

Challenges in genetic counselling for familial breast cancer: what risks to give?

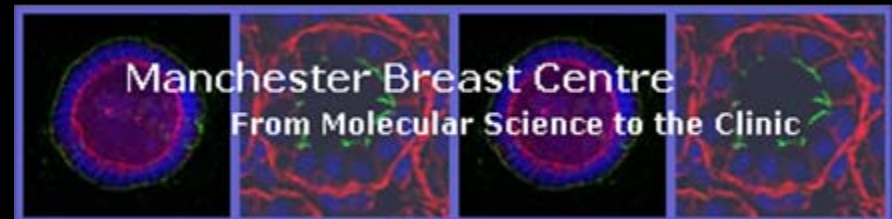
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Larnaca 1st March 2008



Challenges

- What risks to give before testing?
- What risks to give after testing?
- How to present options
- Non directive counselling?

Risk assessment in breast cancer

- Risk of breast cancer over time
- Chances of carrying a mutation in a particular gene

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 –newish model from IBIS1

Risk assessment in breast cancer

Claus

- –no non genetic factors
- +Includes FDR and SDRs
- +Age element included
- -No ovarian cancer/male breast cancer
- -Risks derived from population in 1980s
- Computer models give **LOWER** risks than Manual tables

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	.025	.017	.012	.008	.006	.005
49	.062	.044	.032	.023	.018	.015
59	.116	.086	.064	.049	.040	.035
69	.171	.130	.101	.082	.070	.062
79	.211	.165	.132	.110	.096	.088

Risk next 10 years sister <40 yrs

AGE	Pop risk next 10y	Claus risk 10 y	Million women 10 y risk
20	0.07	0.5	0.36
30	0.44	1.2	2.2
40	1.5	2.7	4.1
50	2.7	4.2	5.1
60	2.8	4.4	3.8
70	3.1	3.5	4.2
Total	10.6	16.5	19.6

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	.096	.074	.069	.050	.045
69	.181	.140	.111	.102	.090	.082
79	.231	.195	.162	.140	.126	.118

Breast Cancer Risk Assessment Manchester FHC

- Since 1987 4536 women assessed
- 3170 with pedigree and hormonal data
- 1933 with mammographic follow up
- Remainder checked for cancers on CR

Cancers detected on screening

	Observed (o)	Expected (E)	E/O	95% CI
Gail	52	25.03	0.48	0.37-0.64
Claus	52	29.15	0.56	0.43-0.75
Ford	52	25.4	0.49	0.37-0.65
Tyrer	52	42.05	0.81	0.62-1.08
Manual	52	46.43	0.89	0.68-1.20

Menarche	-	G	A	I	L	C	L	AUS
≤ 12	840	21	11	0.5	0.35-0.86	11.8	0.5 6	0.37-0.91
> 12	109 3	31	14	0.4 5	0.32-0.66	17.3	0.5 6	0.39-0.82
First live birth	-	-	-					
≤ 30	129 2	28	18	0.6	0.44-0.97	19.9	0.7	0.49-1.07
> 30 or nulliparous	641	24	7.0	0.3	0.20-0.46	9.20	0.4	0.26-0.60

Familial Breast Cancer: Evidence

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ScHARR
School of Health and
Related Research

High Risk (tertiary care)

- Lifetime risk $>30\%$
- 10 year risk $>8\%$
- Chance of BRCA1/2 in family $>20\%$

High Risk (tertiary care) Genetic testing

- Offer testing if >20% chance of BRCA1/2 or TP53 mutation in family
- Start with testing an affected family member
- Must offer full mutation testing-not partial
- By 2005/6 DH target of 8 weeks per gene

BRCA1/2 Testing

- 22 coding exons of BRCA1
- 26 coding exons of BRCA2
- Test for duplication or deletion of single or multiple exons (MLPA)

BRCA1/2 in Manchester

462 families (402 found in Mc)

- **BRCA1 248 kindred**
 - 32 185 del AG (13%)
 - 25 4184 del4 (11%)
 - 14 546G>T (7%)
 - 9 5682C>T (4%)
 - 6 5382 delC (2%)
 - 12 dup exon 13 (5%)
 - 28 exon deletions (12%)
 - 2 other exon dups
 - 42 MLPA positive (17%)
 - 42/207 (20% non AJ)
- **BRCA2 214 kindred**
 - 16 6174 delT (8%)
 - 15 2157 delG (7%)
 - 24 6503 delTT (11%)
 - 13 MLPA pos (6%)

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

Evans et al J Med Genet 2004; 2005

Assessment of Manchester score at 20% level (update 2008)

Combined	<i>Ovarian</i>	Male breast	All families
40+	61/79 (77%) 51/58 (88%)	7/9 (78%)	76/103 (73%)
35-39	21/37 (57%)	4/5 (80%)	33/60 (55%)
30-34	27/56 (48%)	4/9 (45%)	48/102 (47%)
25-29	28/106 (27%)	3/9 (33%)	60/204 (29%)
20-24	25/105 (24%)	2/9 (22%)	67/303 (22%)
15-19	7/74 (10%)	2/17 (12%)	41/389 (11%)
12-14	2/34 (6%)	0/6 (0%)	17/361 (5%)
<12	0/0	0/3	14/521 (2.5%)
Total	171/493 (35%)	22/66 (32%)	347/1900 (18%)

BRCA1/2 testing

	BRCA1	BRCA2	No Mutation
2+Ov 2+ Brca	42 (50%)	12 (15%)	28/82 (35%)
2+Ov 2+ Brca**	38 (66%)	9 (16%)	11/58 (22%)
BCLC 2ov**	38 (66%)	9 (16%)	11/58 (22%)
3+ Ov only	4 (30%)	2 (15%)	7/13 (55%)
2 Ov 1 Brca	12 (39%)	2 (7%)	17/31 (54%)
2 Ov only	3 (11%)	2 (8%)	23/28 (82%)
1 Ov 3+ Brca	29 (26%)	27 (25%)	57/113 (50%)
1 Ov 2 Brca	19 (15%)	12 (12%)	92/123 (73%)
1 Ov+ 1 Brca	8 (9%)	4 (5%)	78/90 (86%)
1 Ov+ 1 MBC	0 (0%)	3 (100%)	0/3 (0%)
1 Ov <50 only	0 (0%)	0 (0%)	18/18 (100%)
Total	110 (25%)	56 (13%)	166/442 (38%)

** confirmed ovarian cancer

Proportion of predictive tests per index sample

Threshold	Proportion of +ve samples	Presymptomatic Predictive tests (per family)	Positive female predictive tests	RRO in positives (planned)	RRM in positives (planned)
20% (20+)	267/725 (37%)	530 (1.98)	152	54 (12)	51 (7)
10-20% (15-19)	42/361 (12%)	41 (0.98)	15	5	6
<10% <15	20/609 (3%)	11 (0.55)	5	1	0

Cost per predictive test

	Unit cost	Cost per predictive test Manchester 20+ (20%+)	Cost per predictive test Manchester 10-20%	Cost per predictive test Manchester <10%
Initial full screen BRCA1/2	\$2-3,000	\$2735-4100	\$17,610- 26,415	\$110,727- 166,090
Predictive test	\$2-400	\$2-400	\$2-400	\$2-400
Full cost		\$3,000- 4,500	\$18,000- 27,000	\$111,000- 166,000

BRCA1/2 in Manchester/Birmingham

530 families

- BRCA1 286 kindred
- 36 185 del AG (12.5%)
- 28 4184 del4 (9.5%)
- 16 546G>T (5.5%)
- 7 5382 delC (2.5%)
- BRCA2 244 kindred
- 26 6503 delTT (11%)
- 15 6174 delT (6%)
- 16 2157 delG (7%)

RISK OF BREAST CANCER IN RELATIVES WHO TESTED NEGATIVE FOR MUTATION

FDRs - no unexplained FH	Number	Observed	Expected	SIR
Tested negative	166	13	3.2	4.1 (2.2 – 7.0)
Untested affected	63	7.7 (12%- 63)	0.1	
Untested unaffected	188	0	3.1	
Total		20.7	6.4	3.2 (2.0 – 4.9)

Updated analysis

- 55 BC phenocopies in 530 families
- 33 in FDRs
- 33/203 (16%) tests in FDR after index
- 33/188 (18%) BC only cases
- 18/97 BRCA2 (19%)
- 15/91 BRCA1 (16.5%)

BC Tests in relationship to family ascertainment

	Pre Ascertain	Post Ascertain	Post predictive
Both	18/130 (14%)	13/60 (22%)	6/15 (40%)
BRCA1	11/72 (15%)	4/31 (13%)	4/9 (44%)
BRCA2	9/70 (13%)	9/30 (30%)	2/6 (33%)

BC incidence in negatives post family ascertainment

	Tested negatives	FDR unknown	Predicted annual inc
Both	13 in 1924	28 in 4419	
BRCA1	4 in 1107 yrs	13 in 2184	5.8/2317 2.50 per 1000
BRCA2	9 in 817 yrs	15 in 2235	11.85/2158 5.36 per 1,000

UK incidence 20-79 =10.7% 1,845 per 1000

Is cancer load in family predictive?

Manch score	Above or =	Below
20	29/161 (18%)	4/41 (9.7%)
23	26/143 (18%)	7/59 (12%)

Is penetrance predicted by cancer load?

