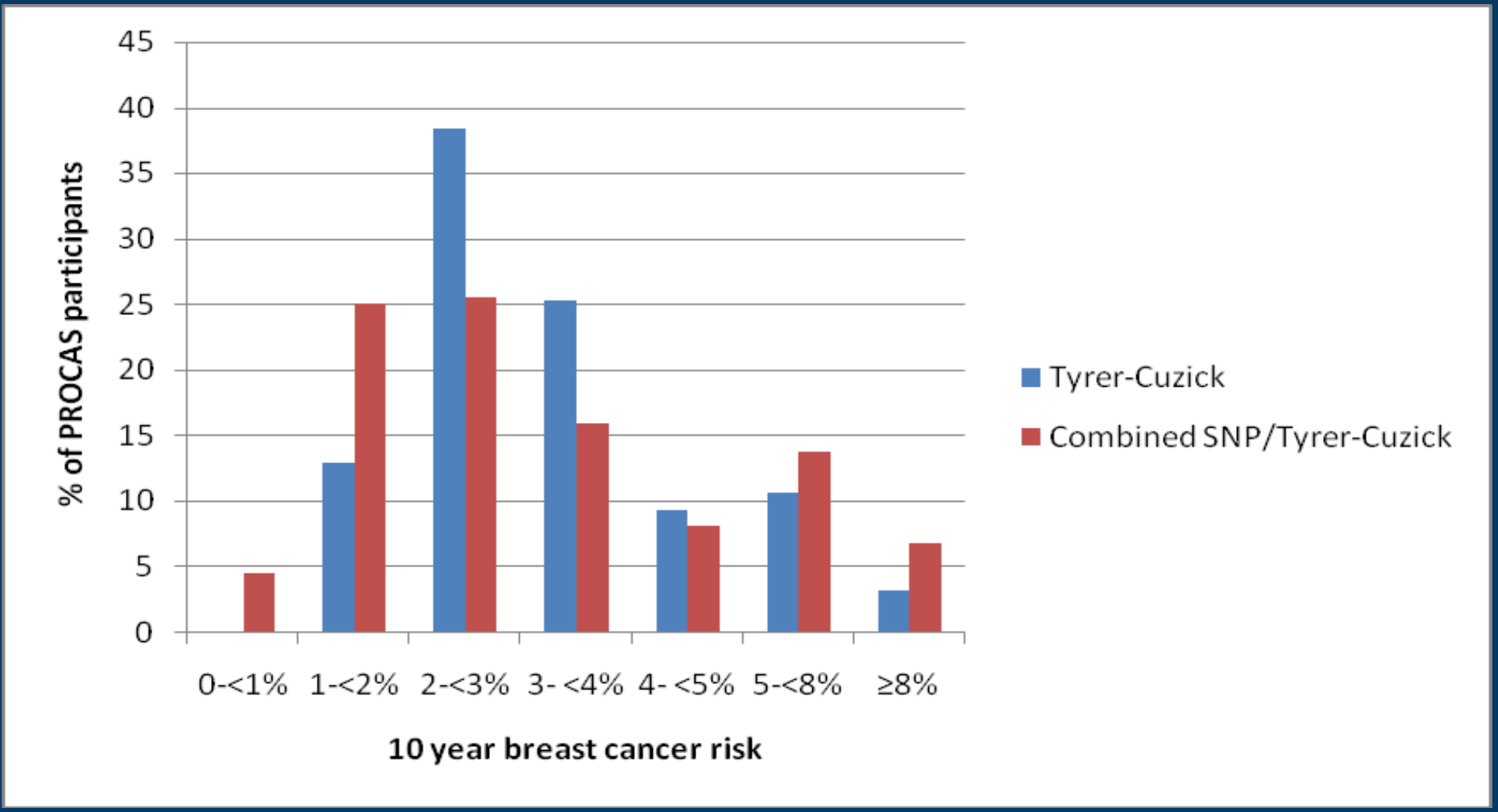
SNP	gene	risk e	RA F	weight 0	weight 1	weight 2	0 freq	1 freq	2 freq	RR	W*F
rs2981579	FGFR2	T	42	0.72	1.03	1.47	34	49	17	1.43	100
rs10931936	CASP8	C	74	1.20	1.06	0.93	7	38	55	0.88	100
rs3803662	TOX3	T	26	0.86	1.12	1.45	55	38	7	1.3	100
rs889312	MAP3K	C	28	0.89	1.08	1.32	52	40	8	1.22	100
rs13387042	2q	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

