How can cancer risks and genetic prediction models help oncologists in the clinic?

- Prof D Gareth Evans
- Genetic Medicine
- St Mary's, UHSM and Christie Hospital Manchester UK

Disclosure slide

- I have no Conflicts of Interest to declare

Types of risk assessment

- Future cancer risks
- Risk of recurrence
- Risk of mortality from cancer
- Likelihood of a genetic mutation

Types of familial risk

- Highly penetrant dominant cancer predisposition syndromes
  - BRCA1/2
  - LI Fraumeni
- Low penetrance syndromes
  - CHEK2
- Familial aggregation

Genetic Factors

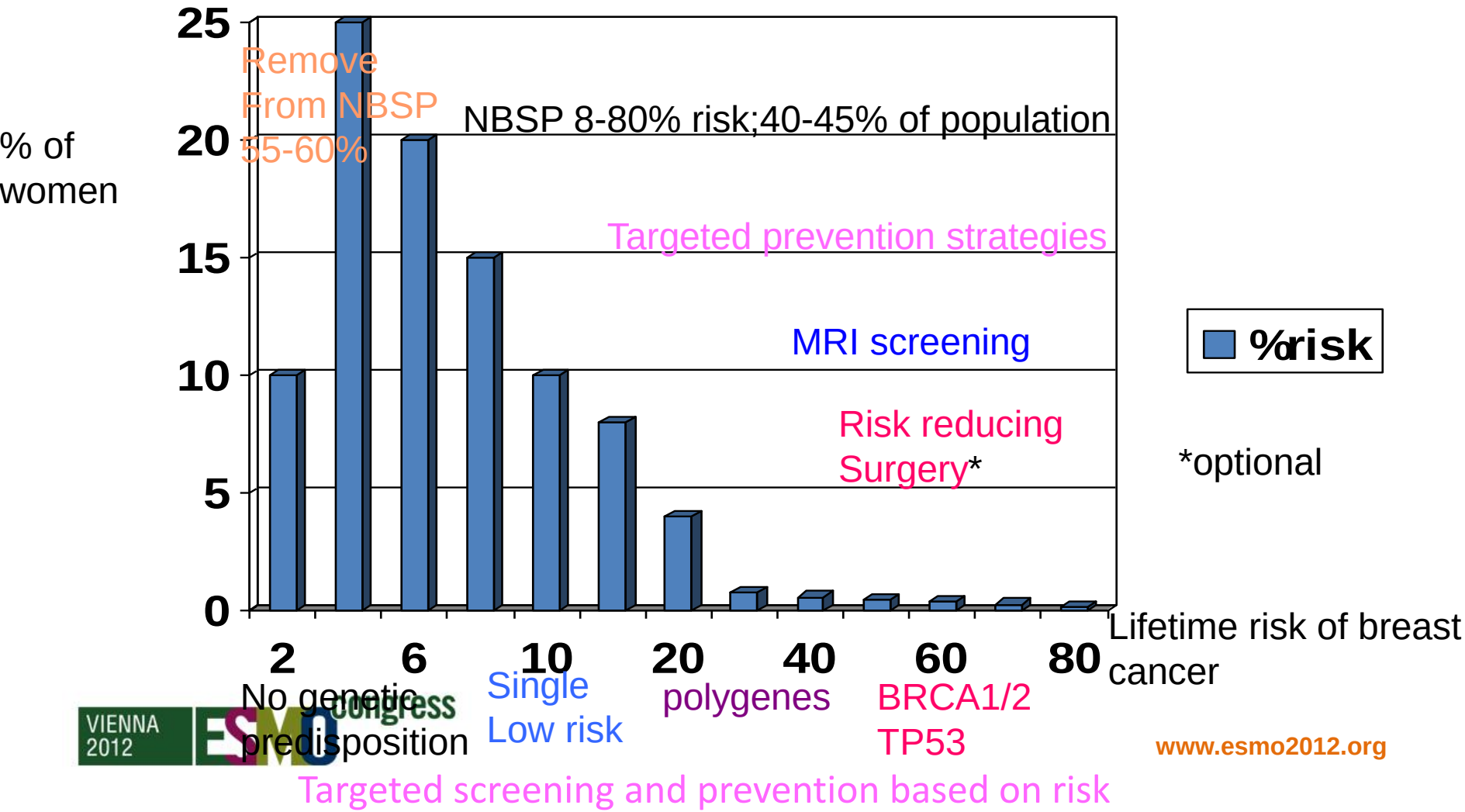
	Gene	Risk (by age 70)	Population Carrier Frequency
High Penetrance	BRCA1 (17q)	5-10 (65-85%)	1 in 860
	BRCA2 (13q)	5-10 (45-85%)	1 in 740
	TP53(p53) (17p)	10 (50-60% by age 45)	1 in 5,000
Moderate Penetrance	PTEN (10q)	?? (25-50%)	1 in 250,000
	ATM (11q)	2.0 (23%)	1 in 100
	CHEK2 (22q)	2.4 (11%)	1 in 90
	PALB2 (16p)	2.3 ??	1 in 1,000

Table modified from Rahman et al. 2006, Willems et al., 2007 and Bradbury et al., 2007)

Genes predisposing to breast cancer GWS

	Allele freq	Het RR	HomoZ RR
FGFR2	0.38 *(0.30)*	1.23 (1.18-1.28)	1.63 (1.53-1.72)
TNRC9/	0.46*(0.60)*	1.14 (1.09-1.20)	1.23 (1.17-1.30)
TNRC9/ LOC643714	0.44*(0.20)*	1.10 (1.05-1.16)	1.19 (1.12-1.27)
MAP3K1	**0.30**	1.06 (1.02-1.11)	1.17 (1.08-1.25)
LSP1	**0.31**	0.94 (0.90-0.98)	0.95 (0.89-1.01)
H19	**0.34**	1.06 (1.01-1.11)	1.18 (1.10-1.25)

Breast cancer risk in general population



Genetic testing: the story so far

High risk (penetrant) dominant genes (BRCA1/2)

- Genetic testing requires mutation in affected individual
- Private (Myriad) tests are uninformative if negative
- Tests give un-interpretable results (unknown variant)
- Reduced sensitivity means even BRCA1/2 cannot be exclude
- Penetrance varies from family to family

Genetic testing: the Future

Multiple genes tested

Tests may include up to 100-150 genes for breast cancer susceptibility

- Results could predict actuarial risks across a huge range
- Tests will not give un-interpretable results
- Sensitivity will be near 100%
- Penetrance can be assessed from all genetic and other info

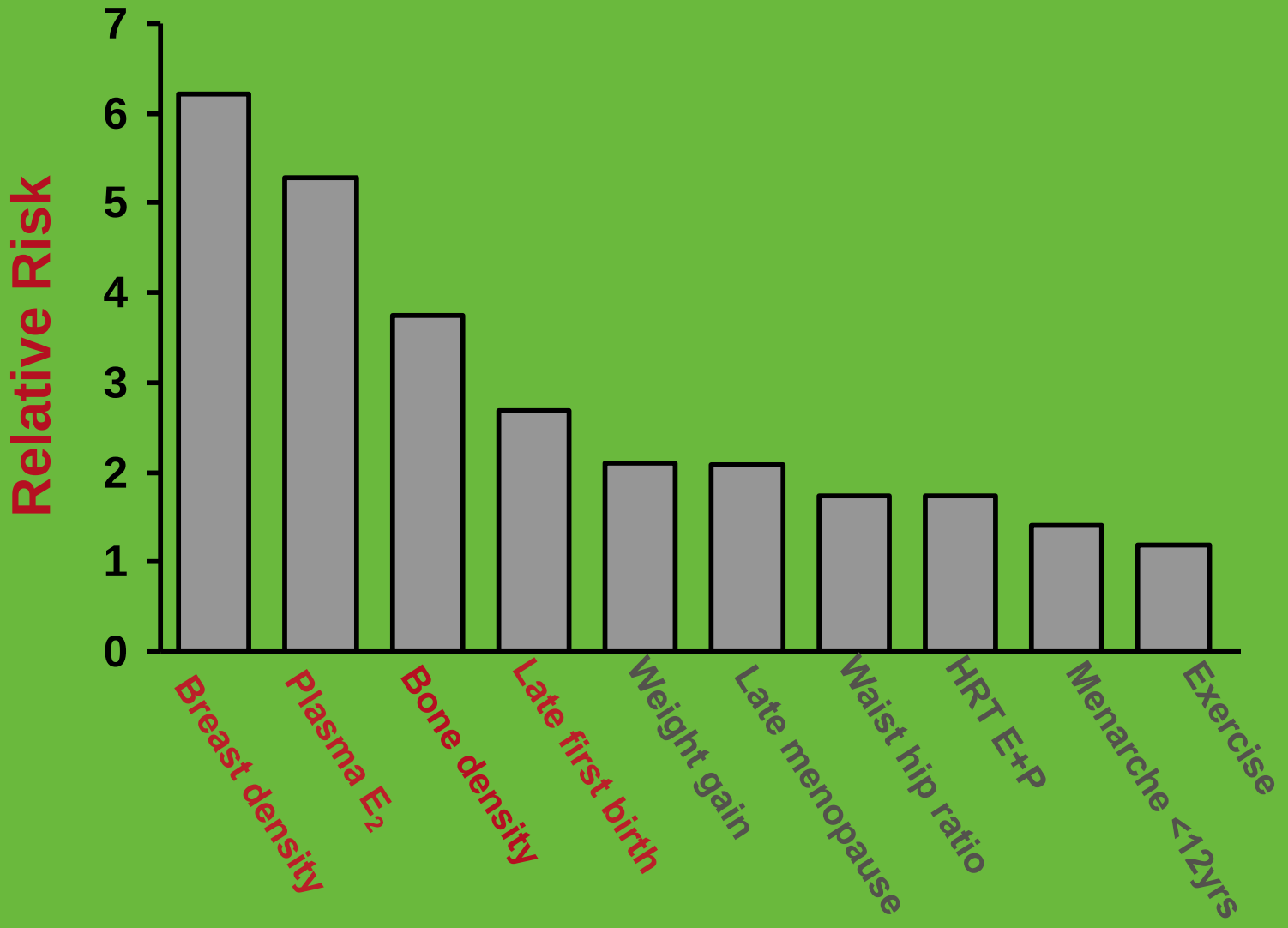
Predicting risk of breast cancer

Risk factors:

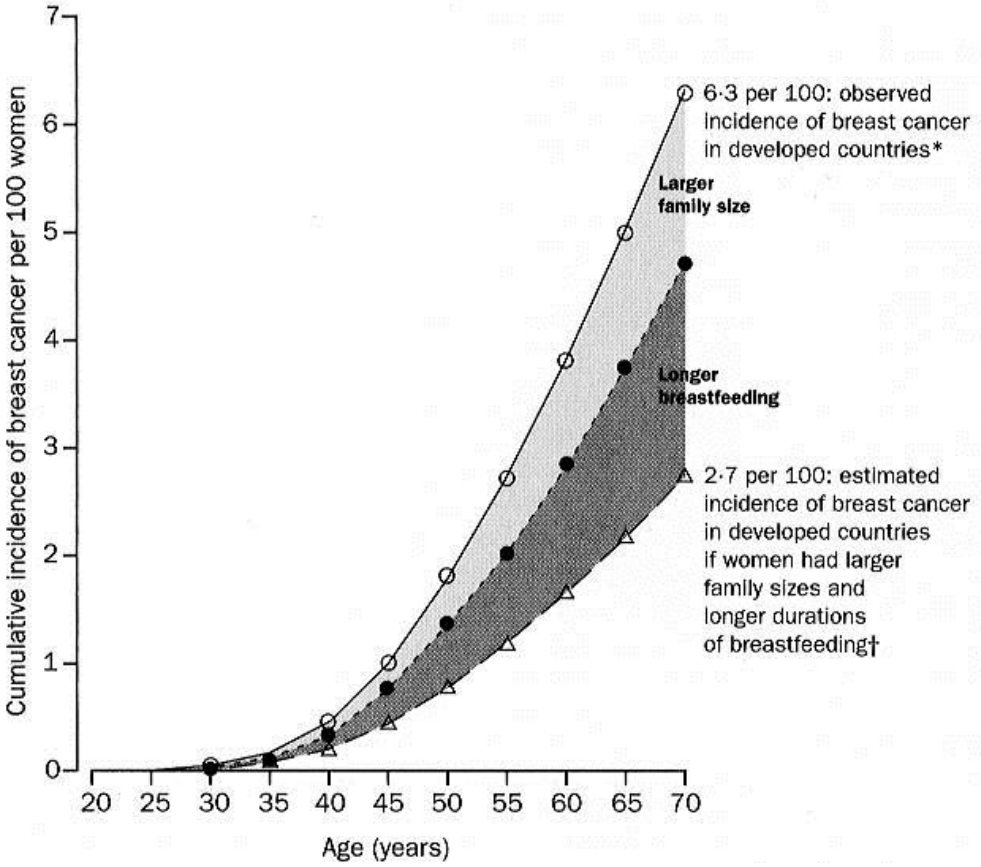
- Lifestyle
- Genetics & family history
- Breast density