Manch score predictives	Above or = % positive	Below %positive
BRCA2 >50 (23)	11/47 (24%)	10/25 (40%)
BRCA2 >50 (20)	13/55 (24%)	8/17 (47%)
BRCA1 >50 (23)	9/51 (17.5%)	4/19 (21%)
BRCA1 >50 (20)	10/57 (17.5%)	3/13 (23%)

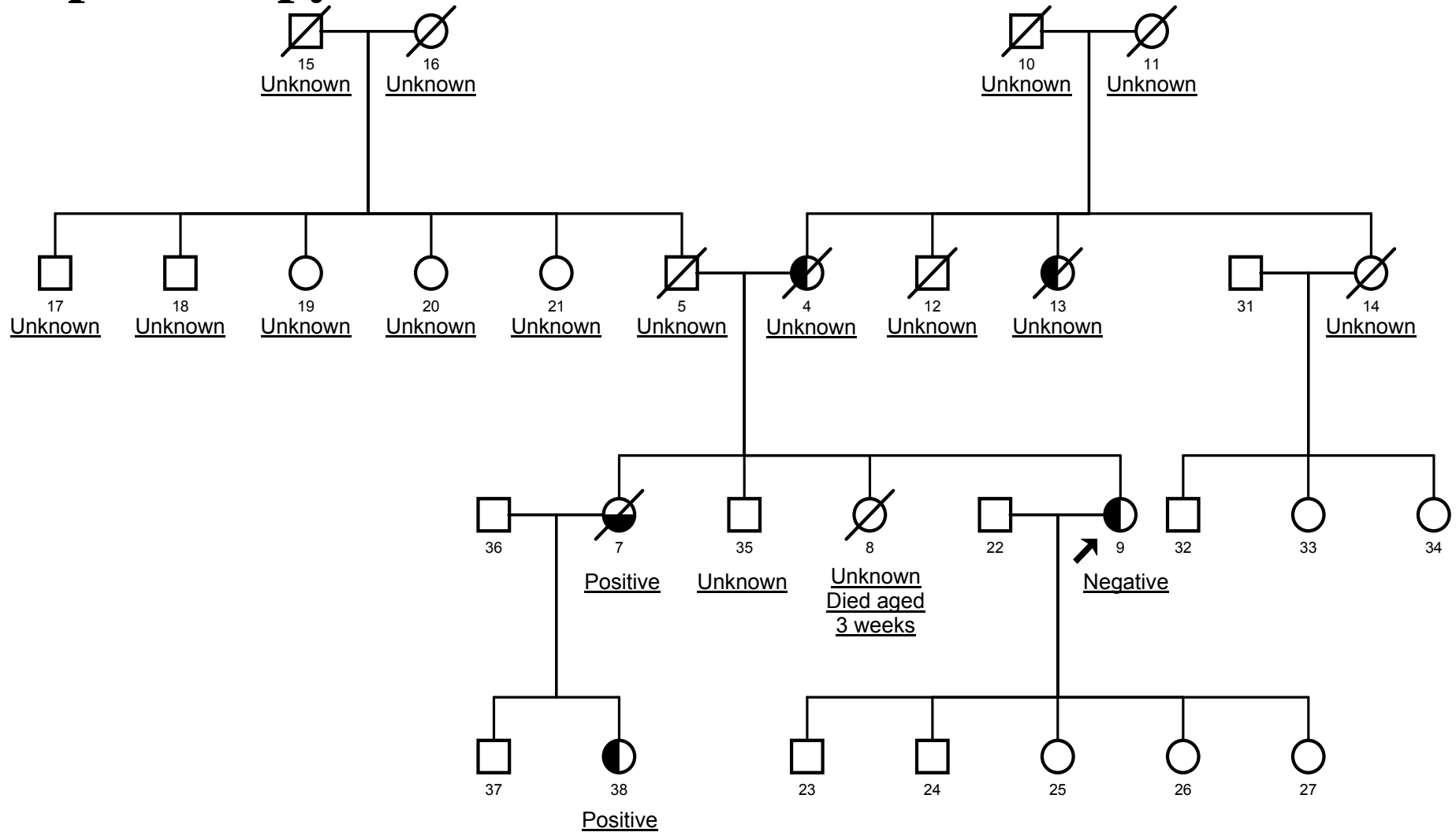
What causes phenocopies

- Chance? -Would only account for 1/3rd
- Ascertainment bias?
- Shared environment?
- Other BRCA1/2 mutations?

15/17 A1 phenocopies negative on full testing

Is this due to the now being identified modifiers?

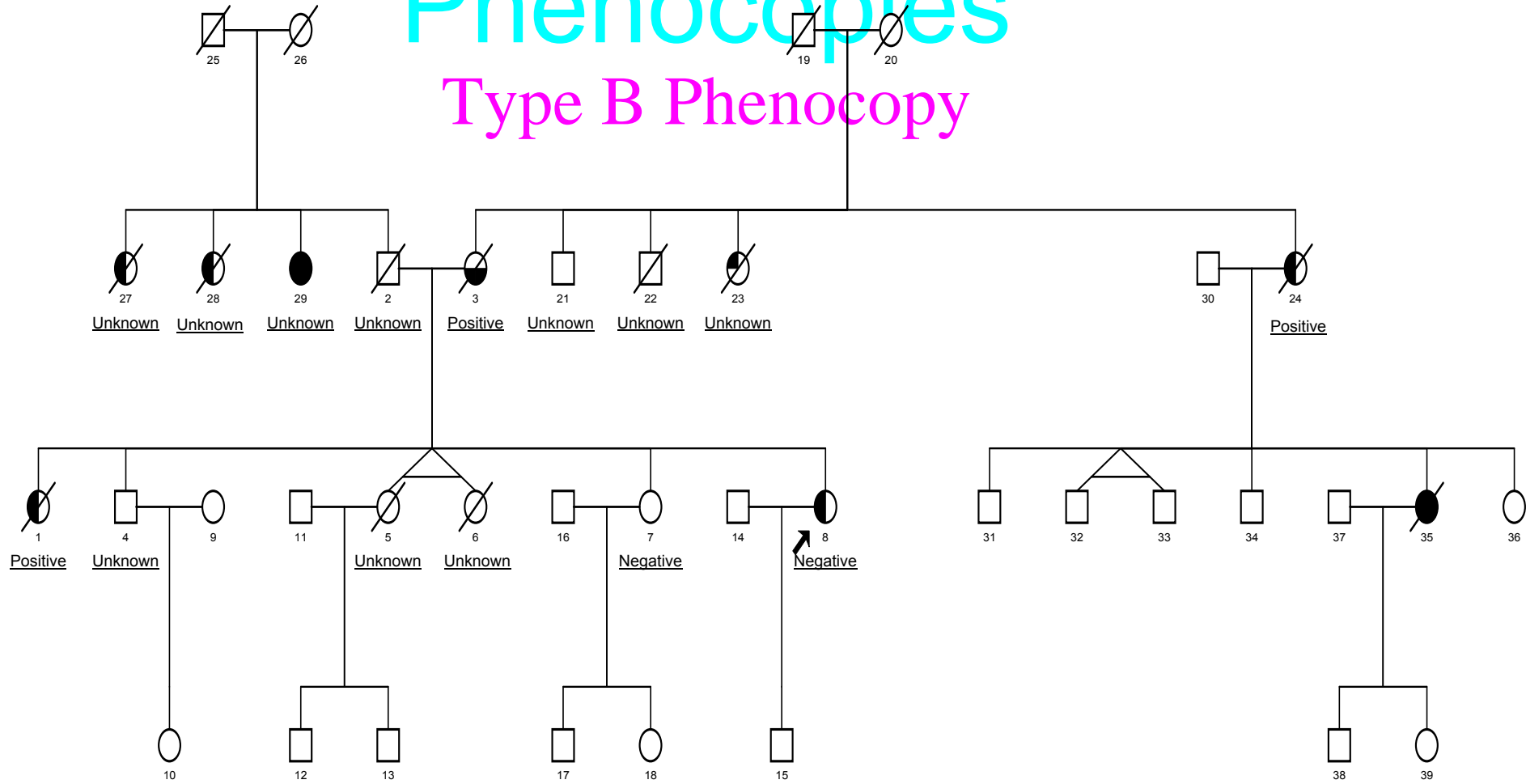
A1 phenocopy



Who to test? Ensure testing of FDR if possible

Phenocopies

Type B Phenocopy



Breast/ovarian cancer

Penetrance from <31 study pop based

- breast cancer 84% by 70 years BRCA1
- breast cancer 91% by 70 yrs BRCA2
- ovarian cancer 60% by 70 years BRCA1
- ovarian cancer 26% by 70 years BRCA2