Comparison of standard risk factors with 18 SNPs on DNA testing 993 samples



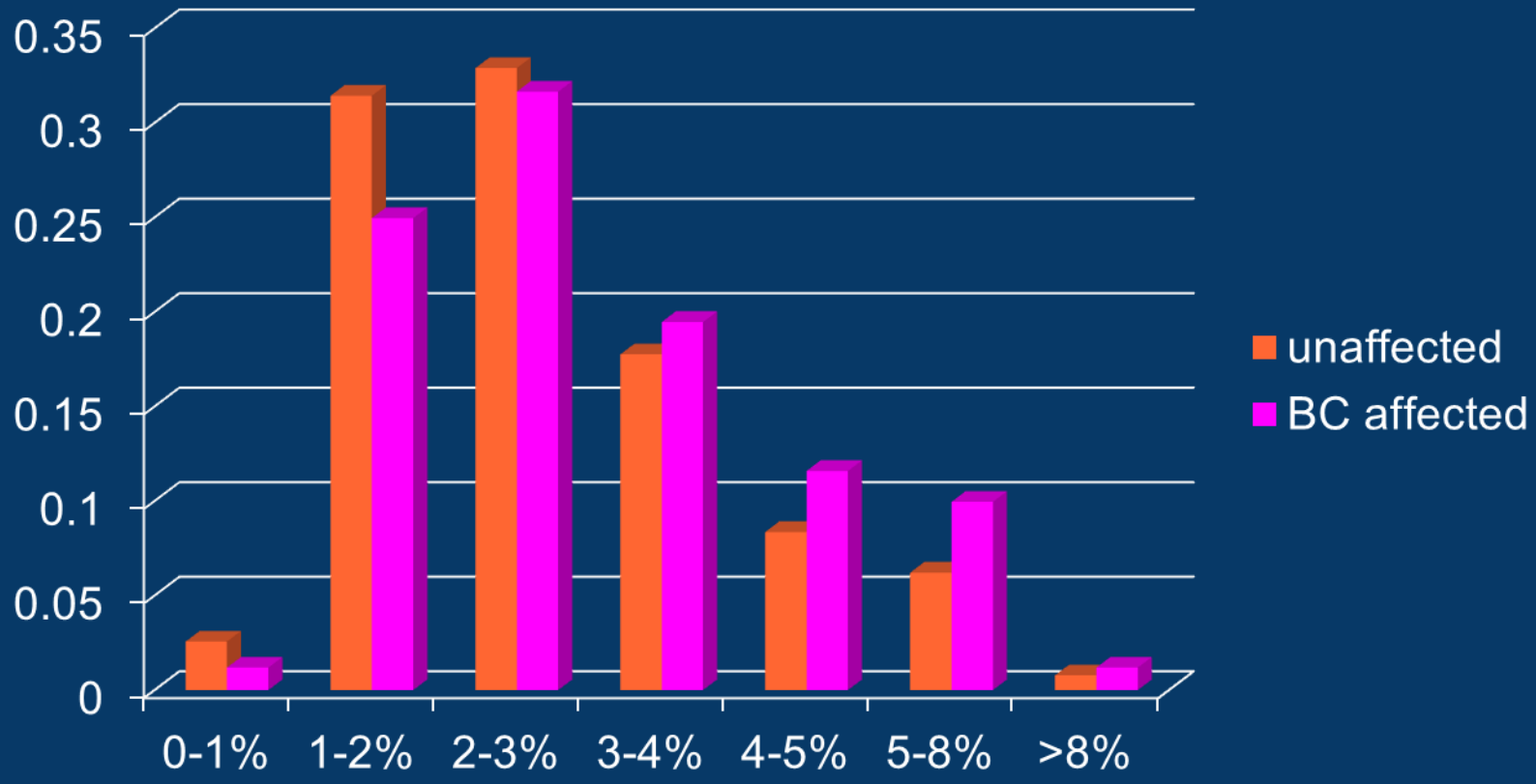
10 year breast cancer risk

Comparison of standard risk factors with 18 SNPs on DNA testing 993 samples