Women participating in the PROCAS study will have their own personal risk of breast cancer calculated

Potential risk factors



Estimated cumulative incidence of breast cancer in developed countries if women had family sizes and breastfeeding patterns typical for developing countries



The Lancet, Vol 360, July 2002

Lifestyle risk factors

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

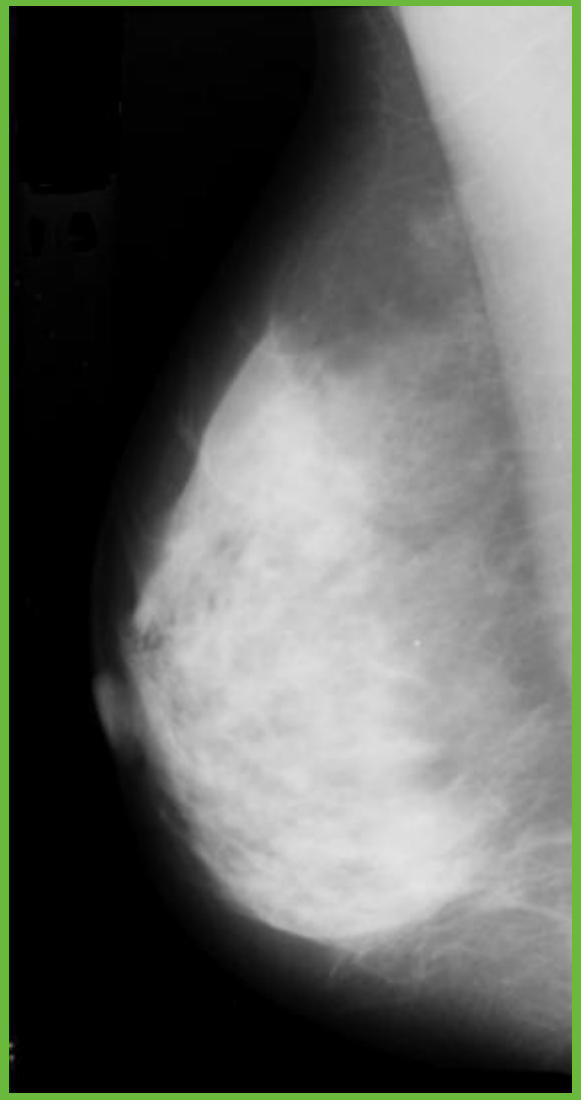
Breast Density

- 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

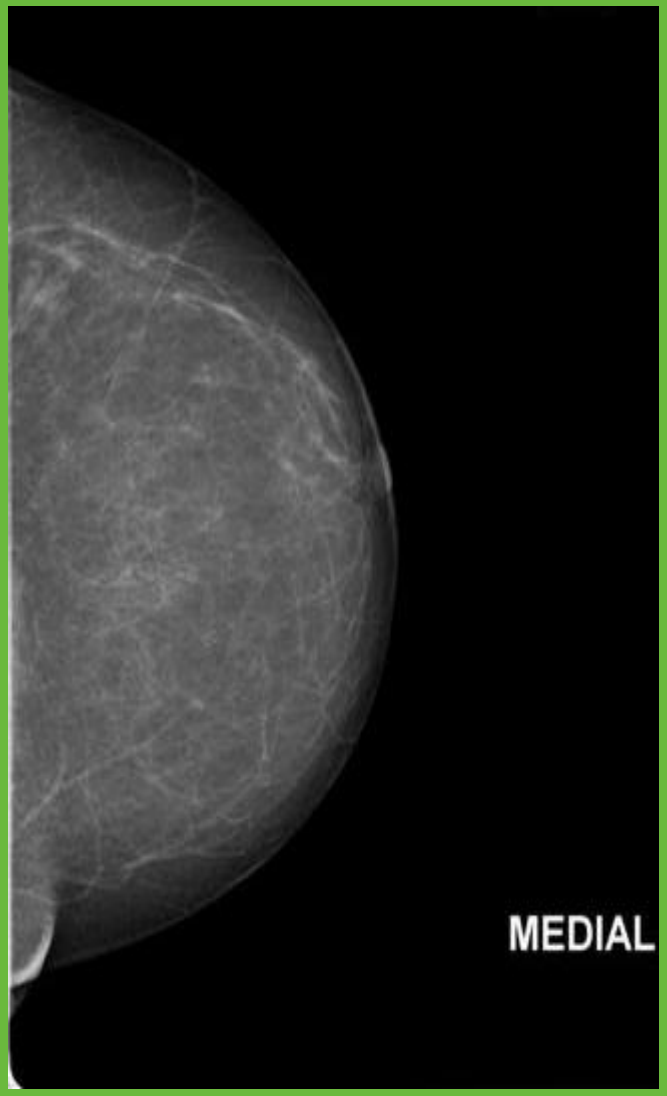
Dense breast

Lifetime risk 25%



Non dense breast

Lifetime risk 4%



Risk Prediction Models

- A number of models used to predict risk.

- Each model uses different risk factors to calculate risk.

Risk is calculated as:

- Risk of having BRCA1/2 mutation
- Risk of developing breast cancer over a given time period.

Appropriate models

- Gail
  - 2852 women with invasive breast cancer and 3146 controls compared for FHx, no of biopsies, age at menarche, first live birth, menopause
  - most useful for women with no family history and regular screening
- Claus
  - 3400 women with breast cancer and 3600 controls
  - Most valuable for women whose major risk is their family history
- BRCAPRO

  -Calculates likelihood of being a mutation carrier
- Tyrer Cuzick

  -Calculates the likelihood of BRCA1, BRCA2 or BRCAx and then breast cancer risk over time

Model					
Variable	Gail	Claus	Ford	Tyrer	Manual
Age	**Y**	**Y**	**Y**	**Y**	**Y**
BMI	N	N	N	**Y**	N
Menarche	**Y**	N	N	**Y**	**Y**
1st Child	**Y**	N	N	**Y**	**Y**
Menopause	N	N	N	**Y**	**Y**
Breast biopsies	**Y**	N	N	**Y**	**Y**
ADH	**Y**	N	N	**Y**	**Y**
LCIS	N	N	N	**Y**	**Y**

Model					
Variable	Gail	Claus	Ford	Tyrer	Manual
1st degree relatives	**Y**	**Y**	**Y**	**Y**	**Y**
2nd degree relatives	N	**Y**	**Y**	**Y**	**Y**
Age of onset of Ca	N	**Y**	**Y**	**Y**	**Y**
Bilateral breast Ca	N	N	**Y**	**Y**	**Y**
Ovarian Ca	N	N	**Y**	**Y**	**Y**
Male breast Ca	N	N	**Y**	N	**Y**

Risk assessment in breast cancer

- Several models in regular use
- Gail –no age, but other factors
- Claus –no other factors
- BRCApro Ford –no other factors, but ovarian
- Tyrer-Cuzick –model from IBIS1
- BOADICEA-not validated for BC risk yet

Claus tables for 1 FDR

AGE	20-29	30-39	40-49	50-59	60-69	70-79
29	.007	.005	.003	.002	.002	.001
39	.028	.024	.018	.012	.010	.008
49	.065	.054	.042	.033	.028	.025
59	.126	.086	.074	.069	.050	.045
69	.181	.130	.111	.102	.090	.082
79	.231	.195	.162	.140	.126	.118

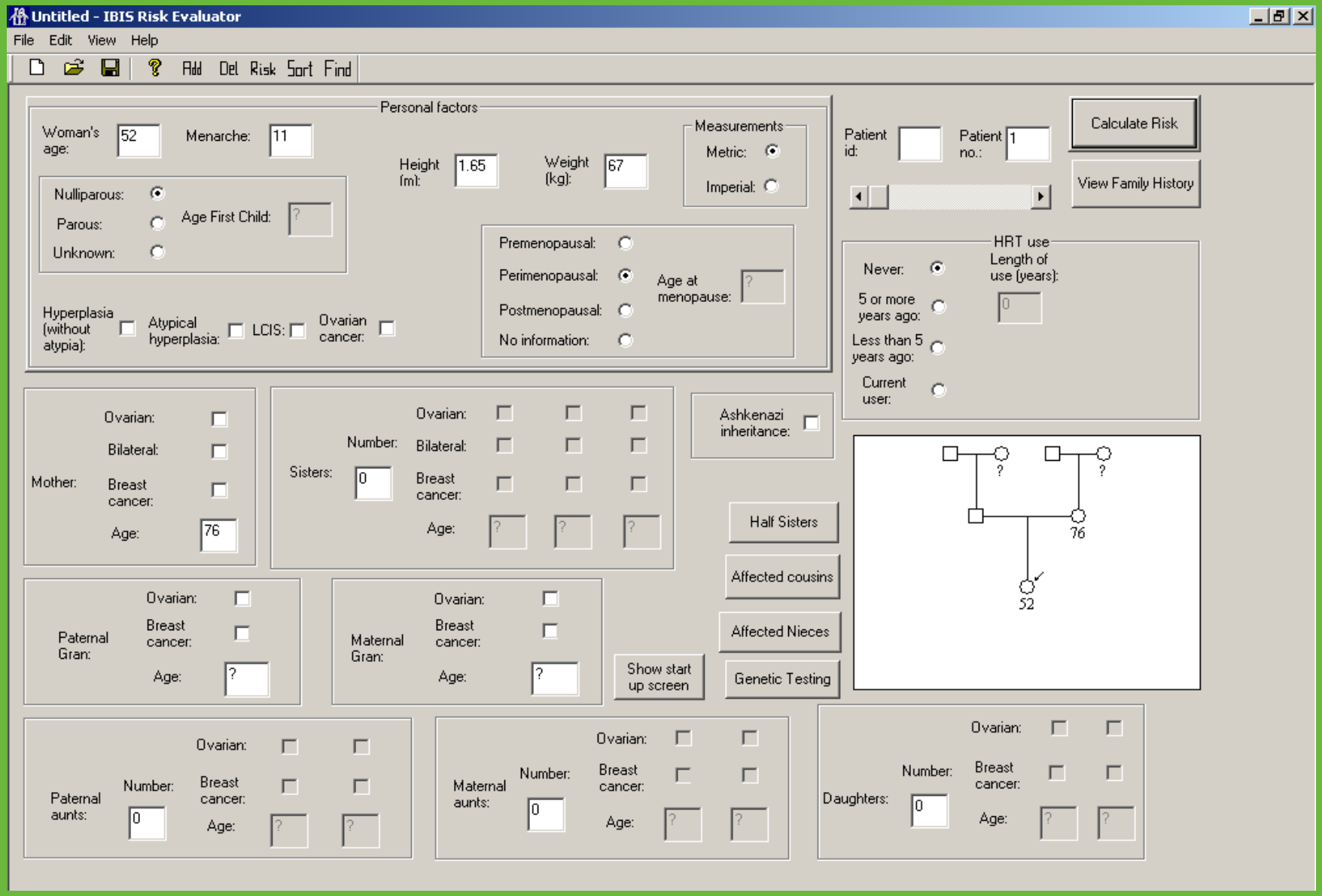
Assessment of risk prediction models

- 1933 women in FHC UHSM – 52 cancers
- Compute Expected to Observed

Amir et al J Med Genet 1993

	E/O	95% CI
• Gail	0.48	0.54-0.90
• Claus	0.56	0.59-0.99
• Ford	0.49	0.52-0.86
• Tyrer-Cuzick	0.81	0.85-1.41
• Manual	0.89	0.95-1.58