Laloo et al, Lancet 2003

Breast/ovarian cancer risk in BRCA1/2 gene mutation carriers

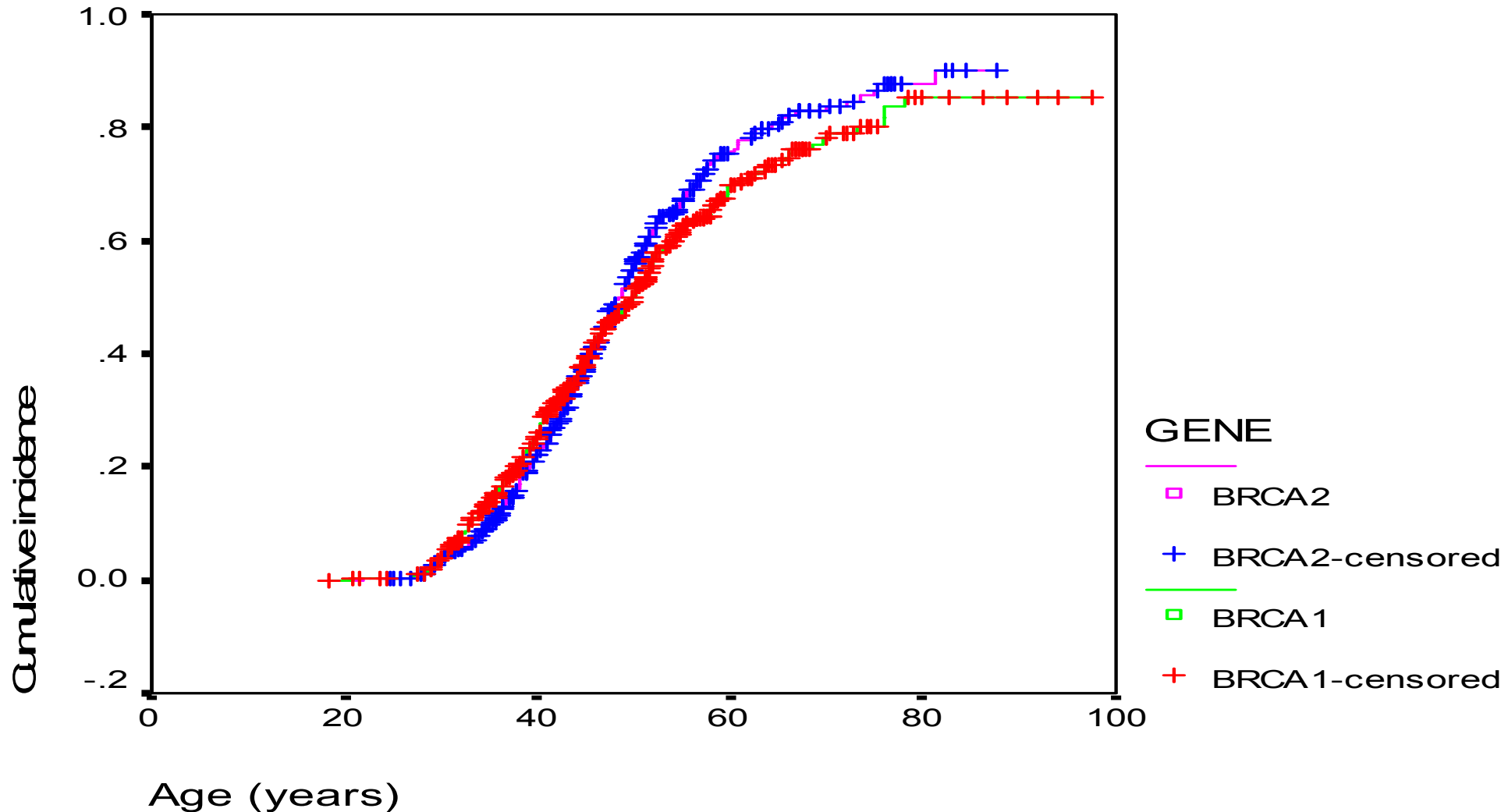
Meta-analysis of population studies (Antoniou et al 2003)

- * Breast cancer risk to 70 years BRCA1 65%, BRCA2 49%
- Ovarian risk to 70 years BRCA1 37%, BRCA2 20%
- However some population studies show risks of only 27%
- Families ascertained from Fanconi have even lower risks

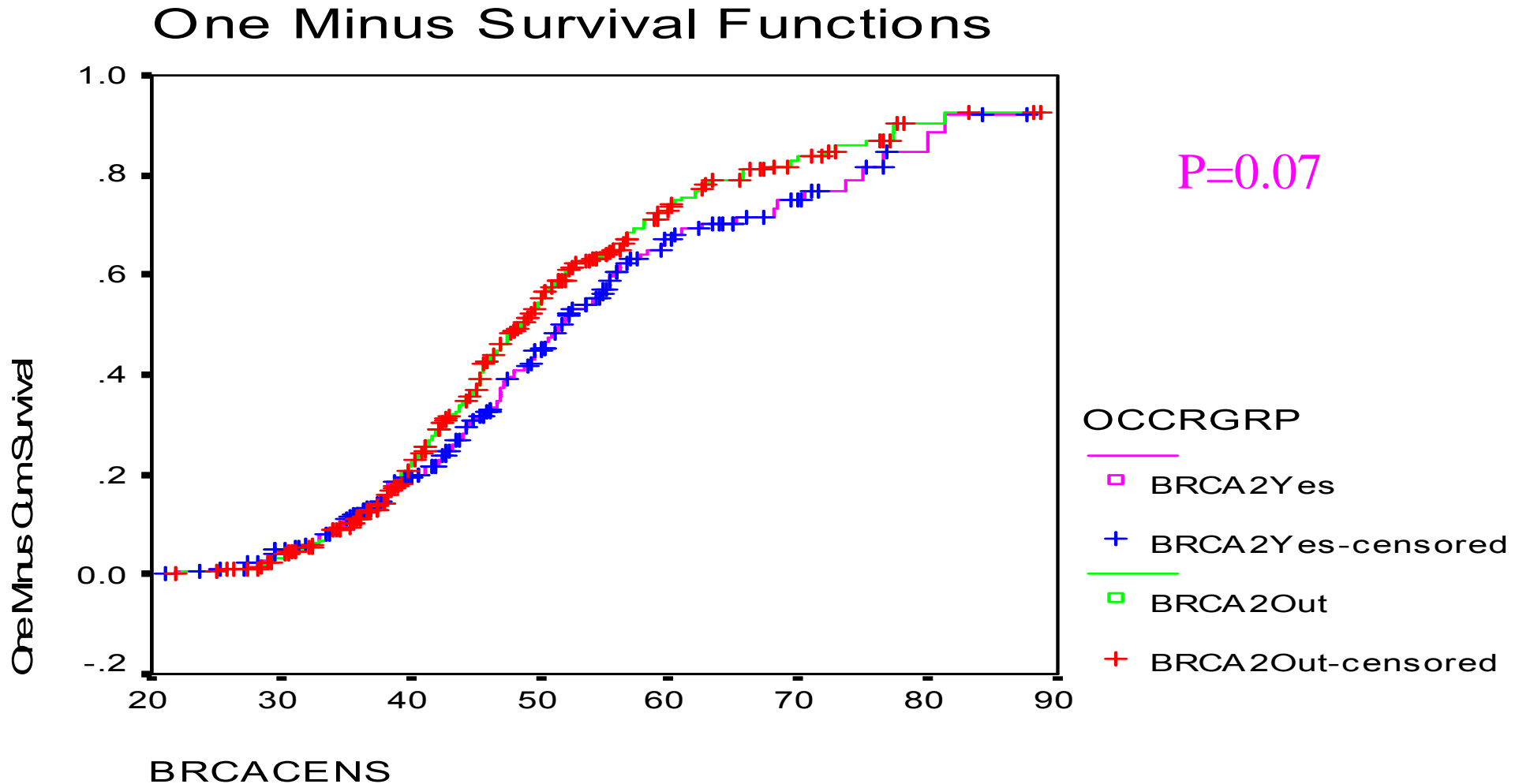
**Distribution of tested/untested female FDRs by
mutation status regardless of censor dates.**

Predictive test result By age	Number positive BRCA1	Number positive BRCA2	Proportion positive BRCA1 assumed	Proportion positive BRCA2 assumed
18-30 yrs	26/55 (48%)	17/35 (48%)	50%	50%
30-40 yrs	51/91 (56%)	48/87 (55%)	50%	50%
40-50	22/66 (33%)	28/47 (59%)	33%	50%
50-60	9/28 (33%)	14/34 (41%)	33%	40%
60+	1/22 (5%)	4/19 (22%)	10% >90% penetrant	20% 70% penetrant

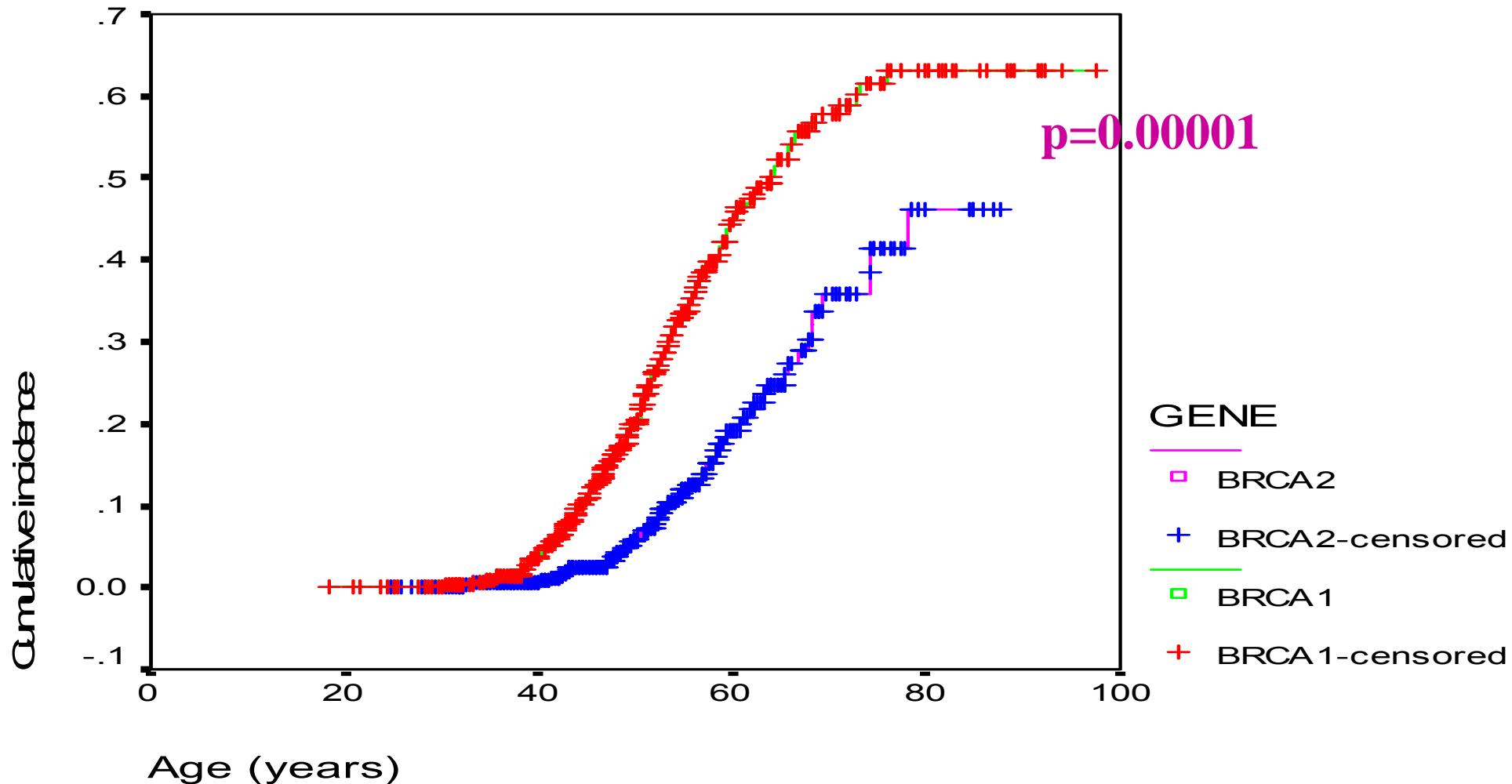
Cumulative breast cancer incidence in *BRCA1* and *BRCA2* proven carriers (p=0.27)