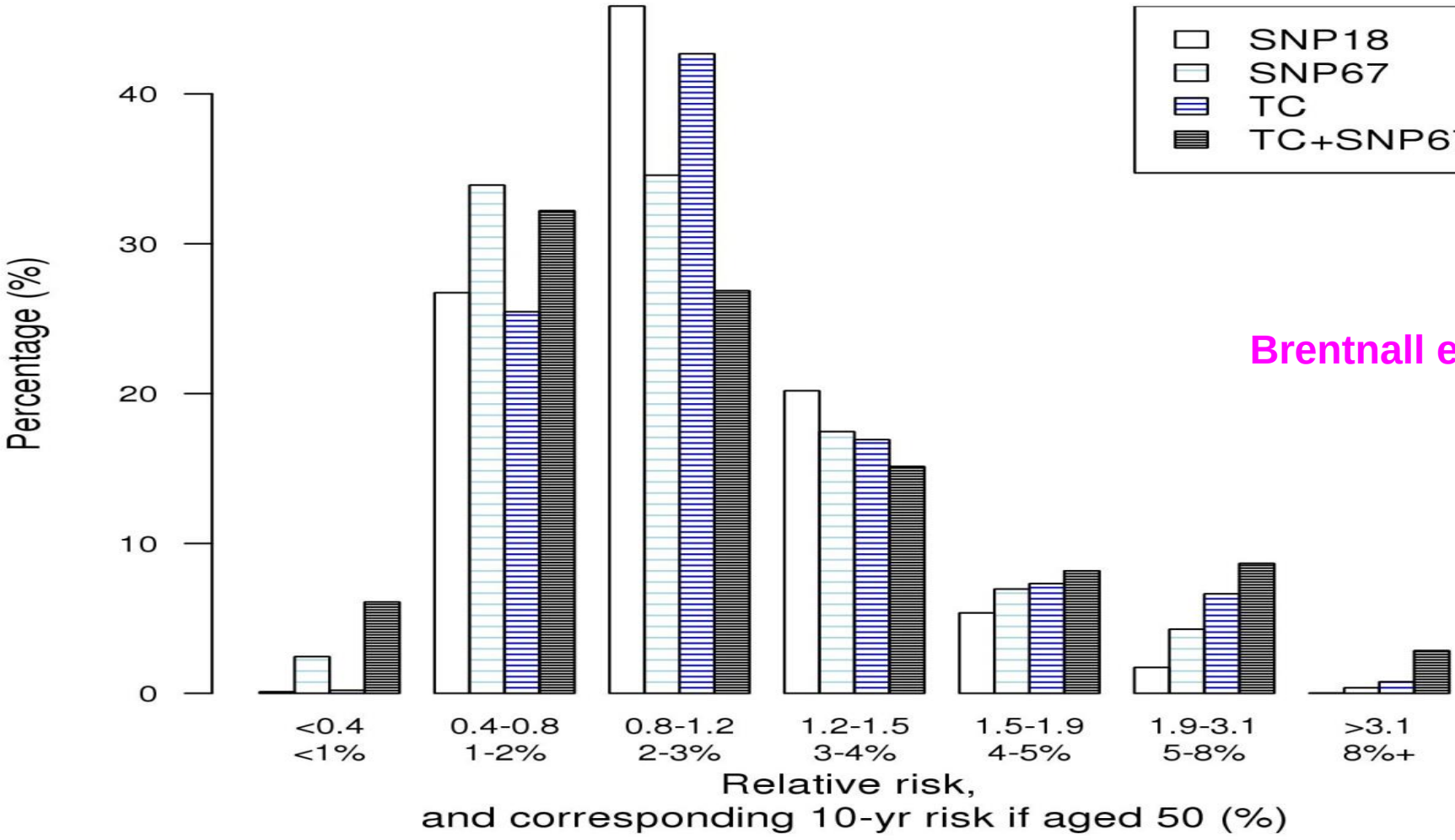


10 year breast cancer risk

10 year 18 SNP risks in 6954 women

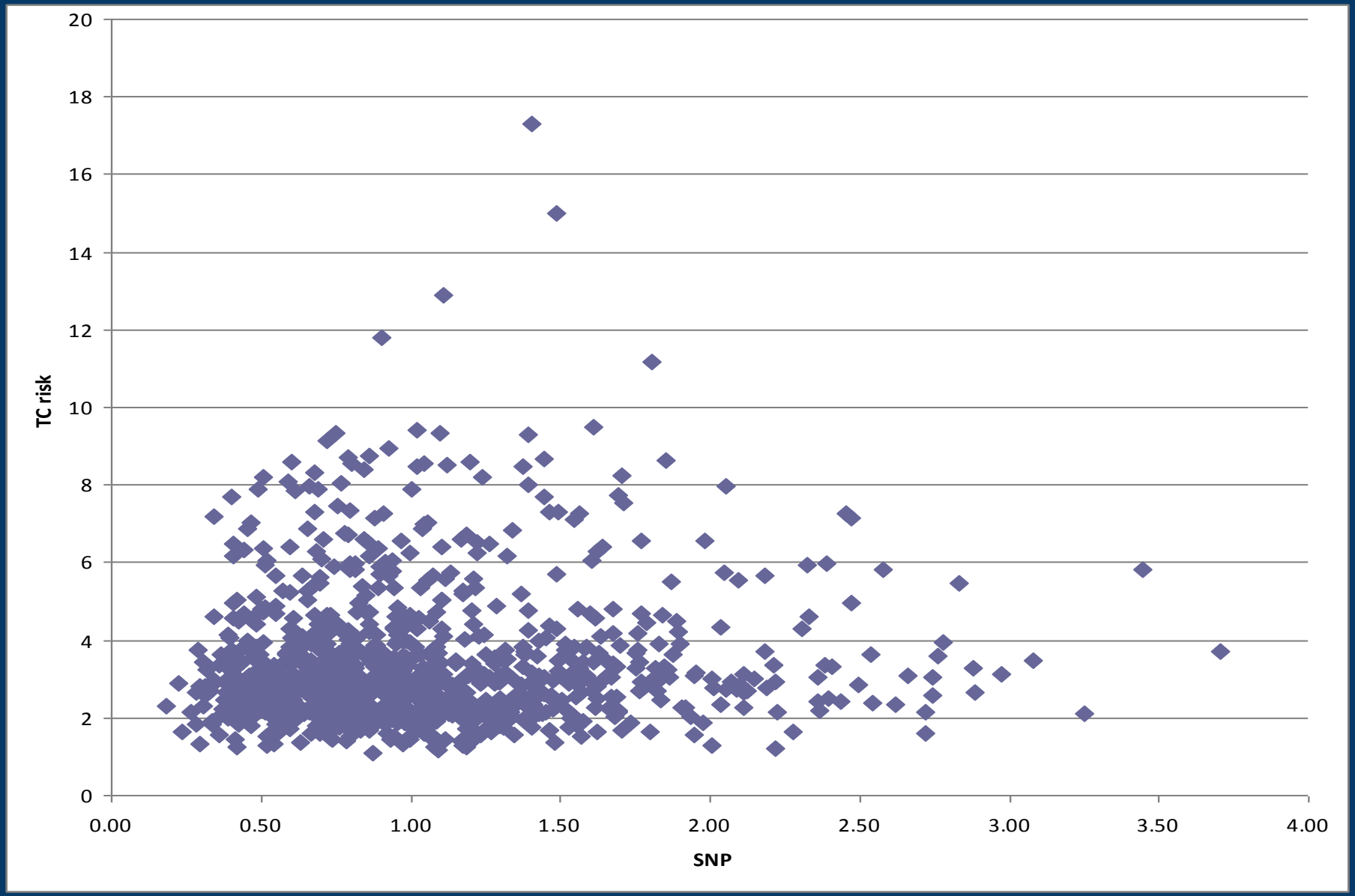


10-yr risk @50 using classical factors (TC), SNP18 the 6
iCOGS SNPs (SNP67), and both combined (TC + SNP67