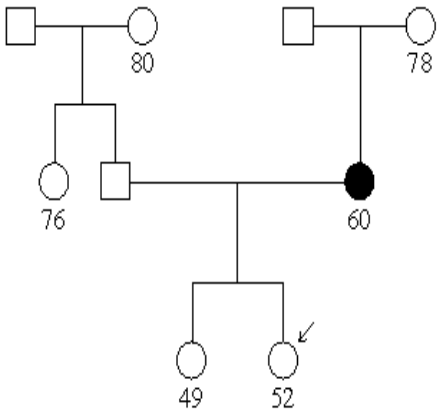
Tyrer-Cuzick Risk Prediction Algorithm

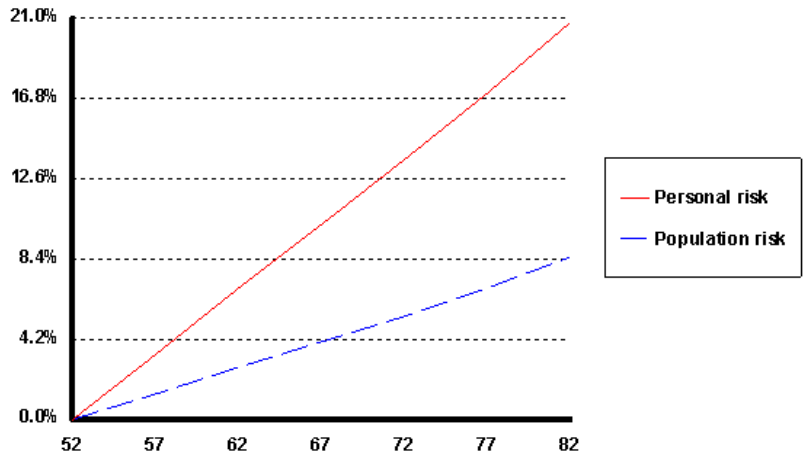


Tyrer-Cuzick Risk Prediction Model

Woman's age is 52 years.
Age at menarche was 11 years.
Person is nulliparous.
Person is perimenopausal.
Height is 5 ft 4 ins.
Weight is 10 st 7 lb.
Woman has never used HRT.

Risk after 10 years is 6.863%.
10 year population risk is 2.674%.
Lifetime risk is 19.23%.
Lifetime population risk is 7.802%.
Probability of a BRCA1 gene is 0.035%.
Probability of a BRCA2 gene is 0.373%.





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

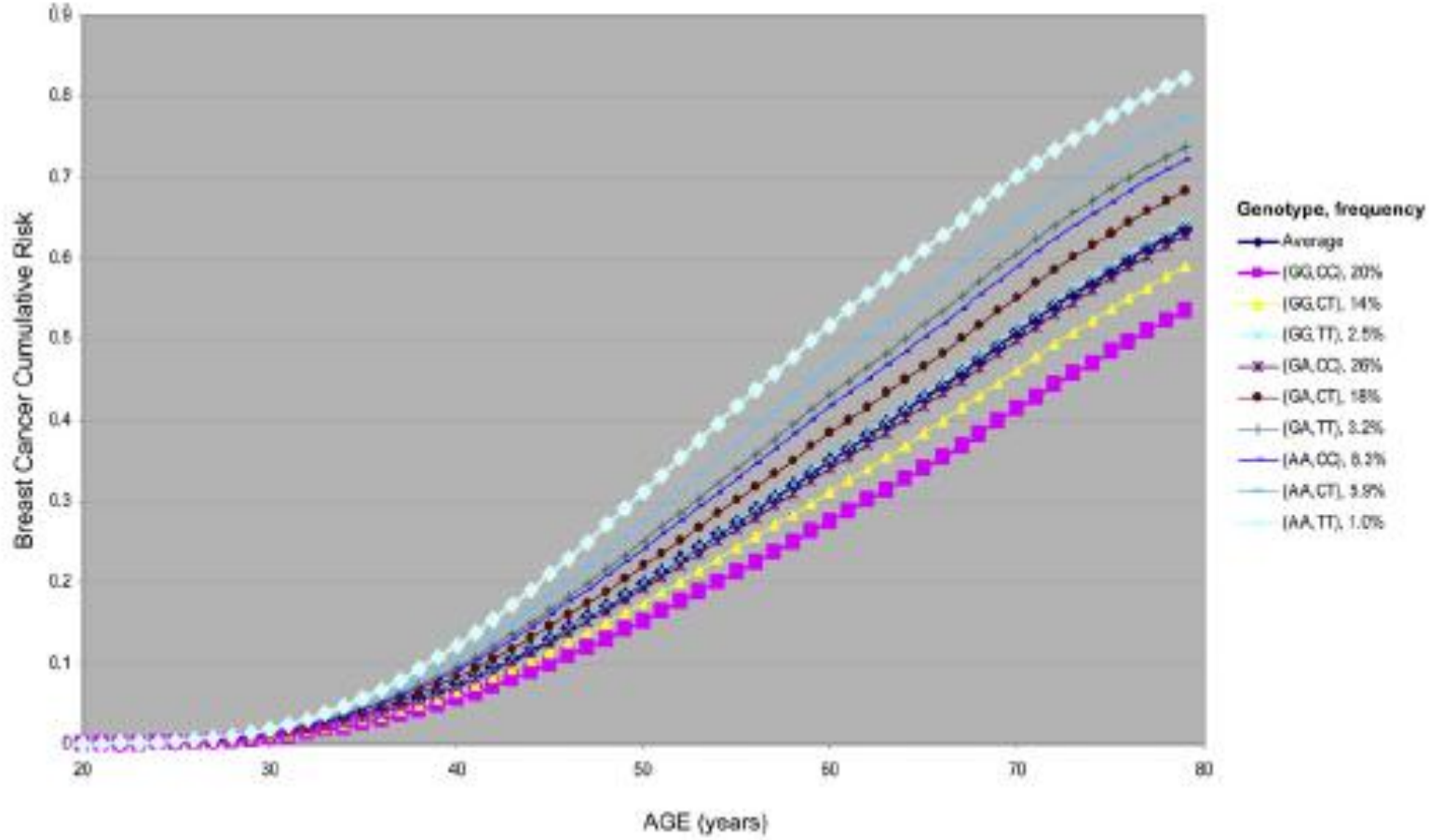
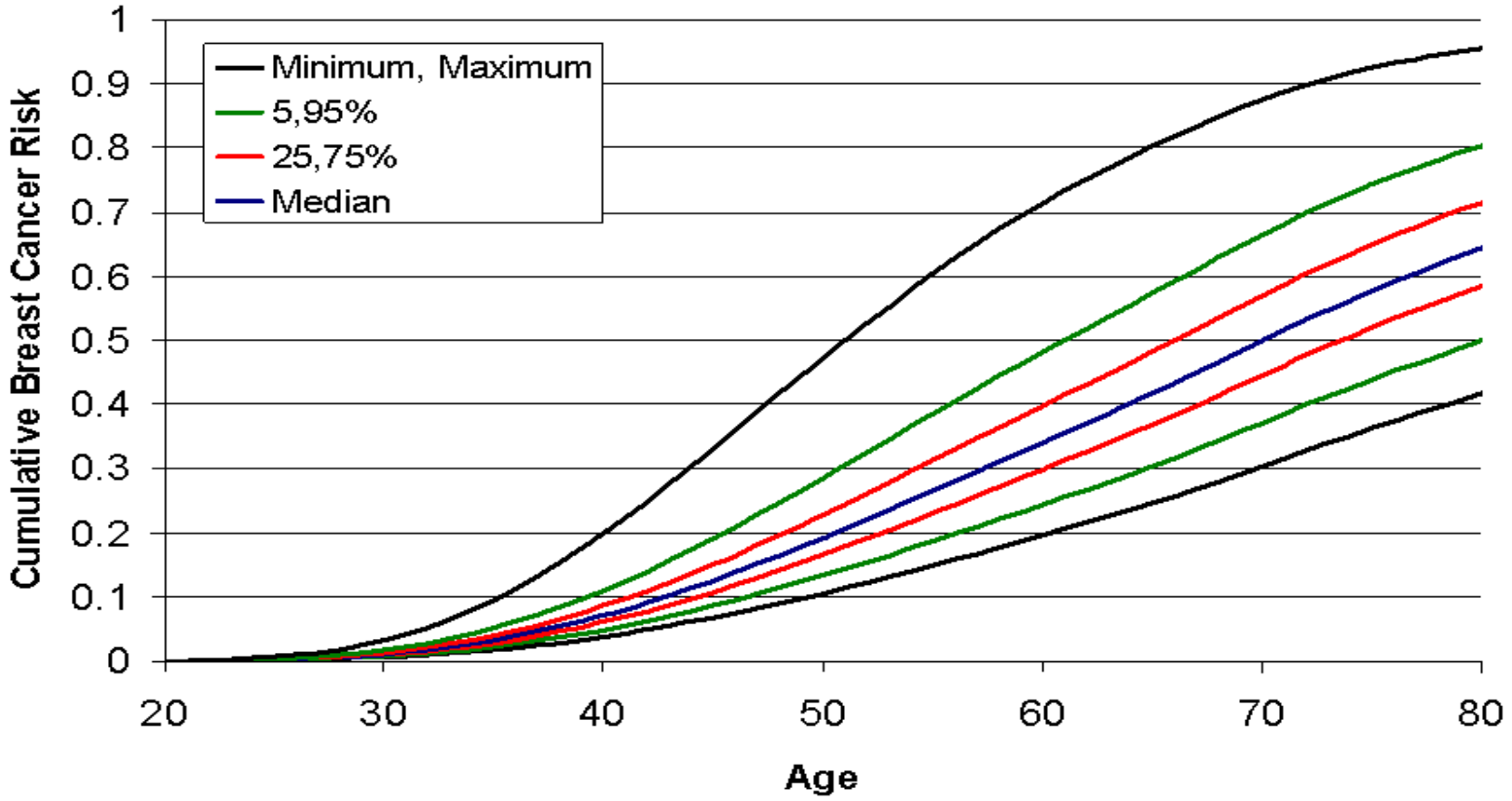