Cumulative risks of breast cancer in BRCA2 carriers in OCCR 223 (3035-6629) 373 outside



Cumulative risks of ovarian cancer in BRCA carriers



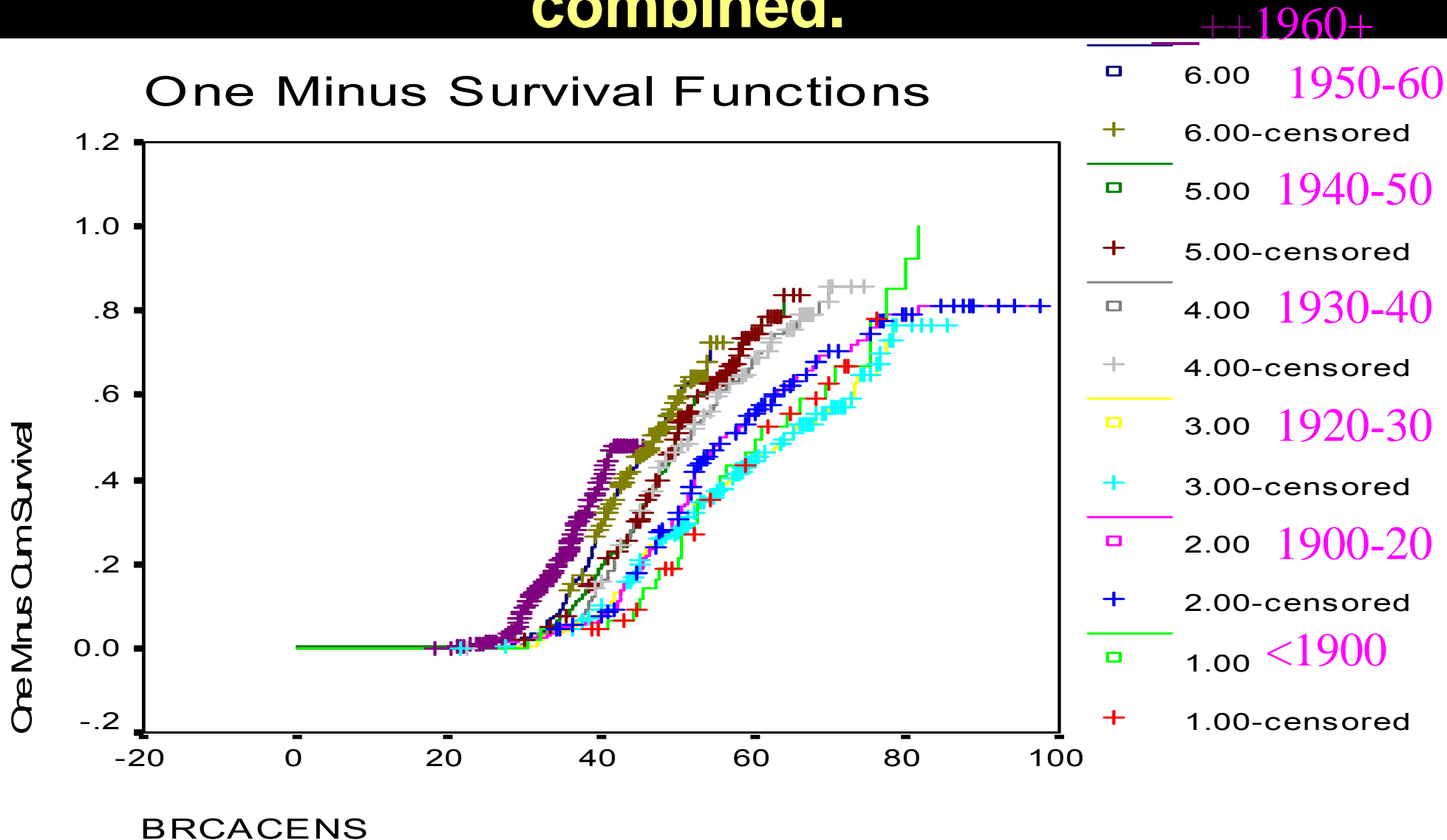
Penetrance for breast and ovarian cancer by age for BRCA1 and BRCA2.

Cancer risk to age	BRCA1 Breast	BRCA2 Breast	BRCA1 Ovary	BRCA2 Ovary
30	3%	4%	0	0
40	21%	21%	3.7%	0
50	44%	51%	21%	4.5%
60	63%	71%	44.5%	18%
70	75% (72-78)	80% (77-83)	61% (58-64)	33% (29-37)
80	85% (82-88)	90% (87-93)	65% (62-68)	38% (34-42)

What breast cancer risks should be quoted?

- NEJM review 2007
- 90% to 80 years for BRCA1; 40% for BRCA2 –actually an OC study
- JCO meta analysis 2007 (10 studies)
- 57% (95% CI, 47-66%) for BRCA1 and 49% (95% CI, 40-57%) for BRCA2 to age 70 years
- But does one size fit all?
- BOADICEA accounts for family history in assessing risk for a carrier
- Given GWA shouldn't we vary risk according to FH?
- Doesn't age cohort effect mean higher risks?

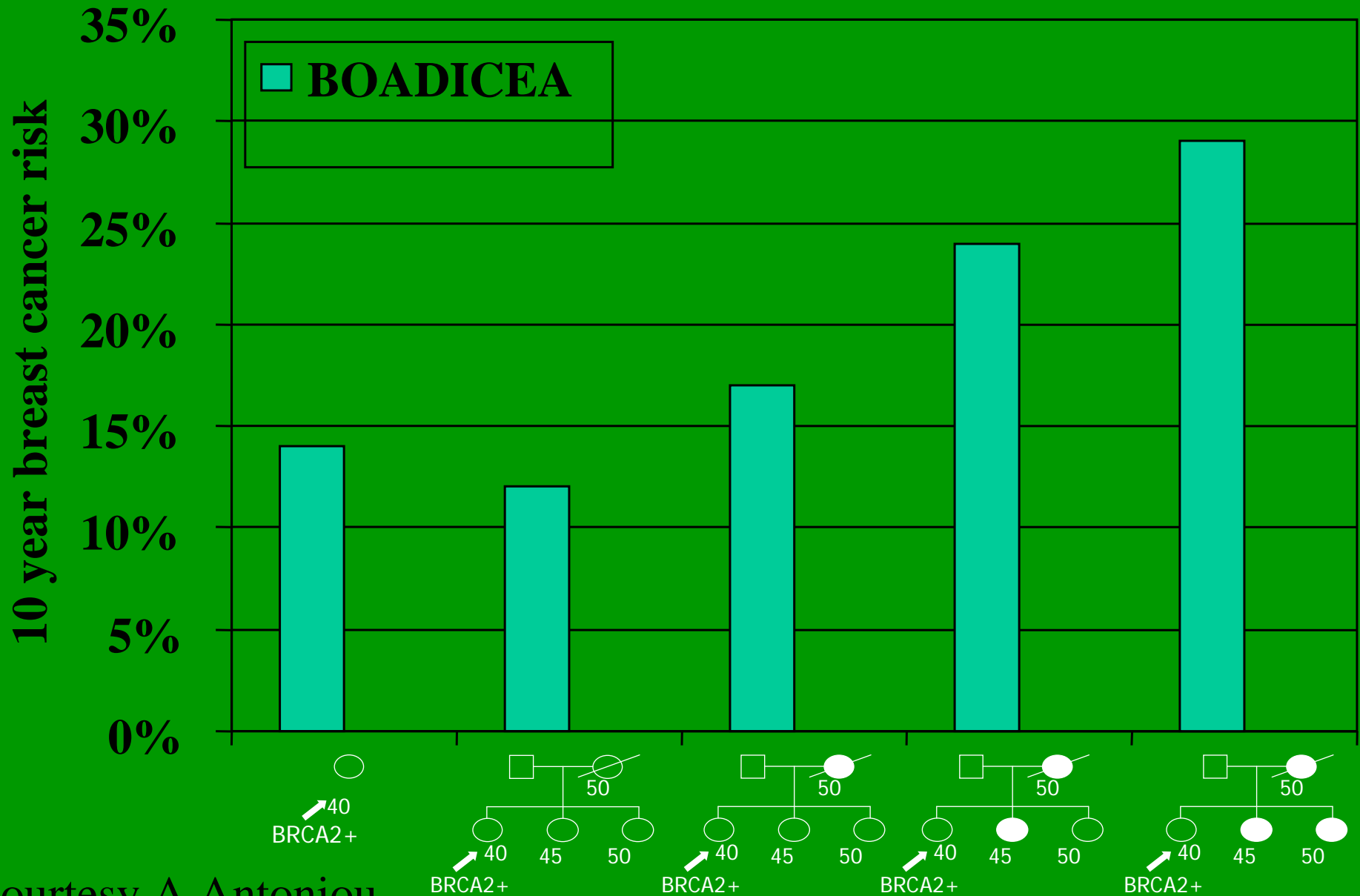
Cumulative risk of breast cancer by age cohort for BRCA1 and BRCA2 combined.