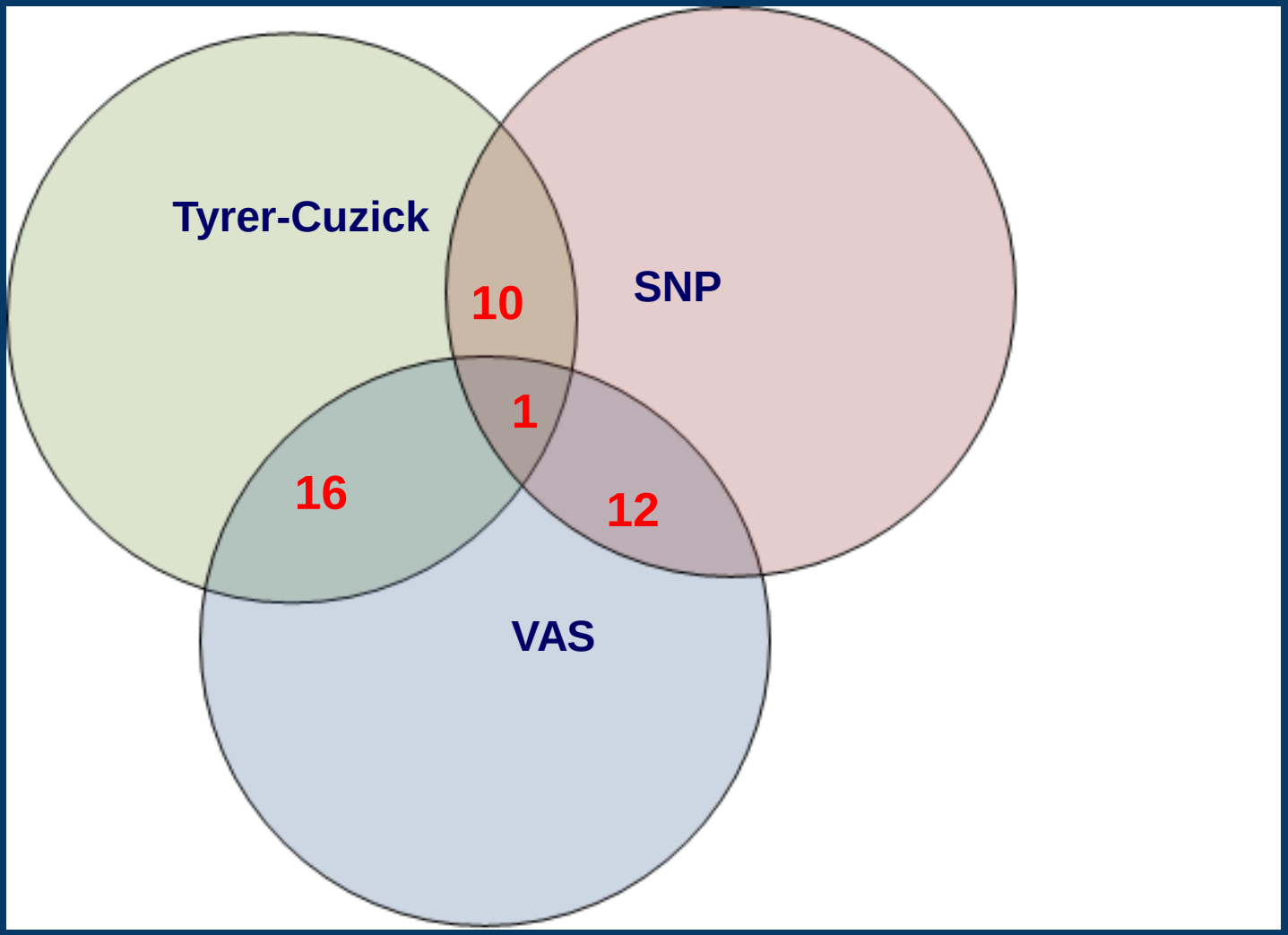


Brentnall et al BJC

Correlation SNPs to T-C RR



Venn diagram of overlap of highest 10% risk from 993 women with SNP, Tyrer-Cuzick score and VAS density



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**
- **200/202 attended next mammogram p<0.0001 compared to usual re-attendance of**

A polygenic risk score (PRS) for each women based on 77 SNPs

Analyses included women of European origin:

33,673 cases : 21,365 ER+ and 5,738 ER-
33,381 controls

$$PRS = b_1 x_1 + b_2 x_2 + \ldots + b_j x_j + b_n x_n$$

b_j per-allele log (OR) for risk allele at locus *j* from logistic regression adjusted for study and 7 PCs

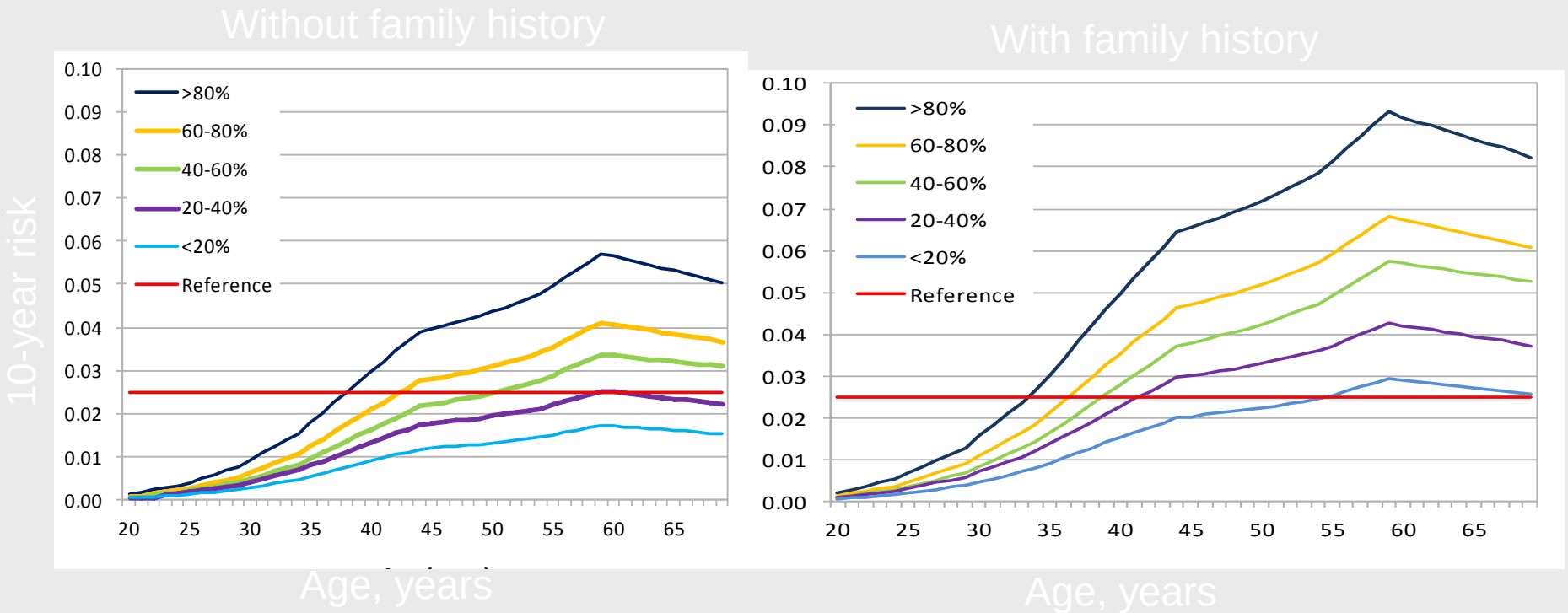
x_j number of risk alleles at at locus (0, 1 or 2)

n number of loci included in the risk score

Mavaddat E et al for BCAC, Under Review

Current PRS can stratify women with and without family history by genetic risk

10-year risk of breast cancer by percentiles of 77-SNP polygenic score by family history of breast cancer



2.4% risk threshold

Mavaddat E et al for BCAC, Under Review

FHC resource

10,500 women screened

Breast cancer

- **533 BC (93 at referral)**
- **438 BC**
- **245 in women in prog.**
- **193 in women discharged**