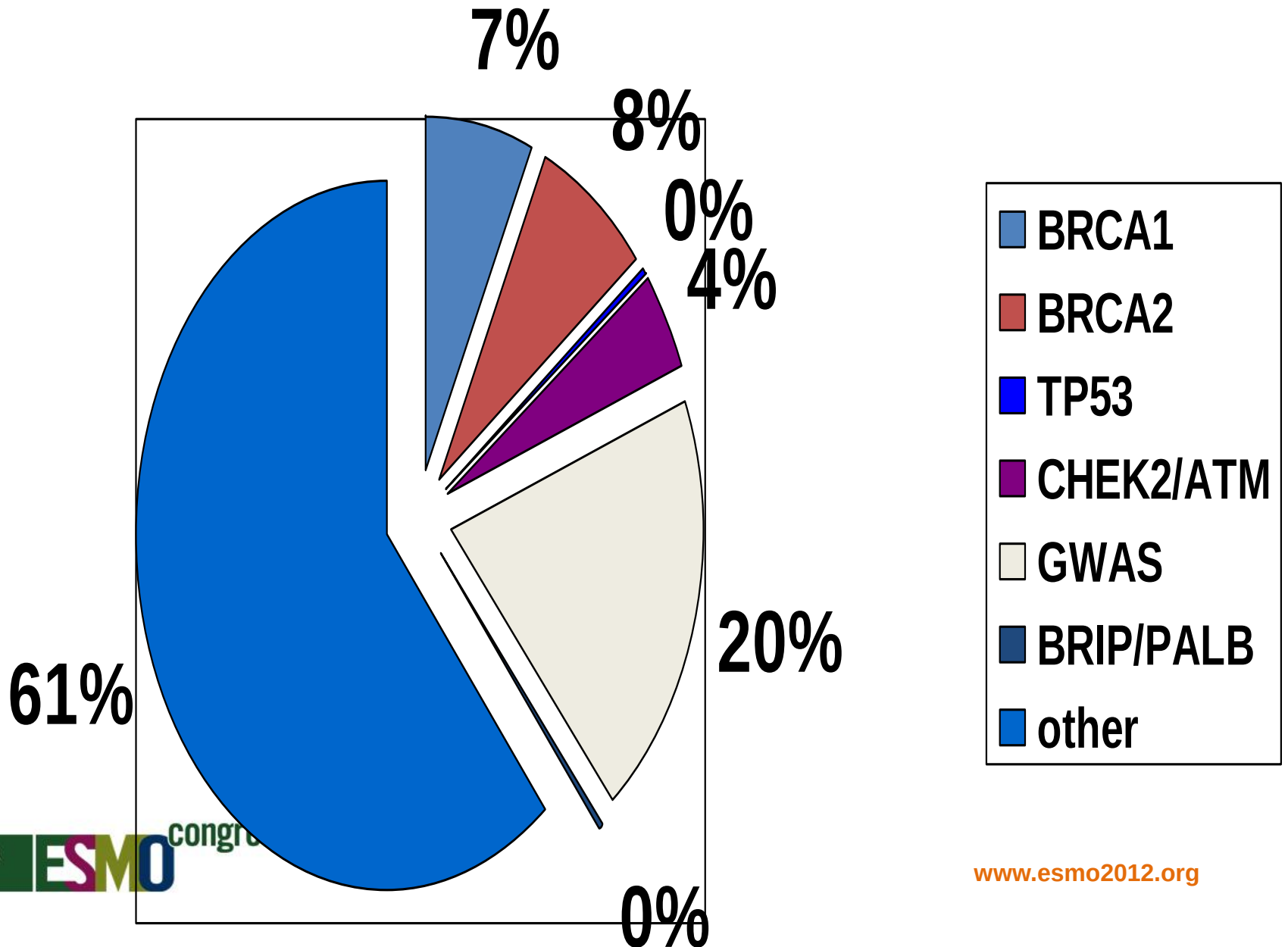
Figure 4. Cumulative Risk of Breast Cancer among *BRCA2* Mutation Carriers by Combined *FGFR2* and *TNRC9* Genotype under a Multiplicative Model for the Joint Effects of the Loci

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



Proportion of familial breast cancer



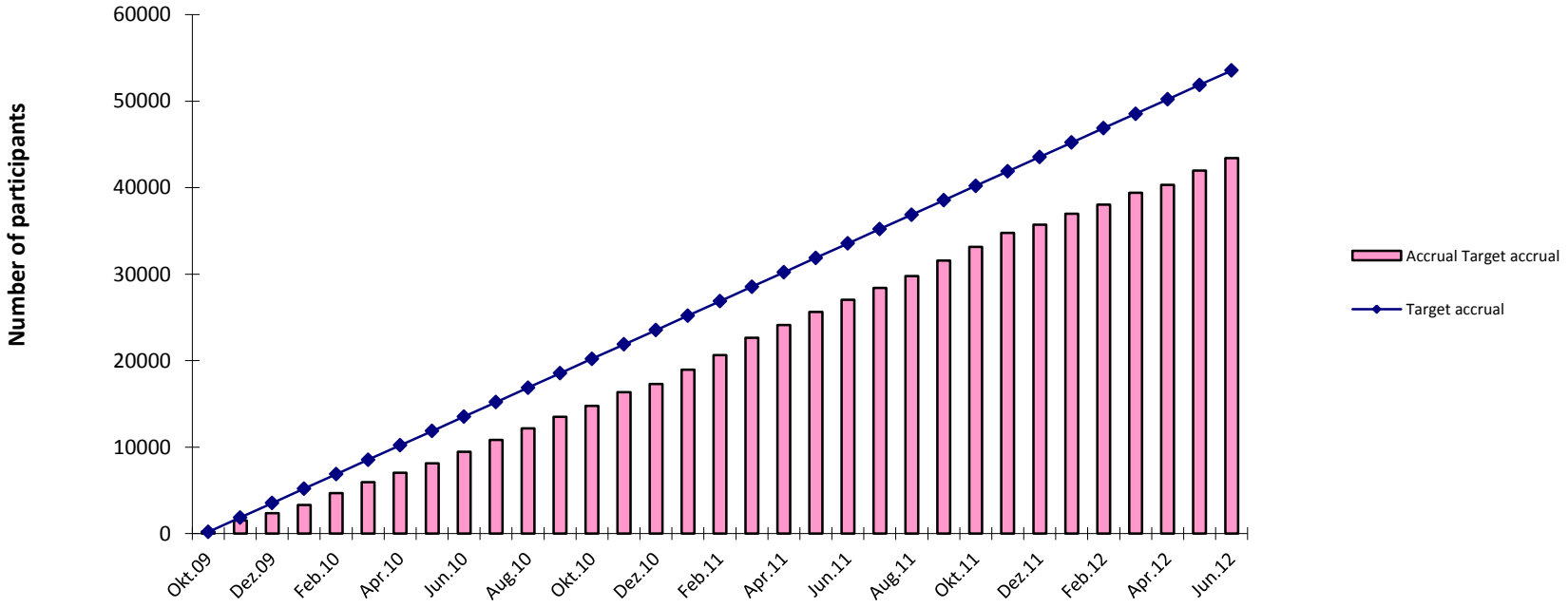
Aims of the PROCAS study

- 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 e.g extra screening, dietary interventions

PROCAS Recruitment

Number recruited to 29/08/2012 - 46519

Target to 29/08/2012 – 56,878

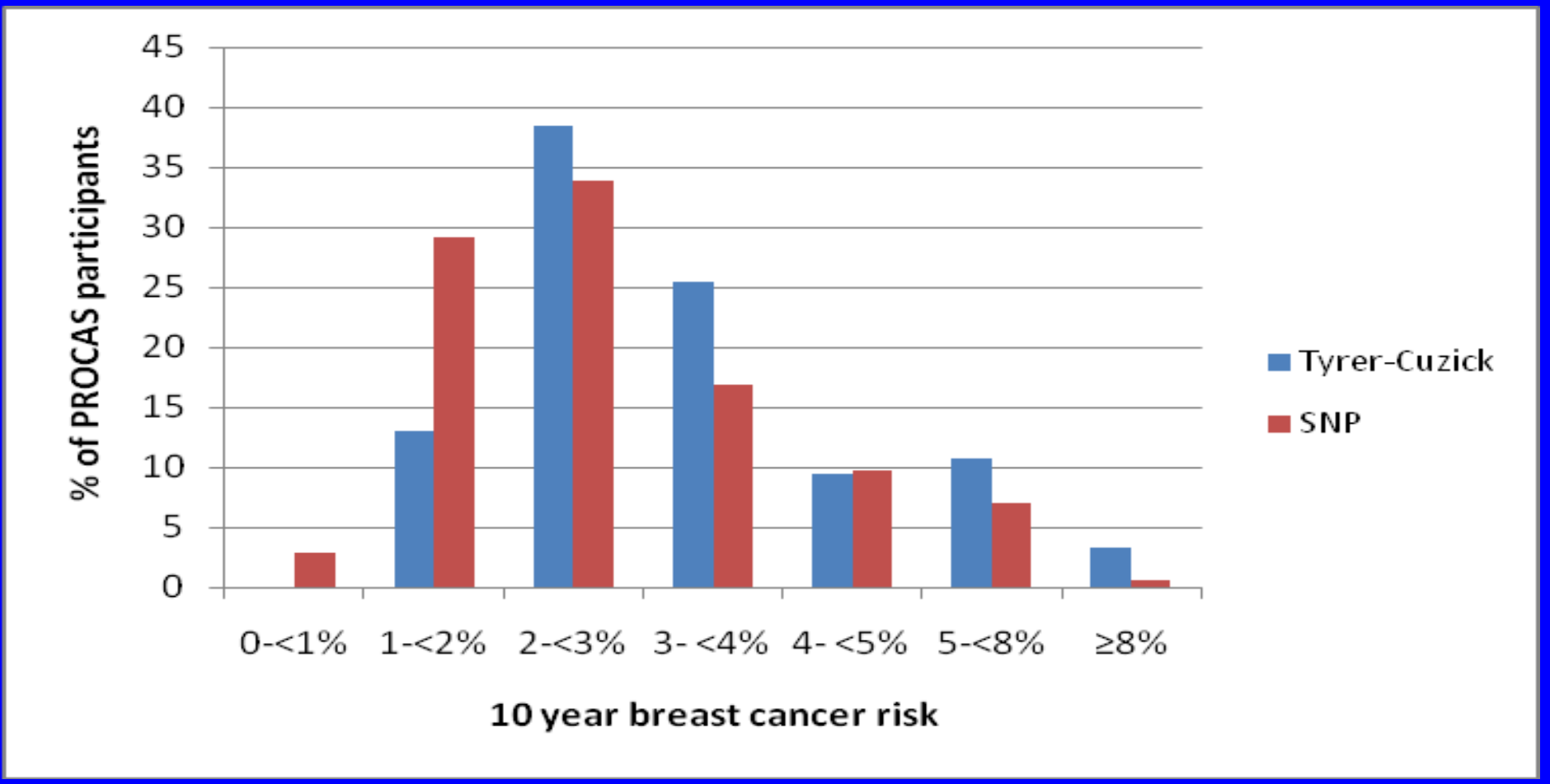


DNA testing

- 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
- 4200 recruited

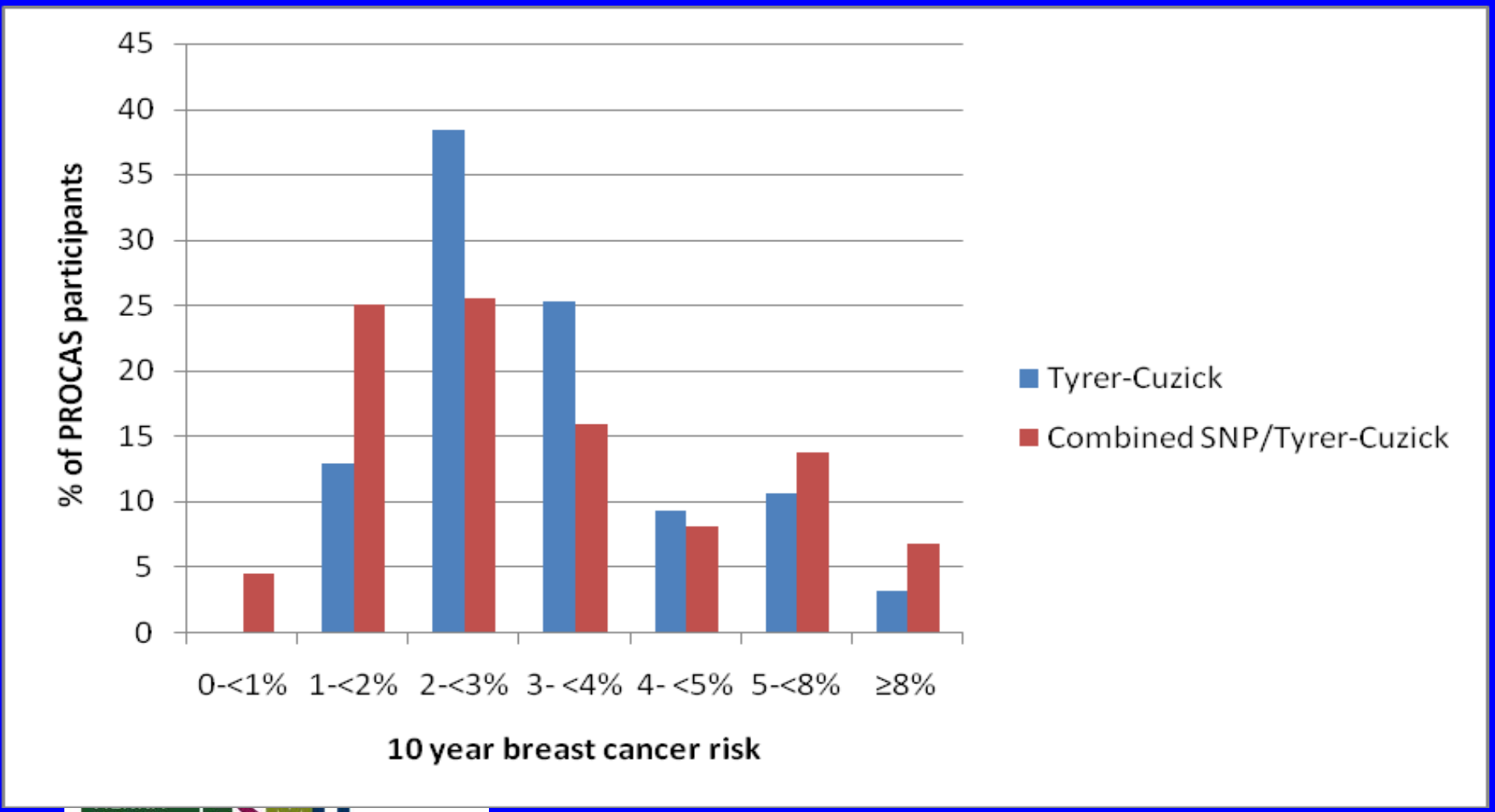
SNP	gene	risk e	RAF	weight 0	weight 1	weight 2	0 freq	1 freq	2 freq	RR	W*F
rs2981579	FGFR2	T	42	0.72	1.03	1.47	34	49	17	1.43	100
rs10931936	CASP8	C	74	1.20	1.06	0.93	7	38	55	0.88	100
rs3803662	TOX3	T	26	0.86	1.12	1.45	55	38	7	1.3	100
rs889312	MAP3K	C	28	0.89	1.08	1.32	52	40	8	1.22	100
rs13387042	2q	A	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	*RAD51L1*	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