Cumulative risk of breast cancer by age cohort for BRCA1 and BRCA2 combined

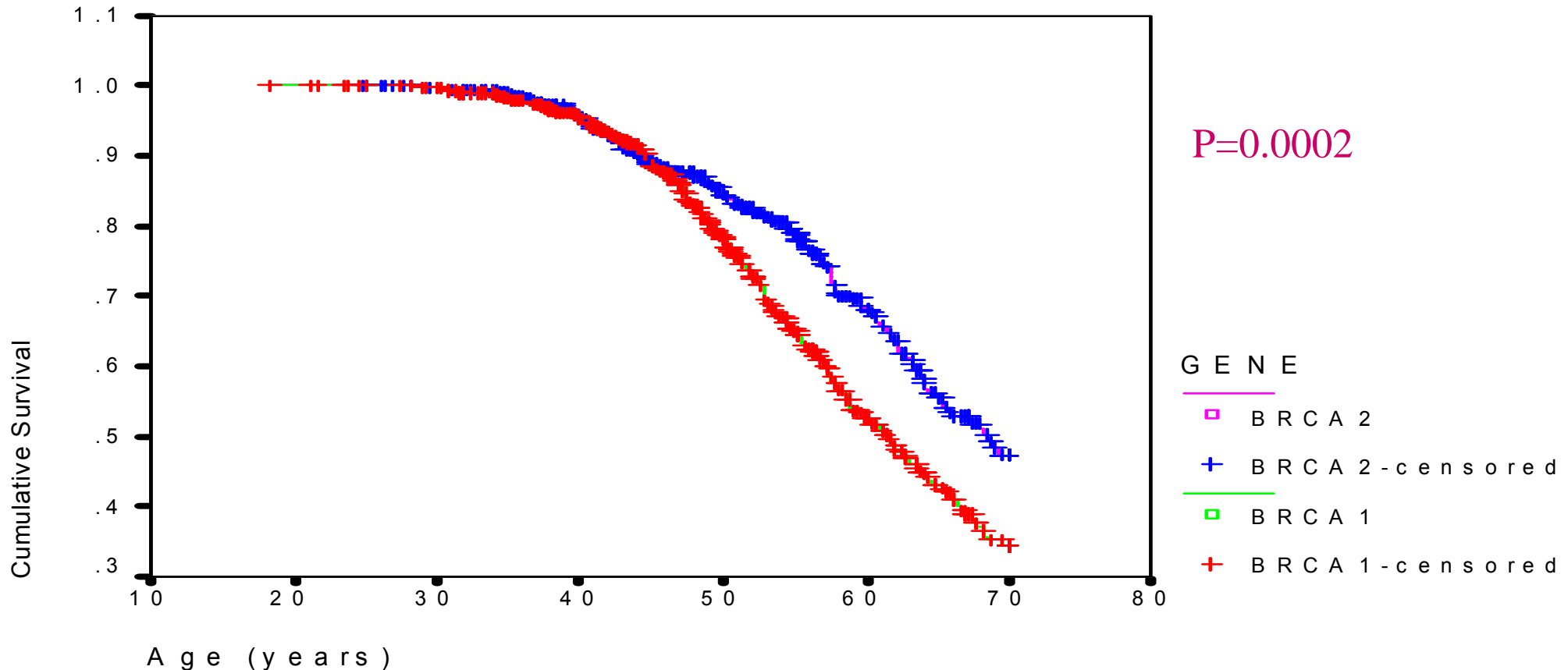
Risk to age	King et al <1940	Iceland <1930	UK <1930	King et al 1940+	Iceland >1930	UK 1940+
40	10%		8%	40%		30%
50	23%		30%	65%		55%
60	45%		45%	90%		75%
70	60%	48%	60%		70%	
80	75%		78%			

Genetic Modification of BC Risk in *BRCA1/2* carriers



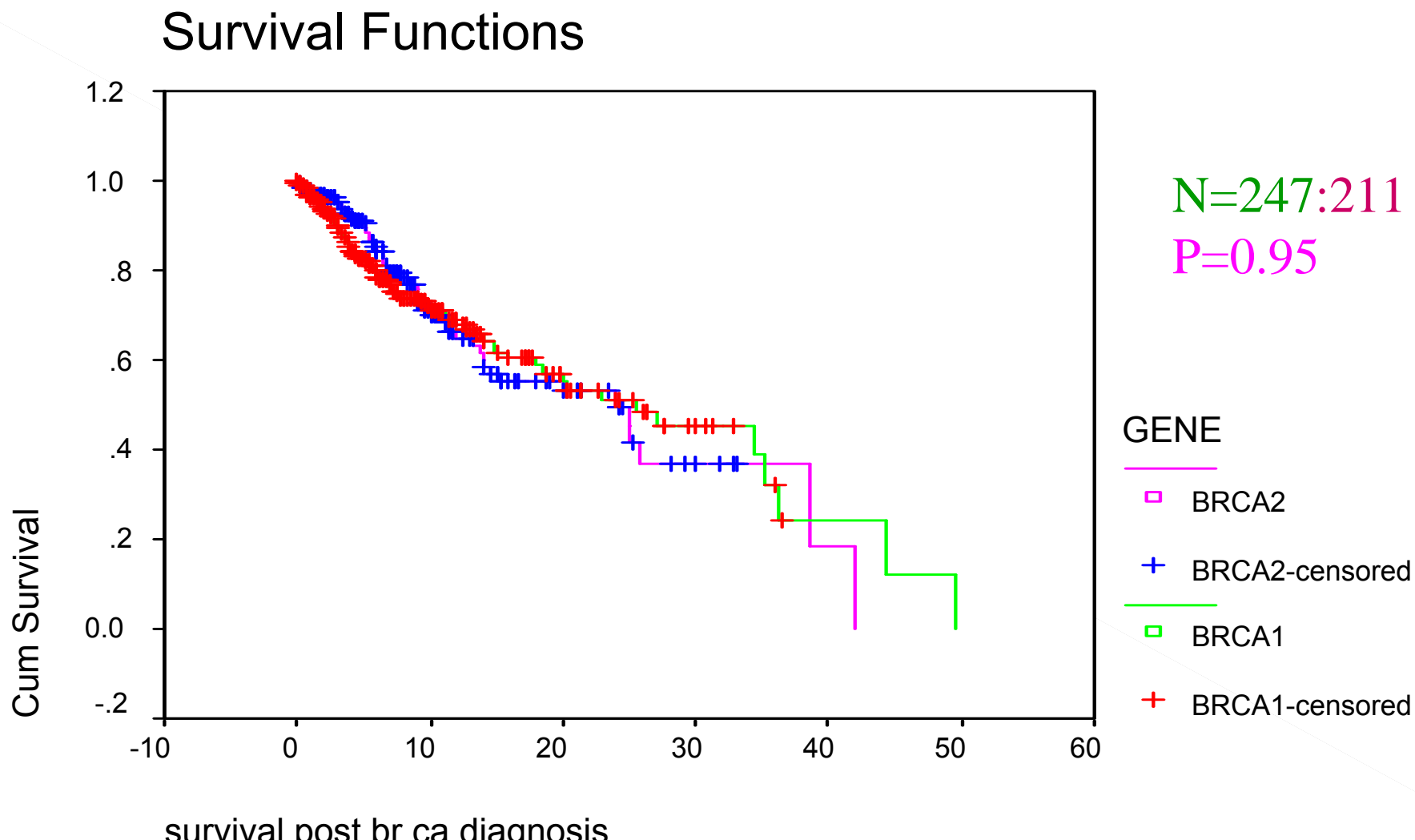
Courtesy A Antoniou

Actuarial survival from birth in female BRCA1 & BRCA2 mutation carriers (censored age 70)