- **DNA on 424 women**

- **129 BRCA carriers**
- **200 BRCA negative**

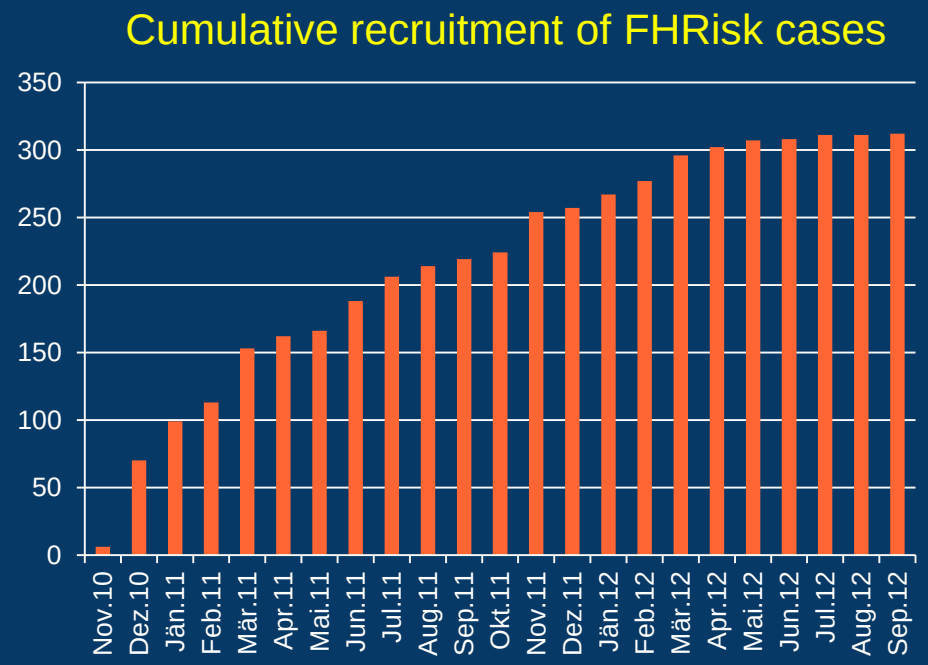
Controls

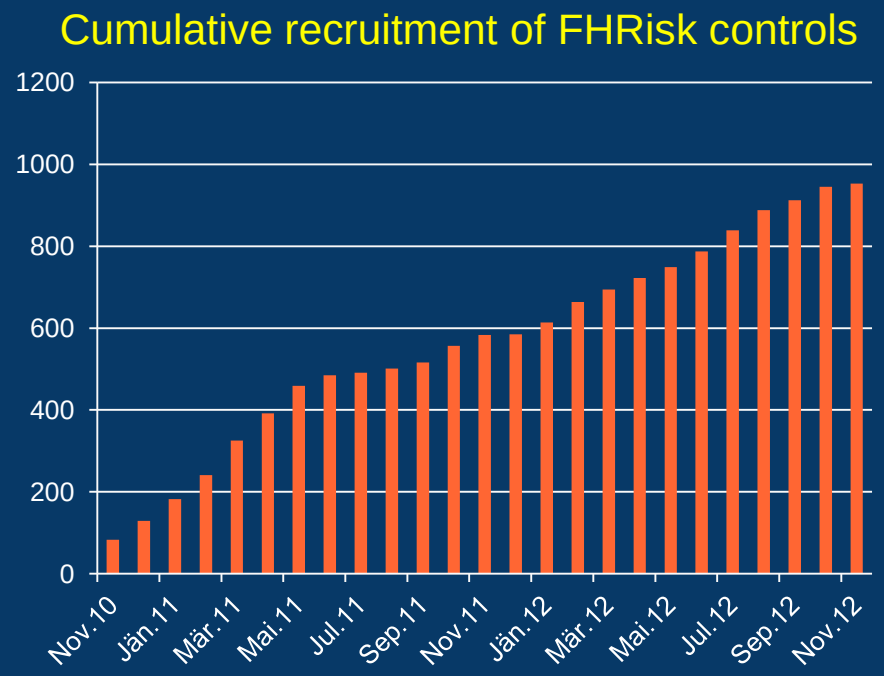
- 1200
- Matched
- Age
- Type of mammogram