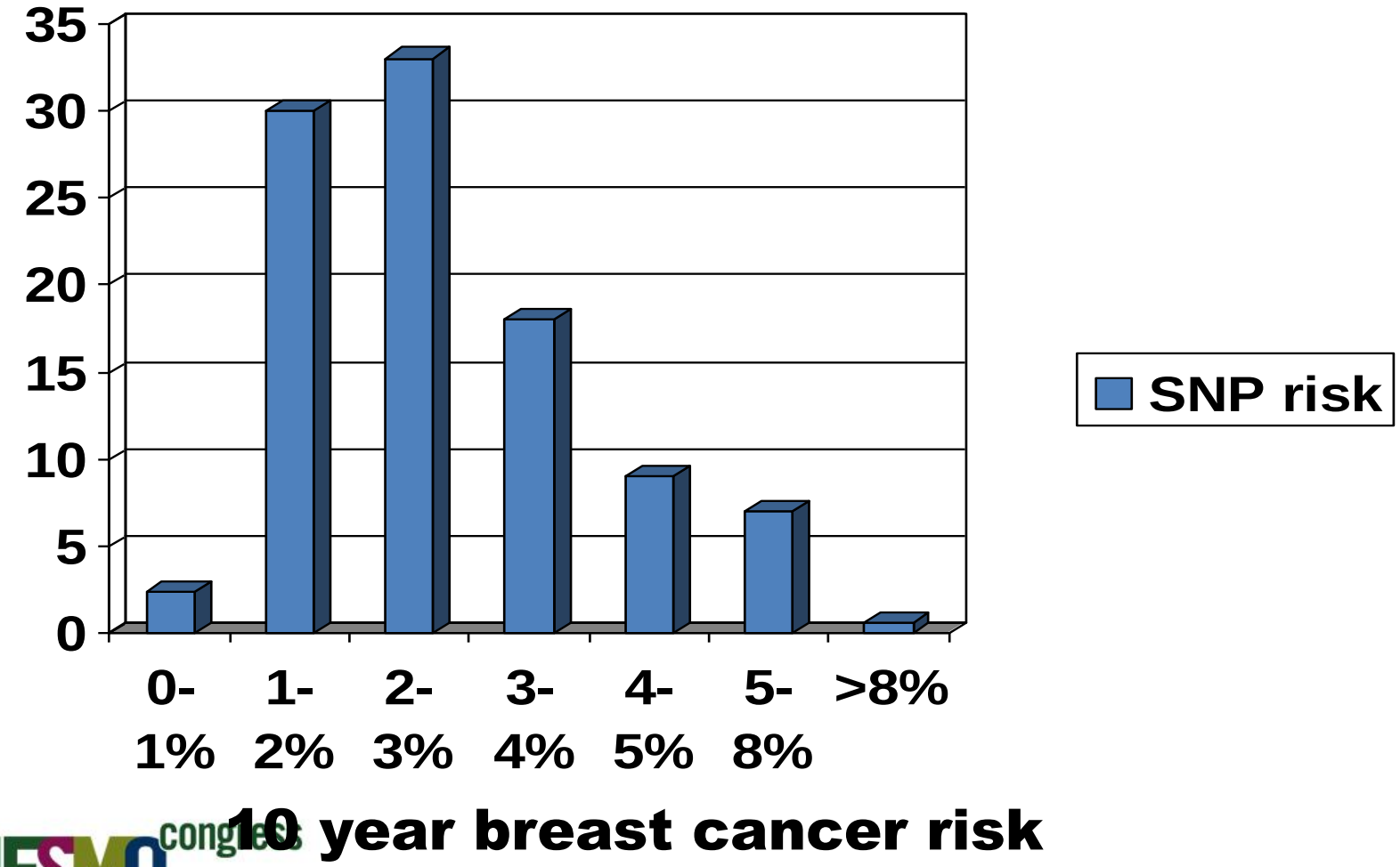


10 year breast cancer risk

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



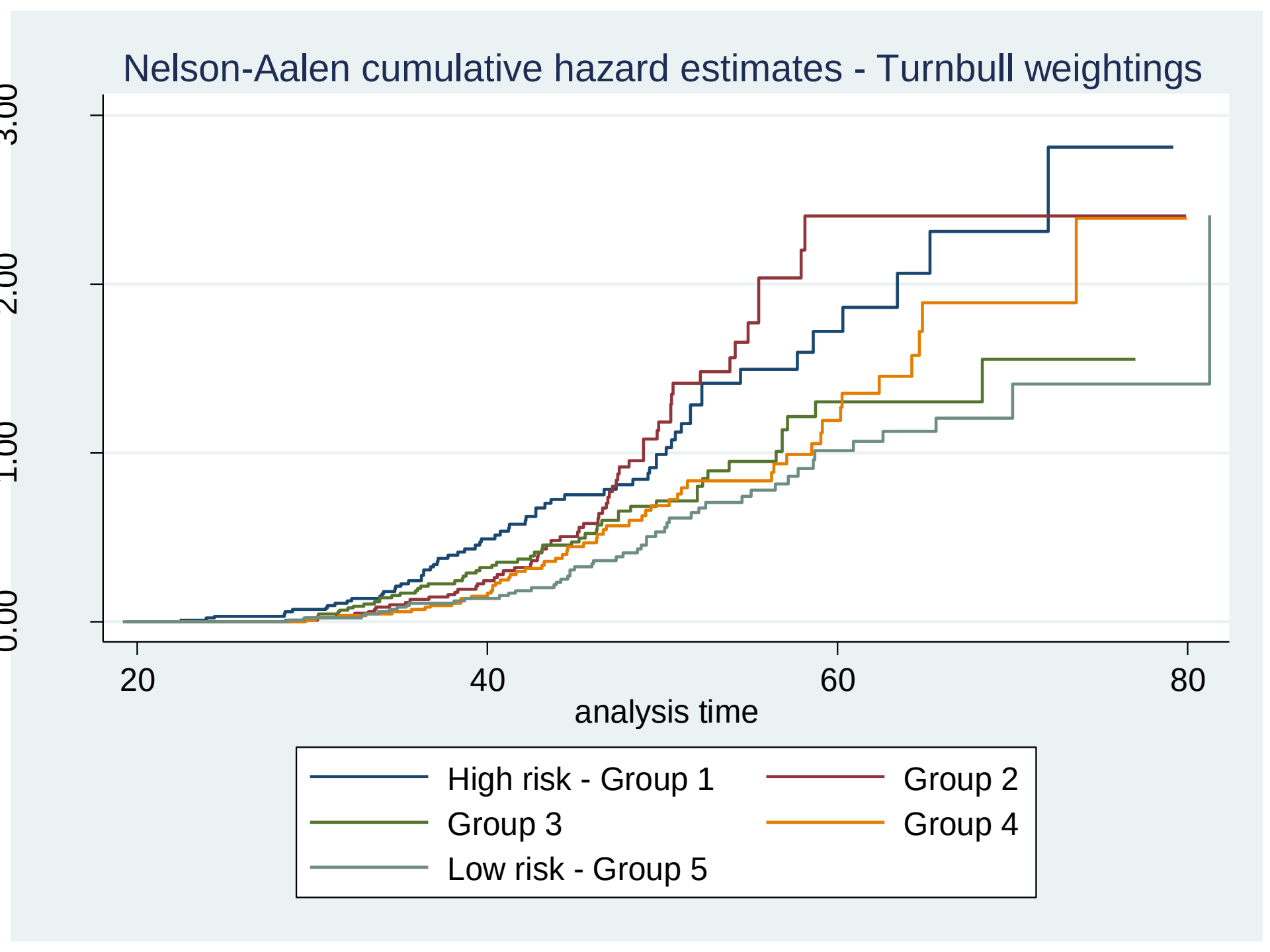
10 year 18 SNP risks in 2678 women



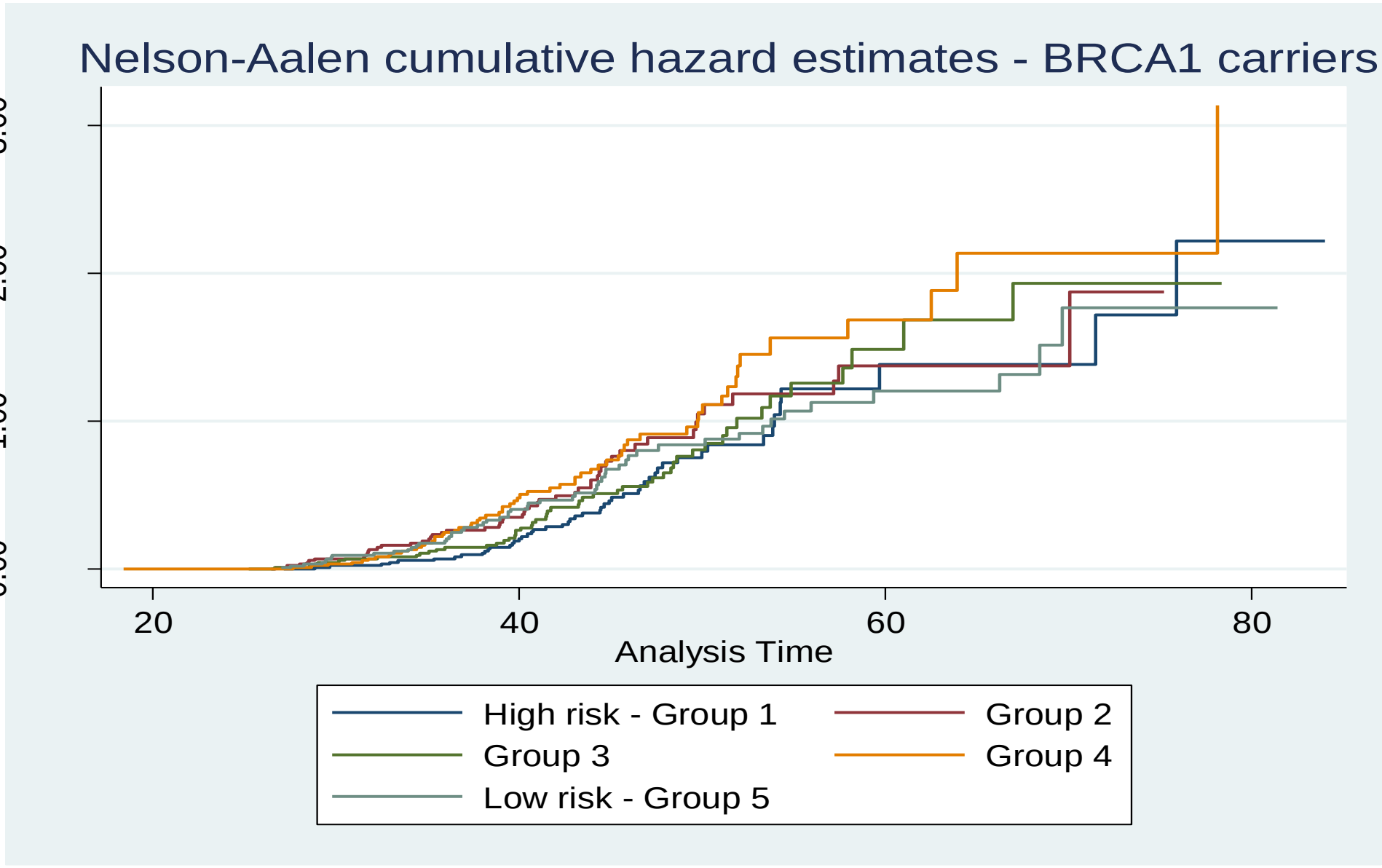
Validation in BRCA1/2

- 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
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