	50yrs	60 yrs	70 yrs
BRCA1	78%	52.6%	35%
BRCA2	82.5%	68%	47%

Survival from diagnosis –BC proven carriers and FDRs post 1980



Survival from diagnosis (1980+)-BC

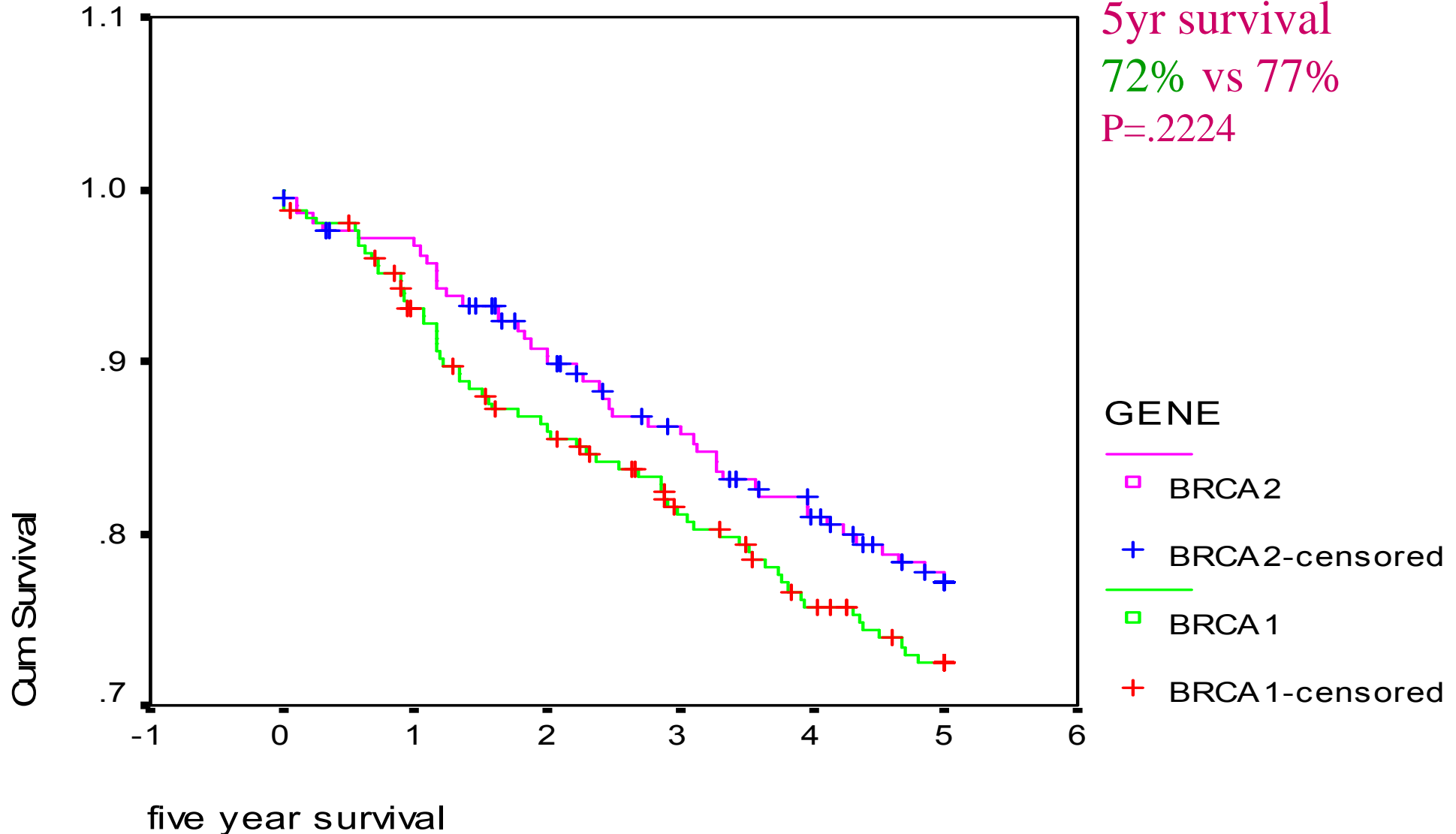
Survival Functions

247:211

5yr survival

72% vs 77%

P=.2224



Survival from 5yrs post diagnosis -BC

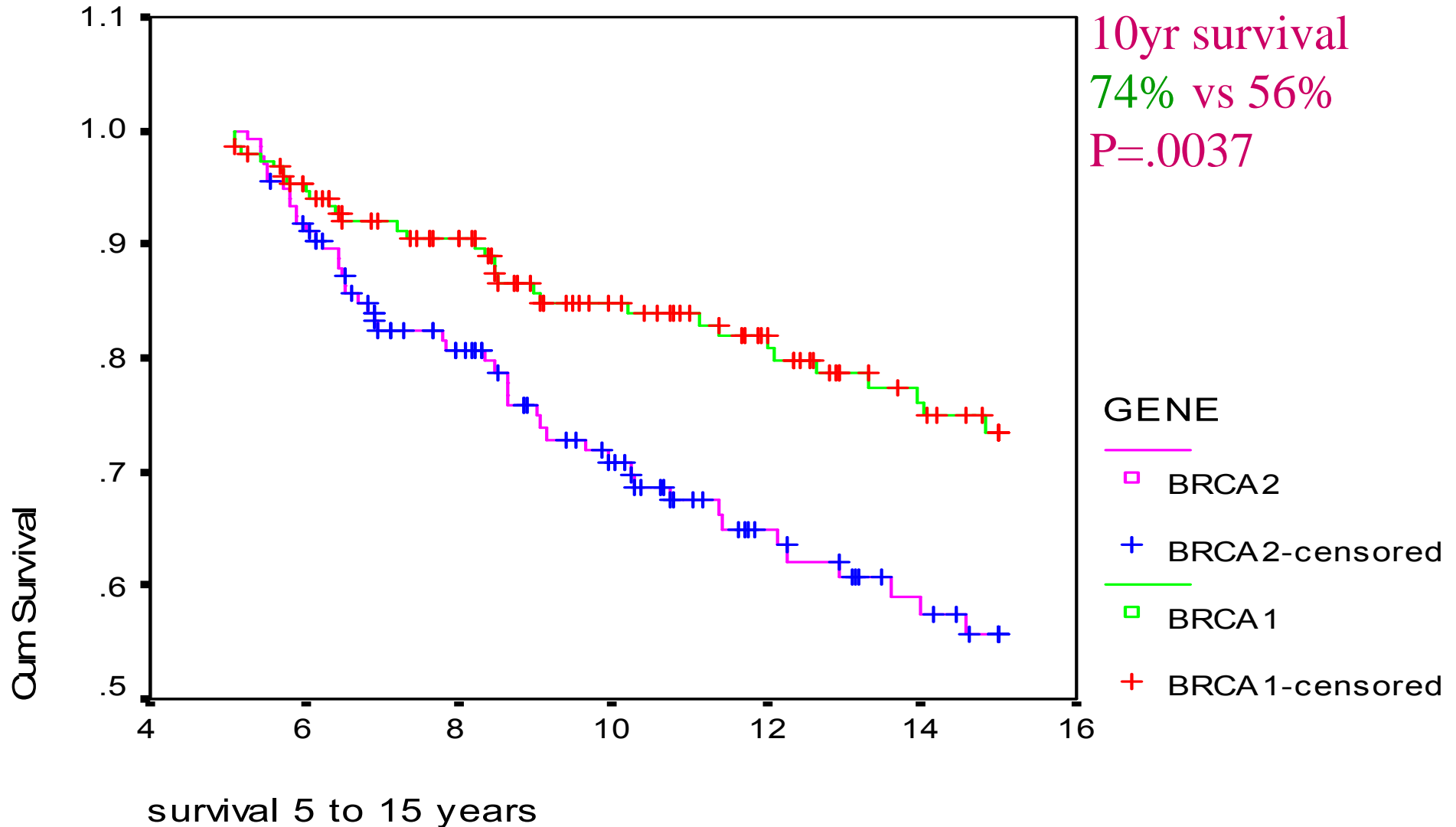
Survival Functions

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10yr survival

74% vs 56%

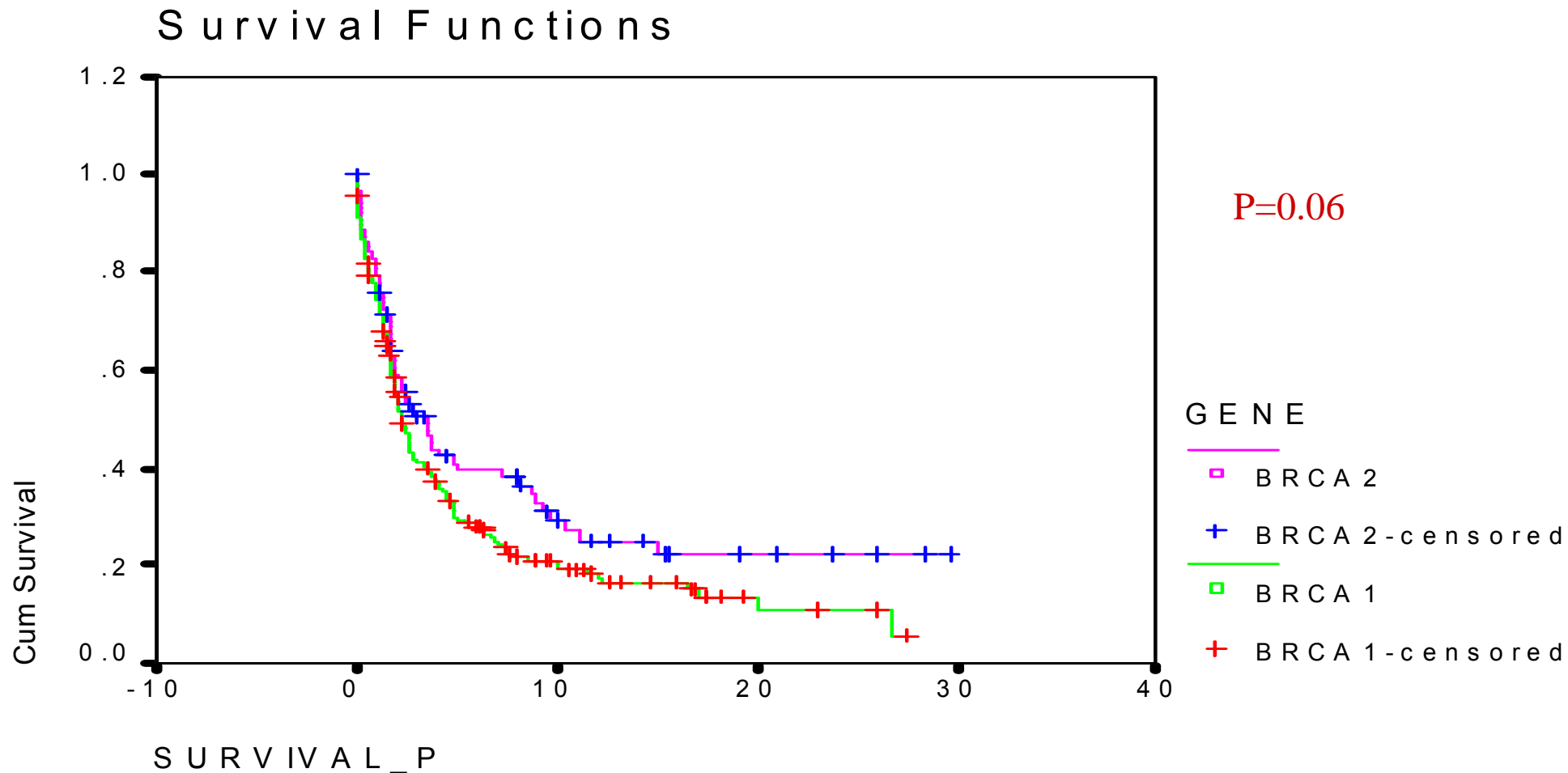
P=.0037



Grade and ER status

	Grade 3	Grades 1/2	ER Pos	ER Neg
BRCA1	91%	9%	23%	77%
BRCA2	58%	42%	74%	26%