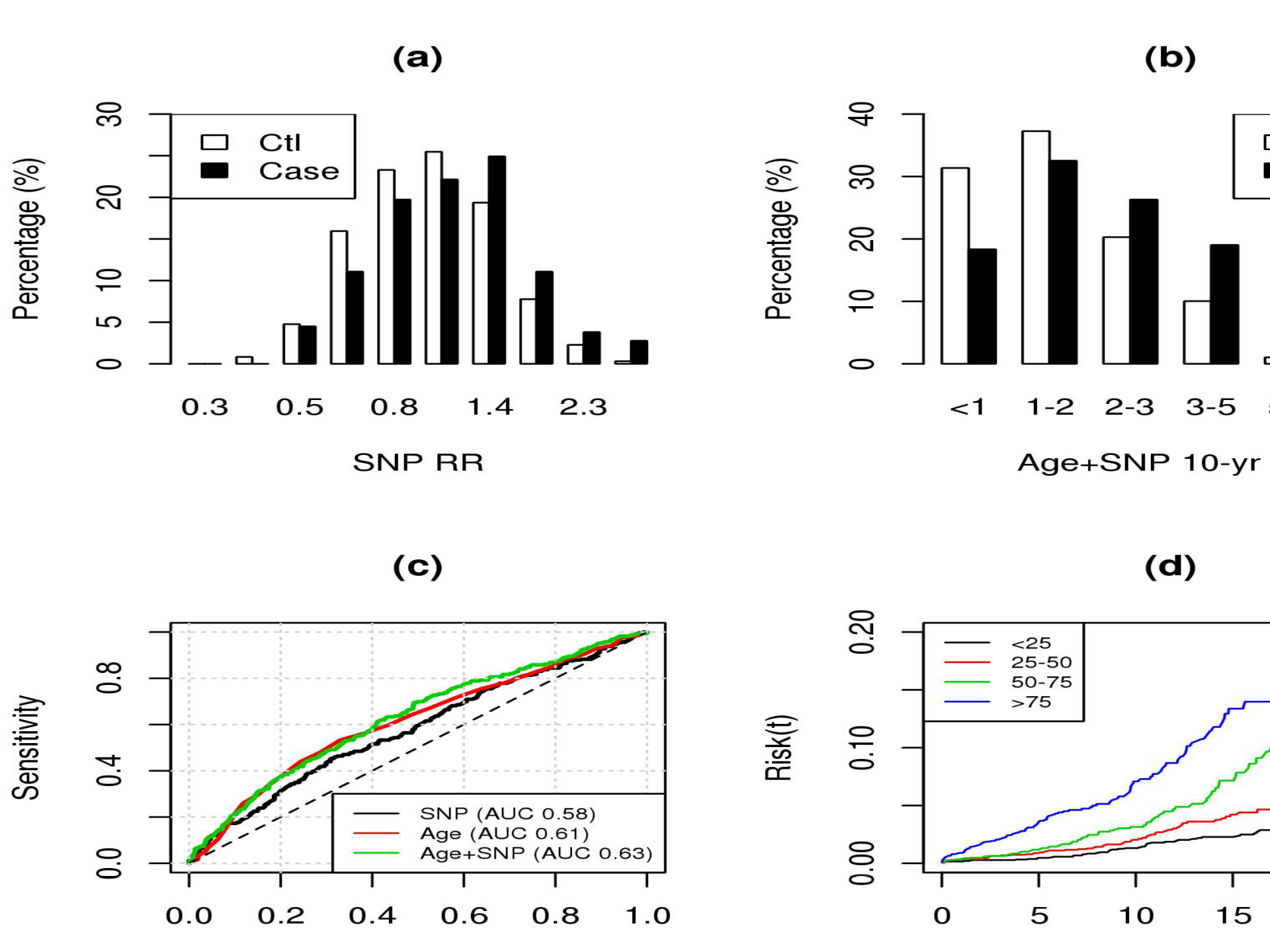
FHRisk recruitment

- Cohort study
  4,394 questionnaires received

- Case control study
  312 cases and 953 controls recruited






(a)
Percentage (%)
0
5
10
20
30
Ctl
Case
0.3
0.5
0.8
1.4
2.3
SNP RR
(b)
Percentage (%)
0
10
20
30
40
<1
1-2
2-3
3-5
Age+SNP 10-yr
(c)
Sensitivity
0.0
0.4
0.8
SNP (AUC 0.58)
Age (AUC 0.61)
Age+SNP (AUC 0.63)
0.0
0.2
0.4
0.6
0.8
1.0
(d)
Risk(t)
0.00
0.10
0.20
<25
25-50
50-75
>75
0
5
10
15

FH Risk Feedback

- 1200 women already advised on SNP scores
- RR <0.5 advised should (have) protect
- RR0.5-2.0 may not have affected risk
- RR >2 likely to (have) increase(d) risk

Validation in BRCA1/2

- FGFR2, Tox3, MAP3K, 2q, 1p11.2, SLC4A7, 6q25.1, LSP1, 5p12 –BRCA2
- Tox3, 2q, 6q25.1 –BRCA1

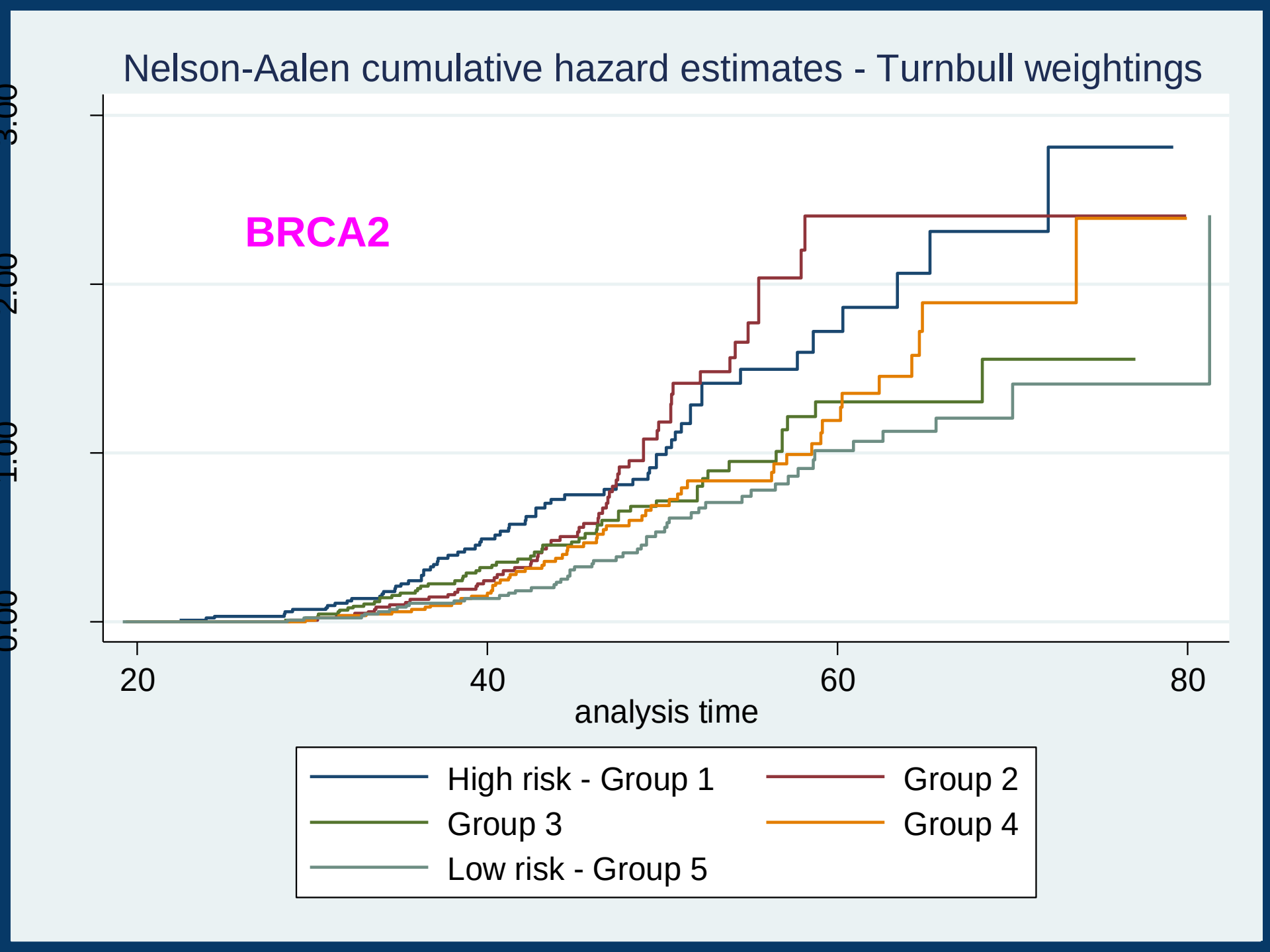
Validation in BRCA1/2

- Use all 18 validated SNPs
- Initially with Turnbull weightings
- Then with Antoniou weightings
- Then adding non validated SNPs