BRCA1 Antoniou weightings 3 SNPs

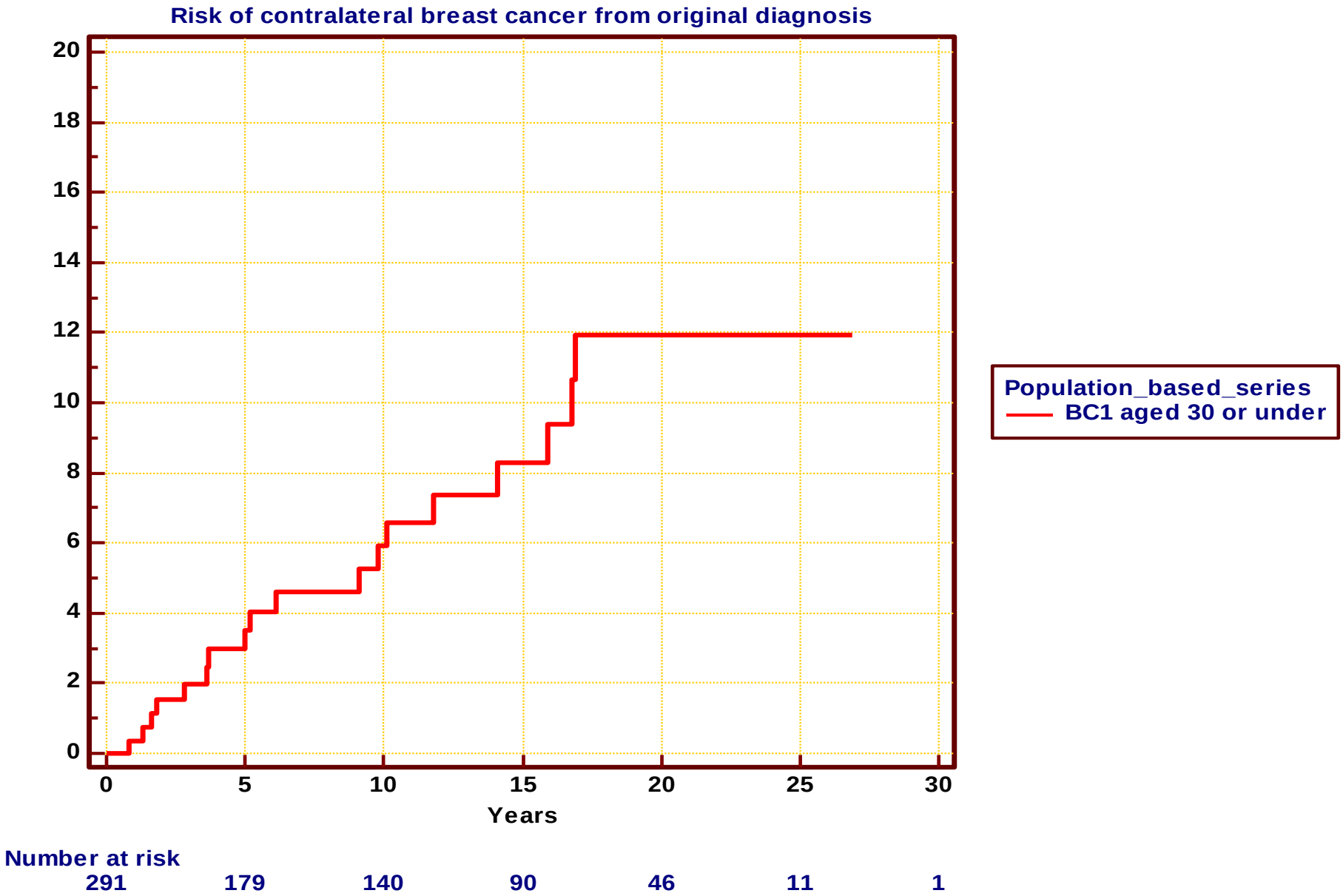


Conclusions

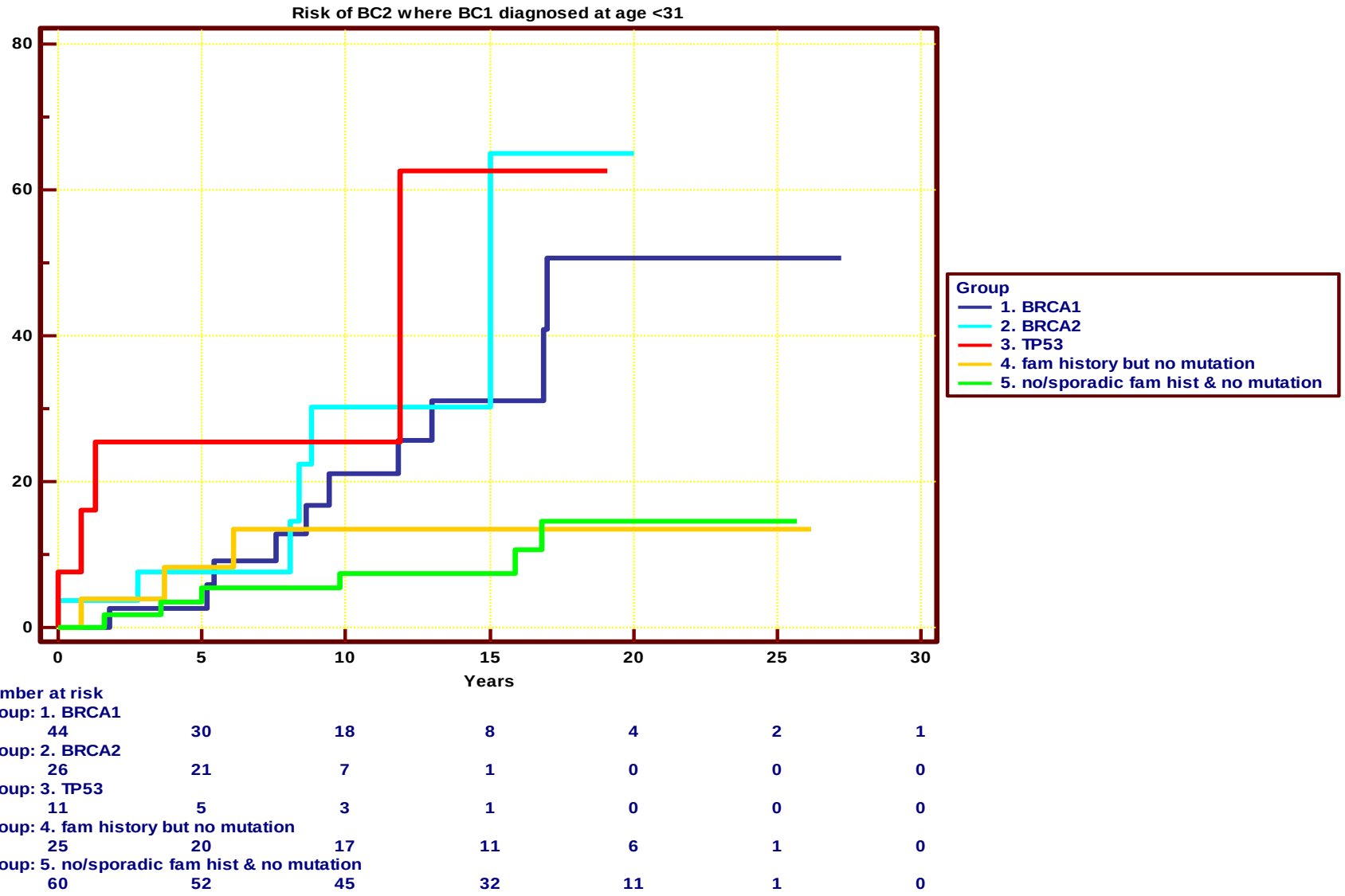
- BRCA2 -9 validated SNPs have good correlation but could be improved by additional SNPs
- BRCA2 SNPs ready for prime time