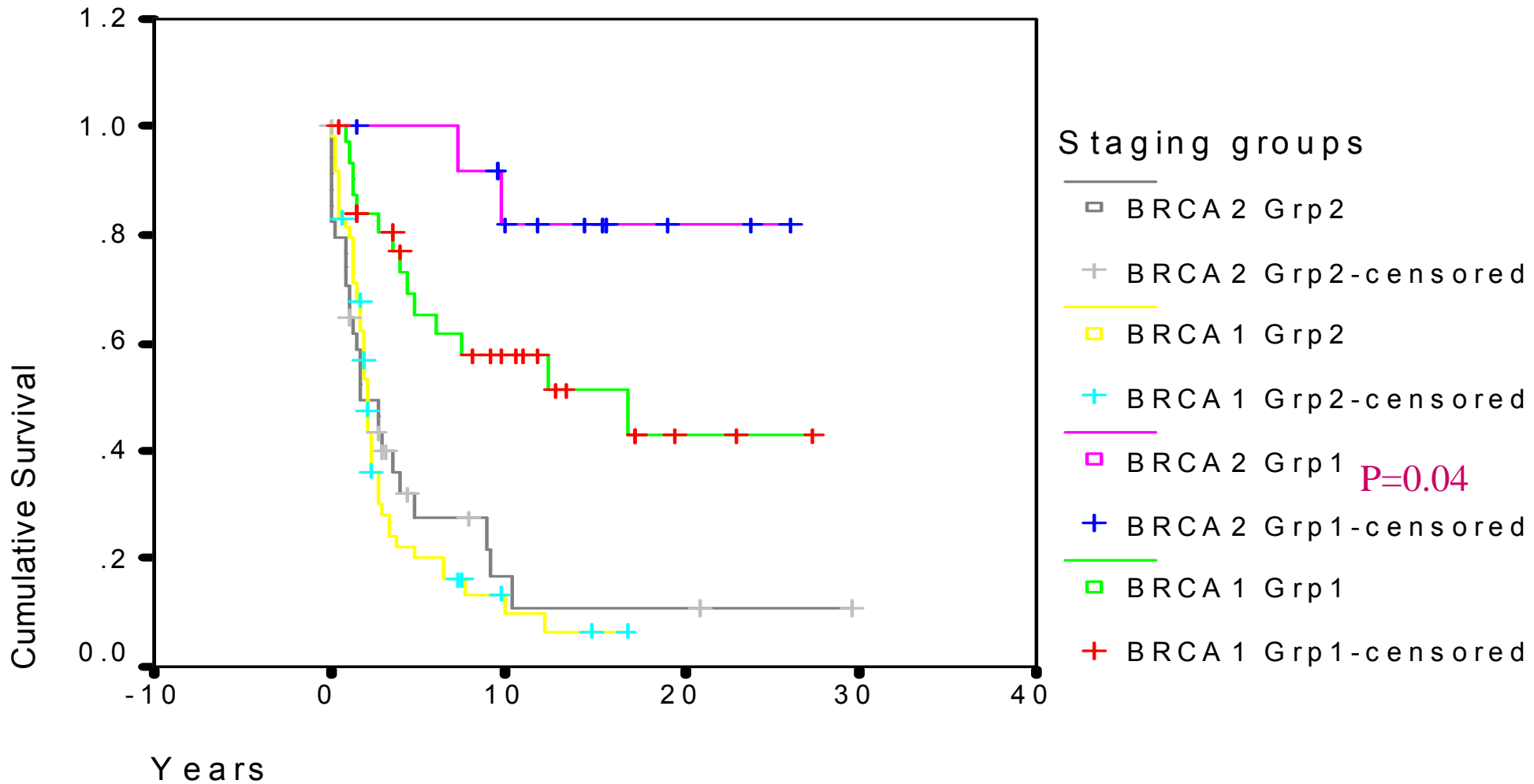
Survival from diagnosis Ovarian Cancer since 1975



	5yrs	10 yrs	20 yrs
BRCA1 (204)	30%	19%	11%
BRCA2 (88)	49%	29%	22%

Survival by stage early stage (I and II) group 1, versus late stage group 2 for 92 BRCA1 and 48 BRCA2 ovarian cancers with reliable stage data 1975

Survival post ovarian cancer



Stage by genetic status in screened women in 5 centres

	Stage 1	Stage 2	3/4	Dead
BRCA1	7	4	24 (69%)	20/35
BRCA2	0	0	4 (100%)	2/4
other	8 (5)	0	8 (50%)	1/16

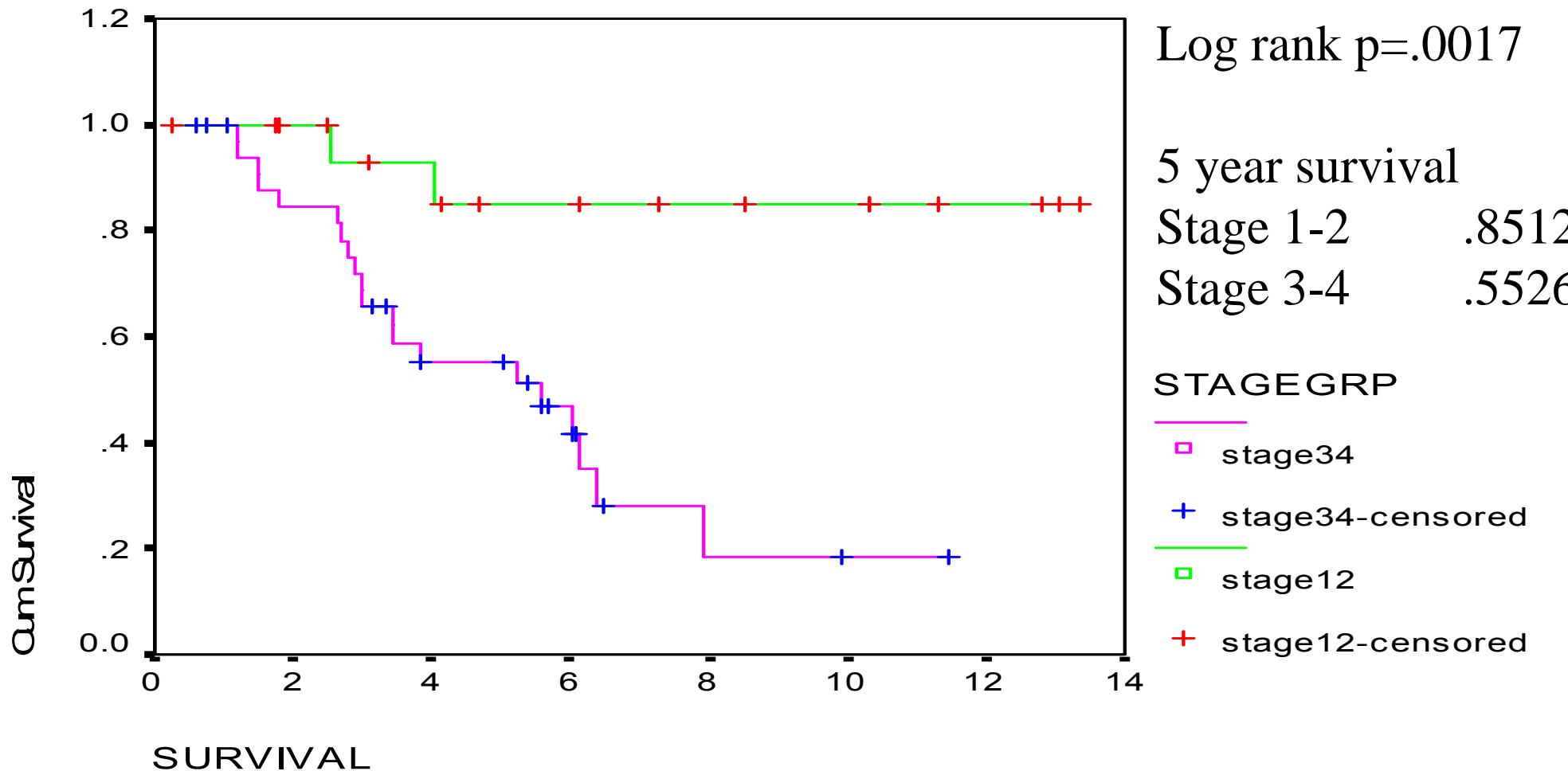
Manchester, Oslo, Leiden, Bergen, Edinburgh