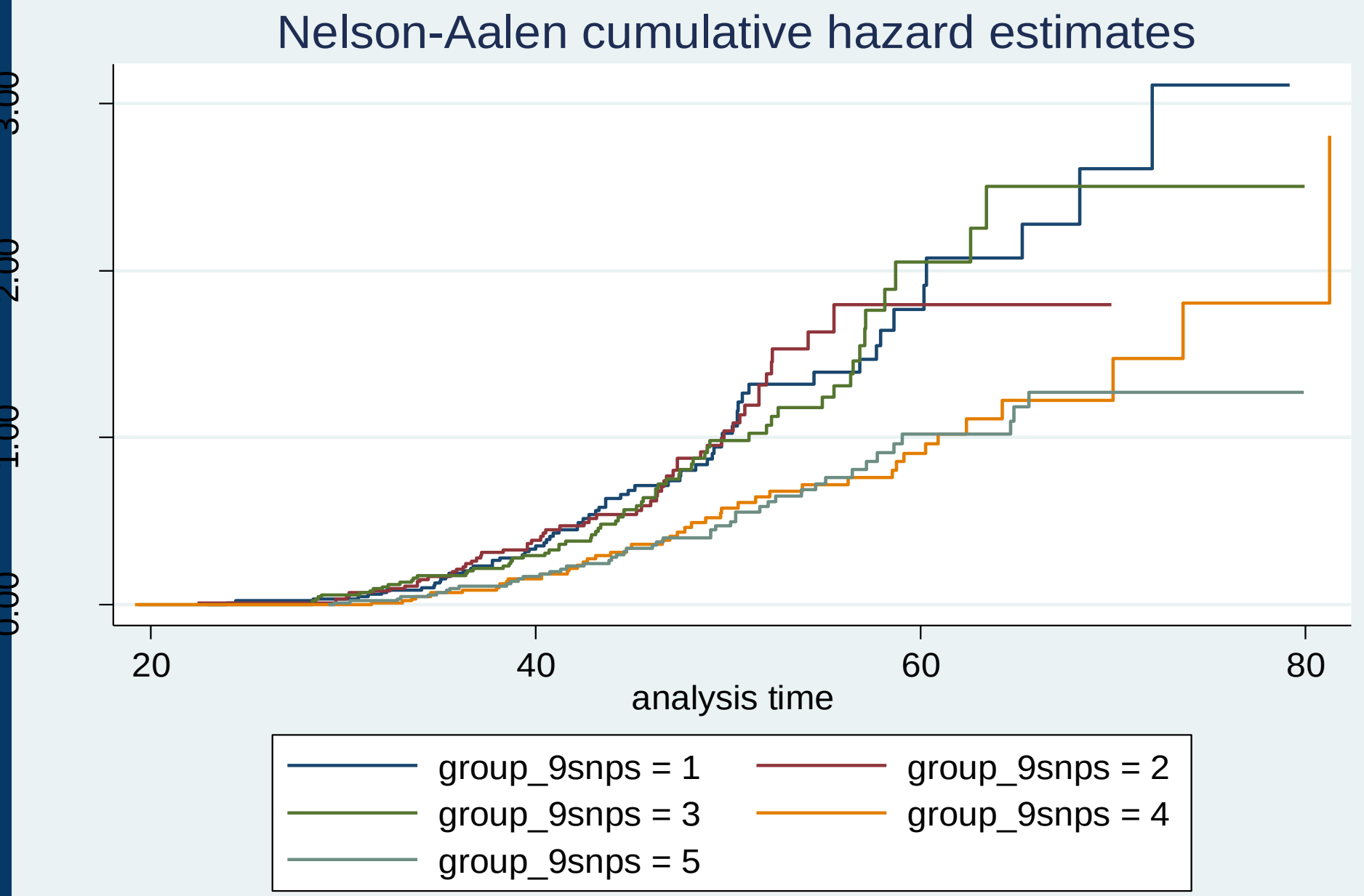
Validation in BRCA1/2

- 445 *BRCA2* carriers, 280 had developed breast cancer.
- 480 *BRCA1* patients, 269 developed breast cancer.

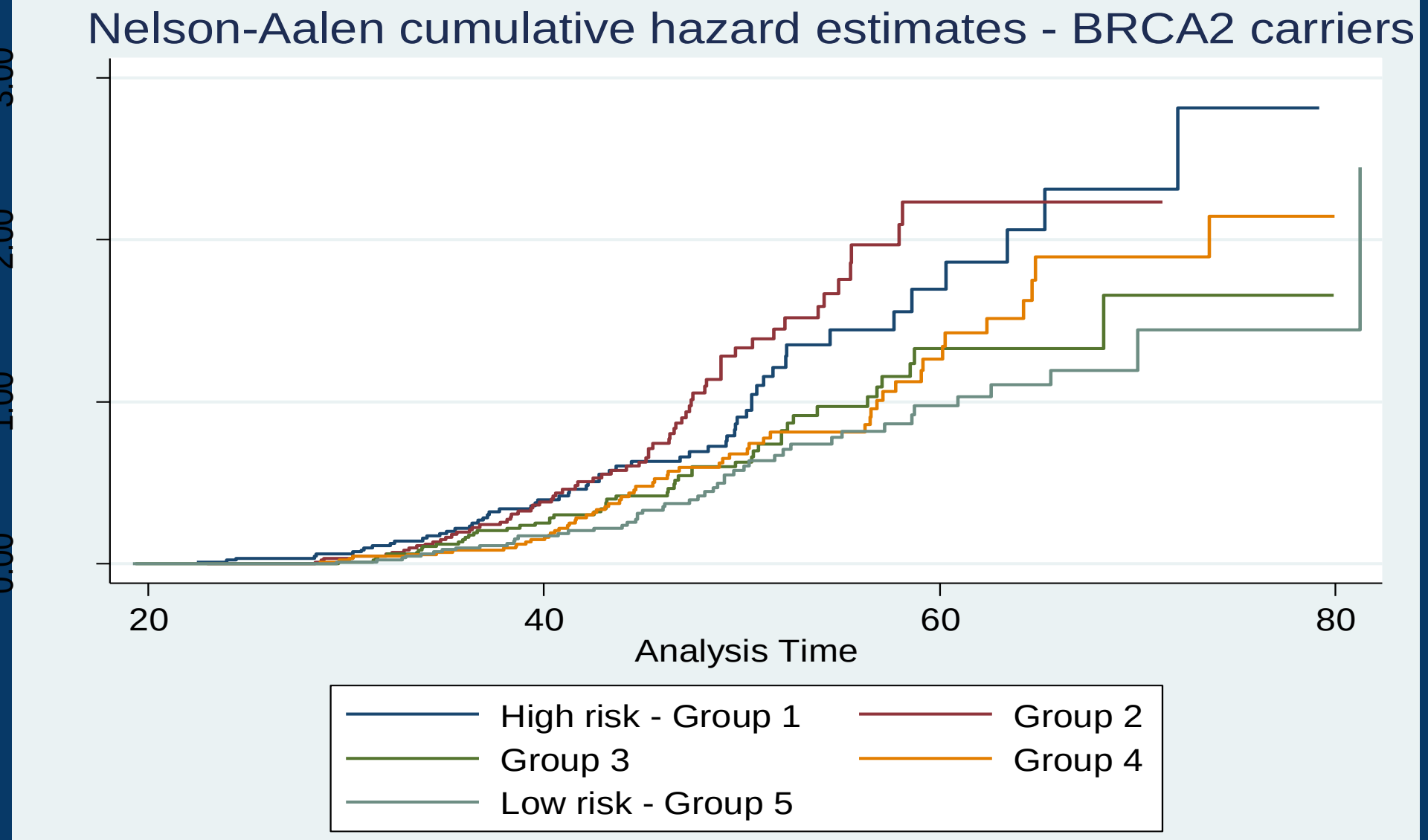
	Mean RR upper quintile	Mean RR lower quintile	Hazard Ratio upper to lower	Actual Hazard ratio from Cox analysis
18 SNPs *BRCA2*	2.10	0.47	0.224	0.47
18 SNPs *BRCA1*	1.96	0.51	0.260	1.19
9 SNPs Antoniou *BRCA2*	1.52	0.67	0.441	0.485
5 SNPs Antoniou *BRCA2*	1.46	0.70	0.480	0.566
3 SNPs Antoniou *BRCA1*	1.14	0.91	0.798	0.941
9 SNPs Antoniou *BRCA2* + non validated SNPs	1.74	0.60	0.345	0.524
3 SNPs Antoniou *BRCA1* + non validated SNPs	1.79	0.55	0.307	1.17