- BRCA1 not good correlation

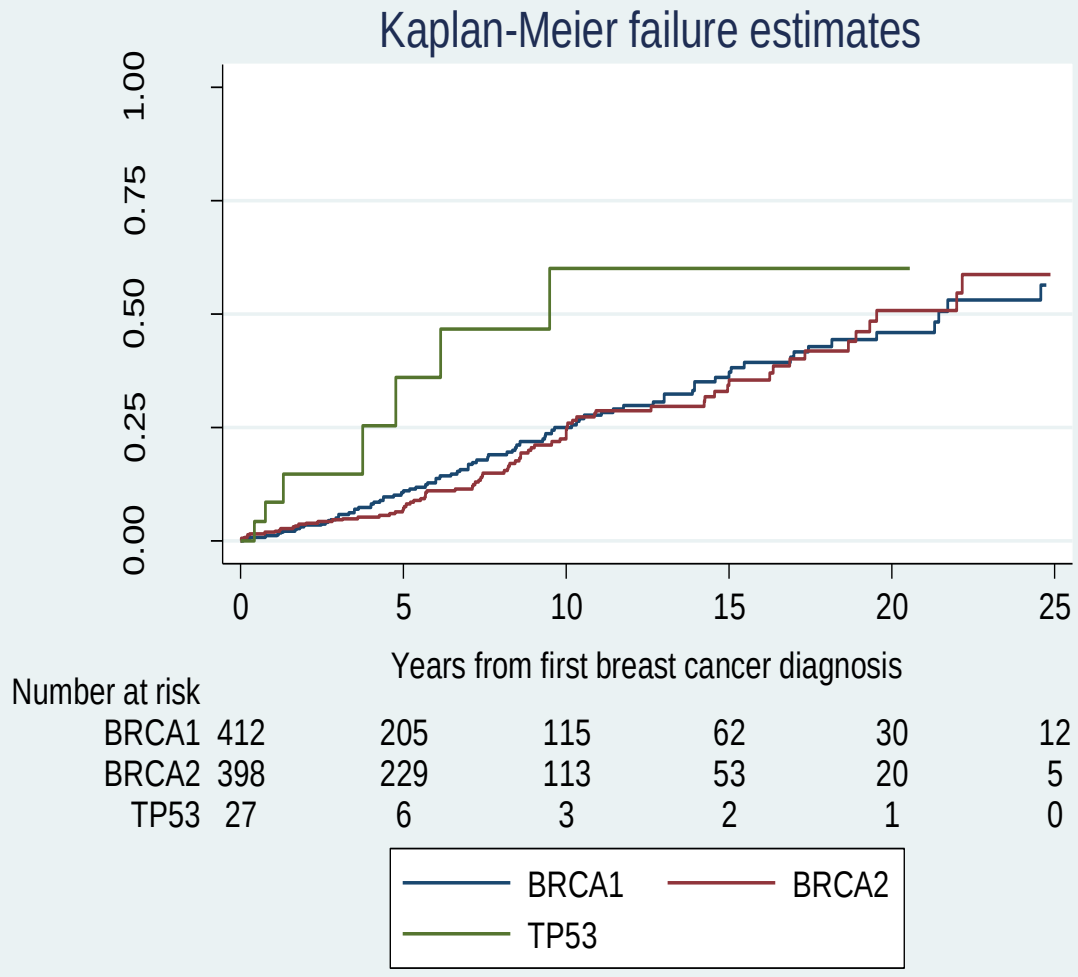
Contralateral incidence



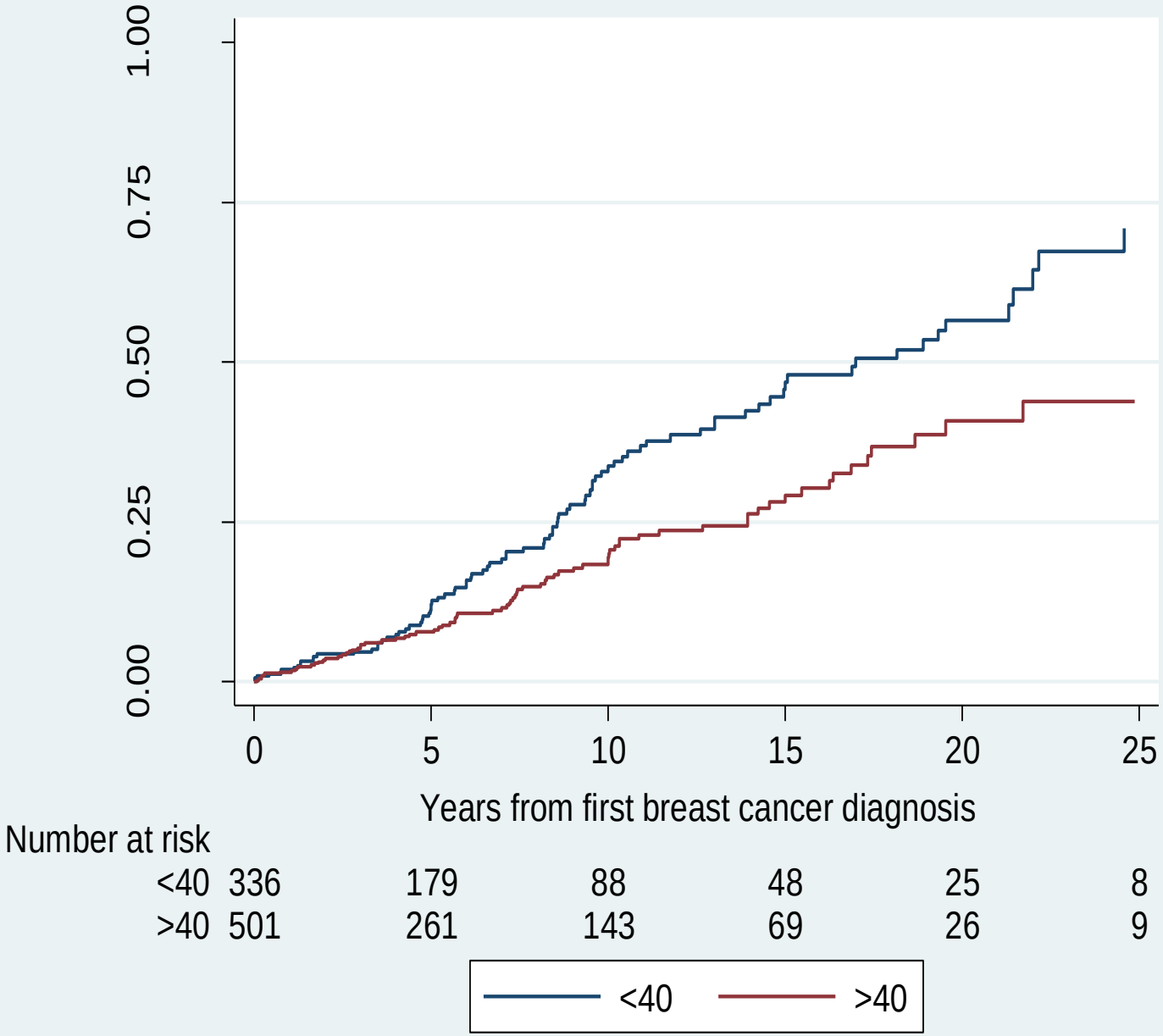
Enriching for inherited mutations



Risk of contralateral breast cancer in *BRCA1/2* and *TP53* mutation carriers



- The risk at 10 years of a contralatera breast cancer in carriers of mutation in either BRCA1/2 was 25%
- There was a constant 2.5% risk over the follow-up period
- The risk at 10 years of a contralatera breast cancer in carriers of a mutation in TP53 was approx 50%

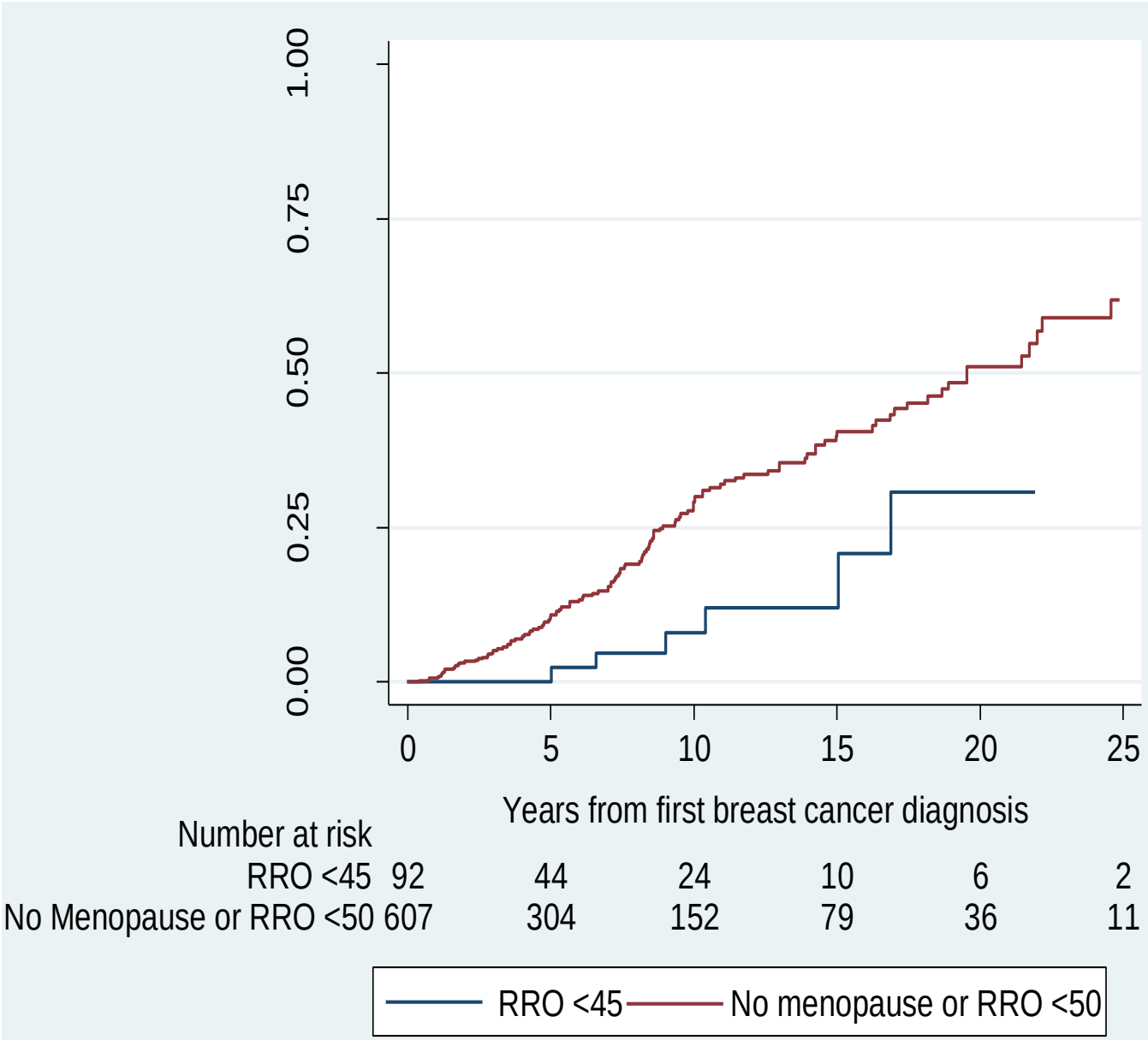


CA1/2

Contralateral risk
HR 0.60 (0.45-
0.82)

BRCA1/2

Contralateral risk
HR 0.37 (0.17-0.79)



Scoring systems

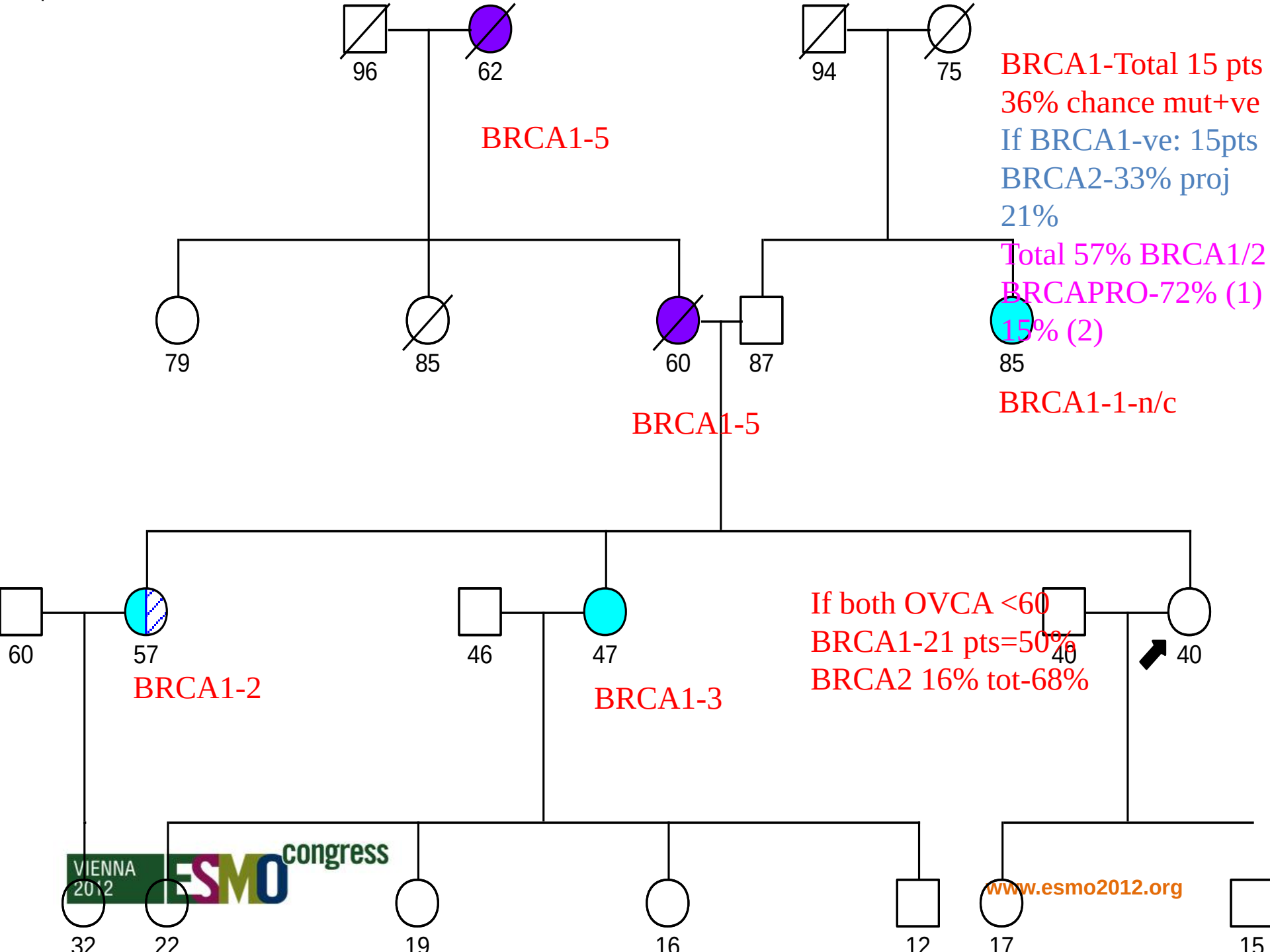
- Manual /ballpark-use BCLC data
- Manchester Scoring
- Myriad tables (Frank JCO; 1998, 2002)
- Couch model
- BRCAPRO –Cyrillic
- BOADICEA –On line only