Stage by prevalent Vs Incident/interval

	Stage 1	Stage 2	3/4
Prevalent	7	1	15 (65%)
Post Prev	8	3	20 (65%)

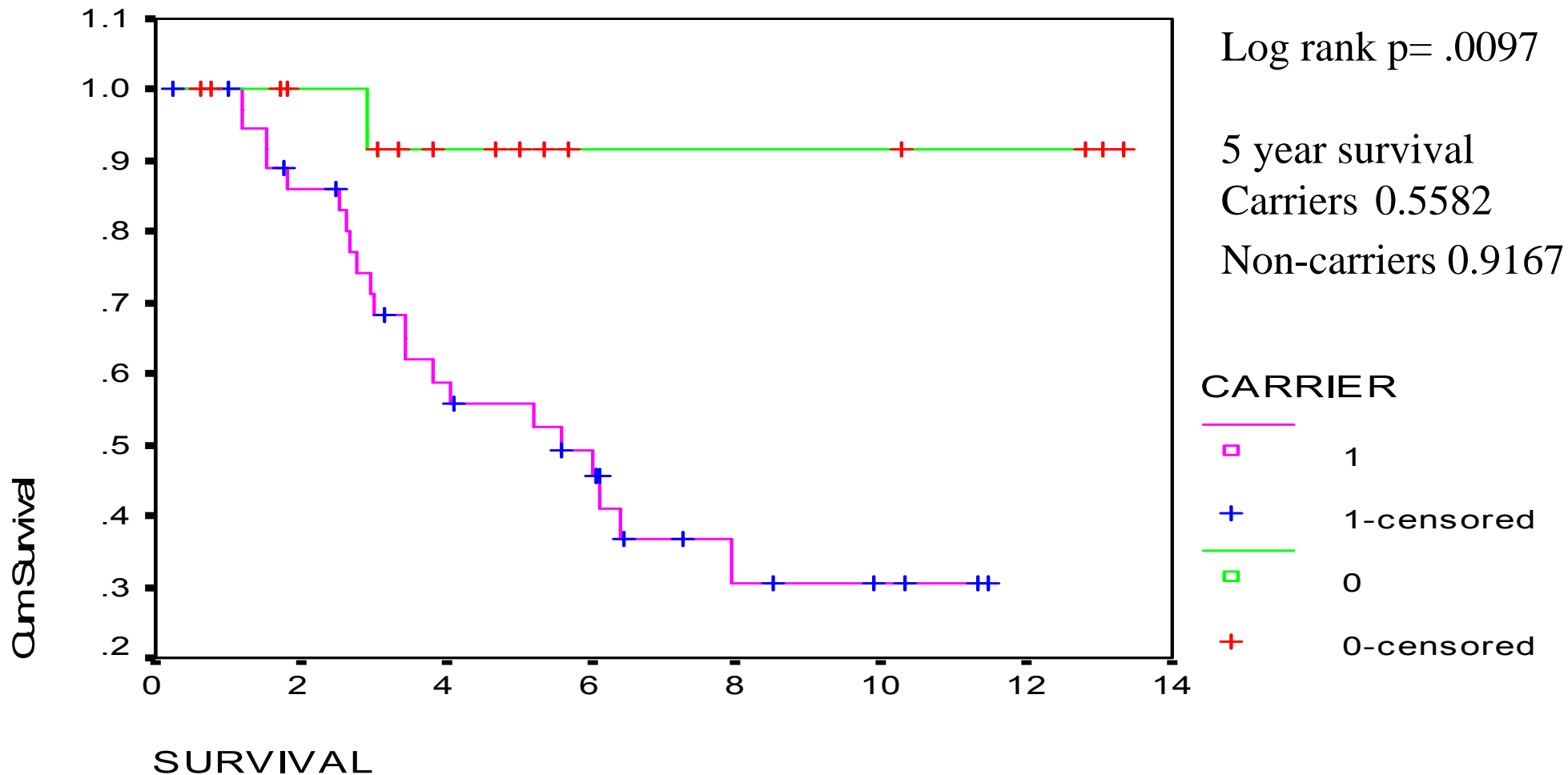
Survival by Stage

Survival Functions



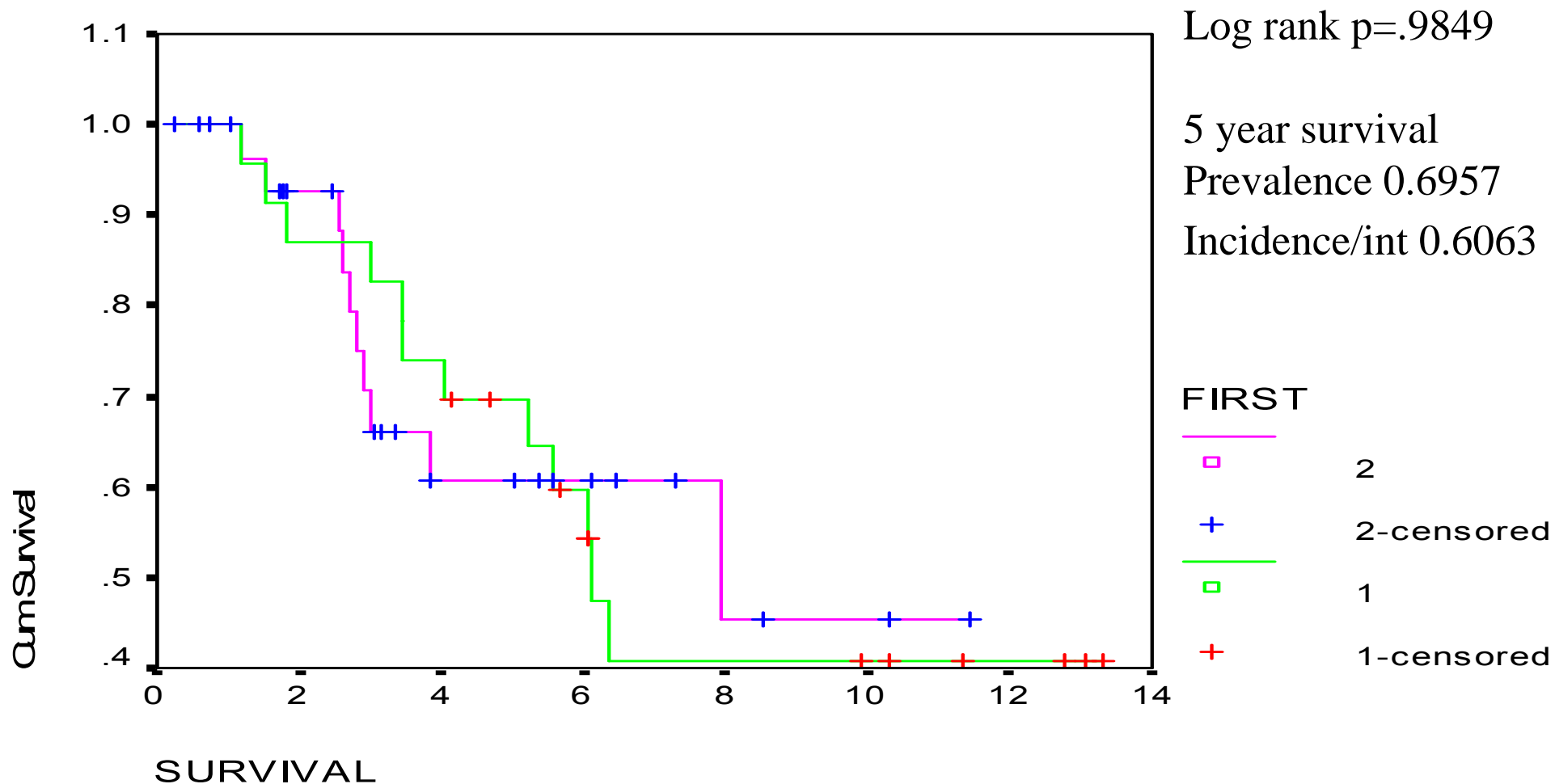
Survival by BRCA status

Survival Functions



Survival by Prev vs Inc/Int

Survival Functions



Ovarian cancer prevention

Conclusions

- No real evidence of down staging of disease with annual USS and CA125
- Survival in BRCA1/2 very poor
- Patients entering ovarian screening should be aware of the very limited evidence of efficacy

Genetic counselling

Conclusions

- Give risks with validated model to reflect TODAYs risks
- Choose which family member to test first (ideally)
- Risks in BRCA families should reflect family history
- May not be possible to be totally non directive especially regarding managing ovarian risk

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