Nelson-Aalen cumulative hazard estimates - Turnbull weightings
BRCA2
0.00
1.00
2.00
3.00
20
40
60
80
analysis time
High risk - Group 1
Group 2
Group 3
Group 4
Low risk - Group 5

BRCA2 Antoniou weightings 9 SNPs



BRCA2 Antoniou weightings 9 SNPs + unvalidated



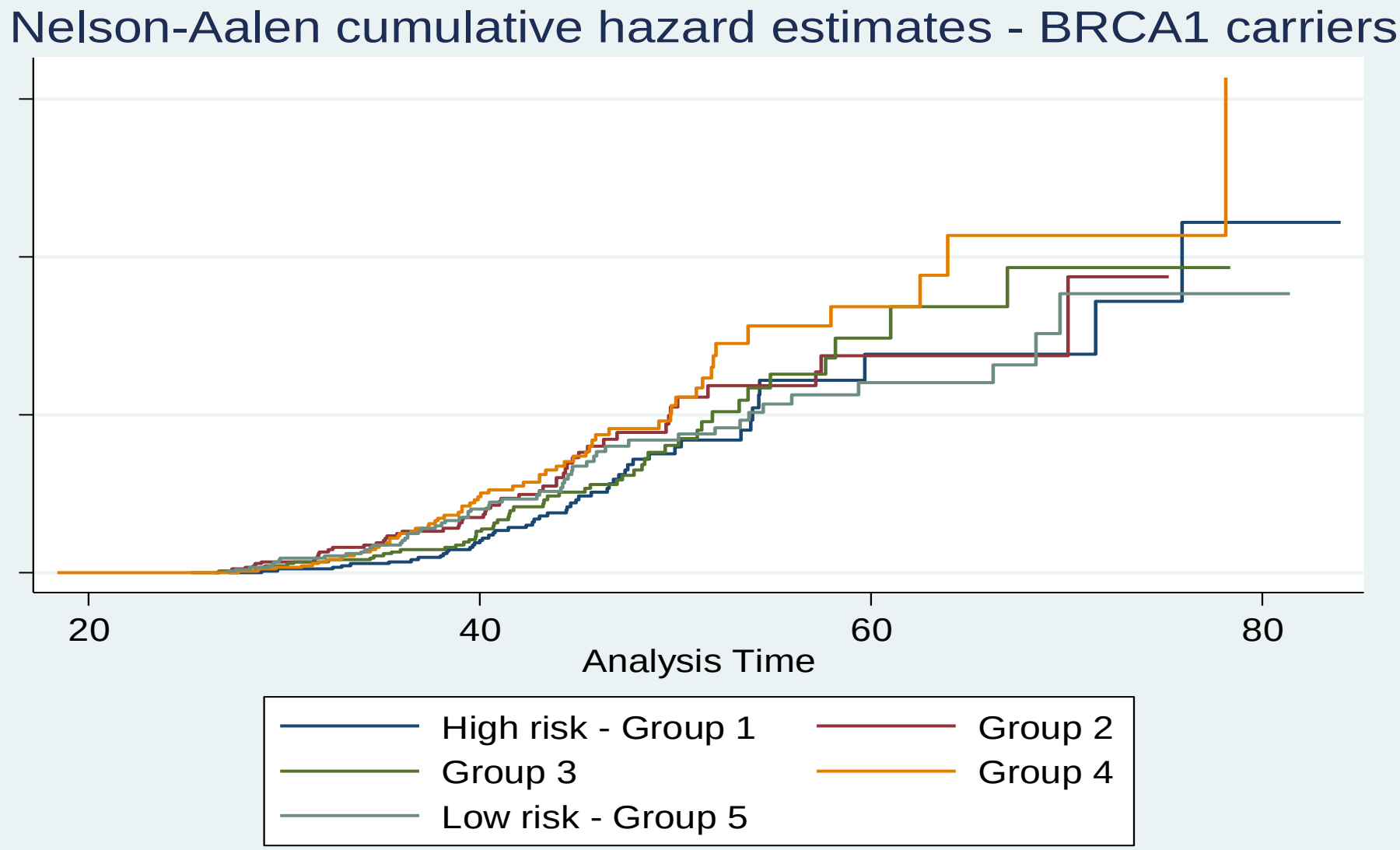
Uptake BRRM in unaffected non mutation carriers

- **50% of BRCA1/2 carriers quoted 60-85% risk have surgery by 5 years**
- **211/3515 (6%) of unaffected high risk women session 2**
- **51/798 (6%) of women at 40-45% had RRM**
- **45/1815 (2.5%) of High (33-39%) risk had RRM**
- **16/902 (1.8%) of high moderate 25-32% had RRM**

P <0.005

Evans et al CEBP 2009

BRCA1 Antoniou weightings 3 SNPs



SNPs in Prognosis

- A number of SNPs have been validated as prognostic markers
- Covered by Gillian Mitchell

Conclusions

- BRCA2 -9 validated SNPs have good correlation but could be improved by additional SNPs
- BRCA2 SNPs ready for prime time
- Can use to guide RRM advice
- BRCA1 not good correlation

Ingham S et al Clin Genet. 2013

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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

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Contacts

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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 Foundation Trust

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Genesis creating a future without breast cancer

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- Mrs Ann Brain
- Mr Gary Ross
- Ms Victoria Rose
- Mr Stuart Wilson
- Prof N Bundred

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Others
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