BRCA2 scoring system

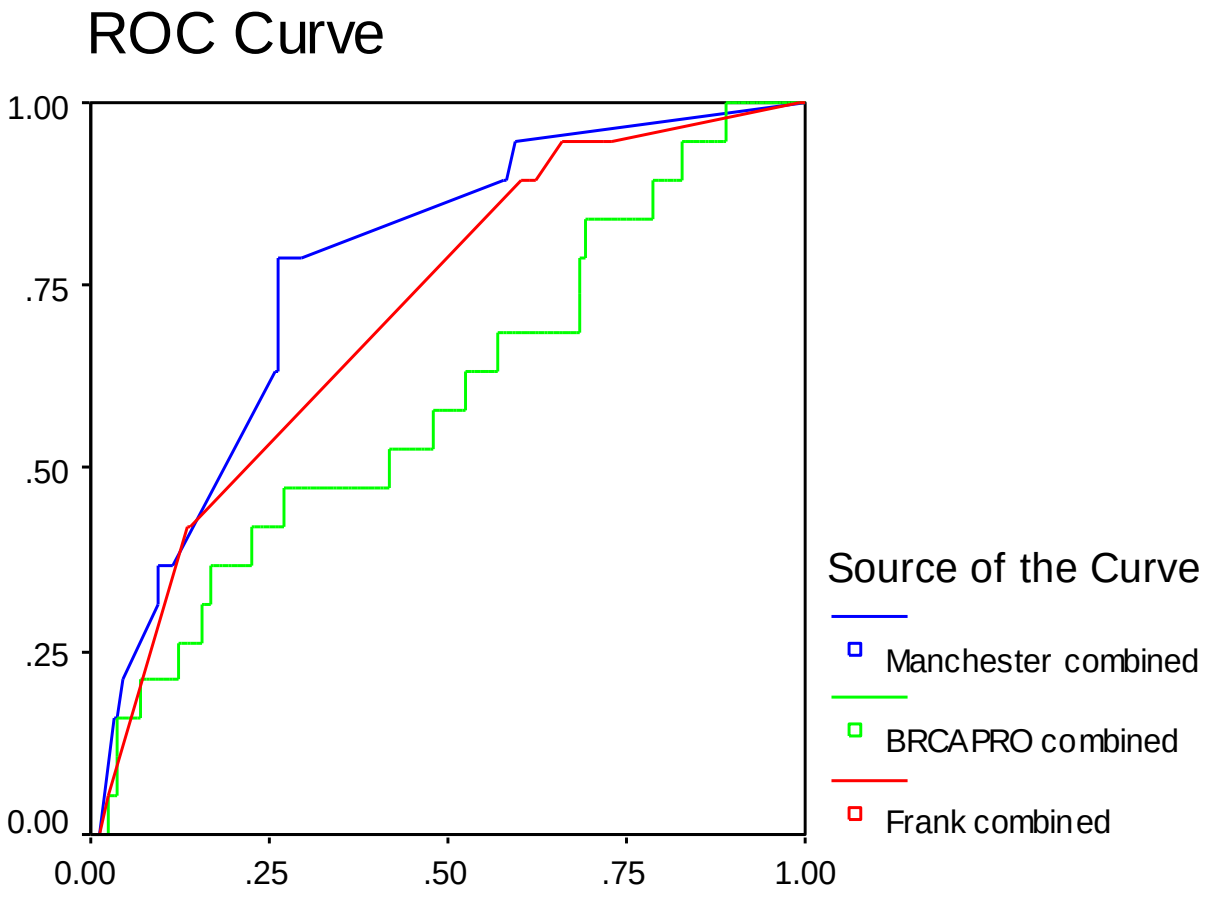
- 8 points MBC <60 yrs
- 5 points MBC >59 yrs
- 5 points Ovary (if BRCA1 screened)
- 5 points FBC <30
- 4 points 30-39; 3 points 40-49
- 2 points 50-59; 1 point 60+
- 2 points prostate, pancreas <60
- 1 point prostate, pancreas 60+

BRCA1 scoring system

- 5 points MBC
- 8 points Ovary<60 yrs
- 5 points Ovary
- 6 points FBC <30
- 4 points 30-39; 3 points 40-49
- 2 points 50-59; 1 point 60+


96
62
94
75
BRCA1-5
BRCA1-Total 15 pts
36% chance mut+ve
If BRCA1-ve: 15pts
BRCA2-33% proj
21%
Total 57% BRCA1/2
BRCAPRO-72% (1)
15% (2)
79
85
60
87
85
BRCA1-1-n/c
BRCA1-5
60
57
BRCA1-2
46
47
BRCA1-3
If both OVCA <60
BRCA1-21 pts=50%
BRCA2 16% tot-68%
40
40
32
22
19
16
12
17
15
VIENNA 2012
ESMO congress
www.esmo2012.org

ROC Curve for models comprising both BRCA1 + 2 using a 10% detection prediction in 252 samples with full gene testing.



VIENNA 2012

mo2012.org

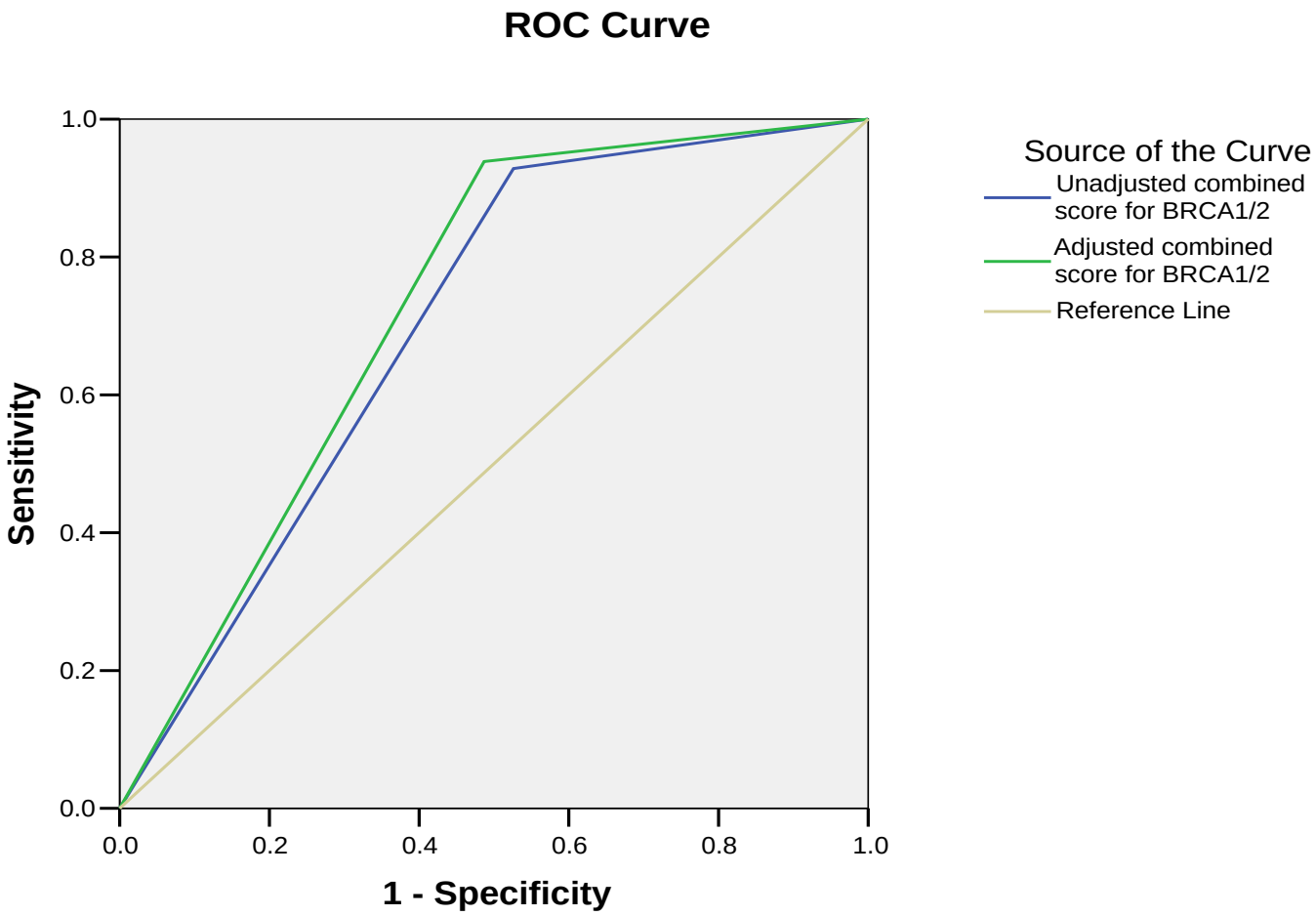
Diagonal segments are produced by ties.

Modified Manchester score

	BRCA1	BRCA2
Her2+	-4	0
Lobular	-2	0
DCIS only (no invasive cancer)	-2	0
LCIS only	-3	0
Grade 1 IDC	-2	0
Grade 2 IDC	0	0
Grade 3 IDC	+2	0
ER pos	-1	0
ER neg	+1	0
Grade 3 triple neg	+4	0

Assessment of Manchester score at 20% level (update 2012)

Combined	*Ovarian*	Male breast	All families
40+	87/109 (83%) 65/71 (91%)	9/11 (81%)	101/132 (77%)
35-39	30/51 (59%)	5/10 (50%)	49/88 (55%)
30-34	36/84 (43%)	8/12 (67%)	75/154 (49%)
25-29	53/161 (33%)	3/15 (20%)	100/312 (32%)
20-24	35/142 (25%)	4/14 (28%)	97/440 (22%)
15-19	18/130 (14%)	2/25 (8%)	56/650 (9%)
12-14	2/44 (5%)	0/8 (0%)	20/497 (4%)
<12	1/33 (3%)	0/3	13/564 (2%)
Total	259/740 (35%)	31/98 (32%)	511/2837 (18%)



ROC curve with path adjusted score at 20% combined

Assessment of score at 10-20% level

(Grade 3 TNT)

Combined score	numbers	BRCA1	BRCA2
0-9	0	0	0
10-13	0/18	0	0
14-15	3/10 (10%)	1/30 (3%)	2/30 (7%)
16-19	7/37 (19%)	6/37 (16%)	1/37 (3%)
20-24	20/44 (45%)	17/44 (39%)	3/44 (7%)
25-29	21/41 (52%)	18/41 (44%)	3/41 (8%)
30-39	27/33 (81%)	24/33 (72%)	3/33 (9%)
40+	22/23 (96%)	19/23 (83%)	3/23 (13%)
Total	100/226 (44%)	85/226 (37%)	15/226 (7%)

Conclusions

- Oncologists already well served by recurrence algorithms
- Future risks of Contralateral BC need more attention
- Good models to predict breast cancer in unaffected women will be improved with DNA and density additions

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