The BOADICEA model of genetic susceptibility to breast and ovarian cancer: updating, validation, predictions

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BOadicea

CANCER RESEARCH UK

Model Development (version 1)

- Data:
  - Anglian Breast Cancer Study (**ABC families**)

    1484 breast cancer cases, unselected for family history
  - British Families (**B families**)

    156 multiple case families
  - BRCA1/2 status available.

Antoniou et al, Br J Cancer (2002)

Methods (v.1)

- Complex segregation analysis of breast and ovarian cancer occurrence.
- Modelled simultaneous effects:
  - BRCA1
  - BRCA2
  - "BRCAx"
  - Polygenic
- Polygenic = large number of genes, small effect, multiplicative effect on risk
- Best fitting model for residual familial clustering of breast cancer: **Polygenic**

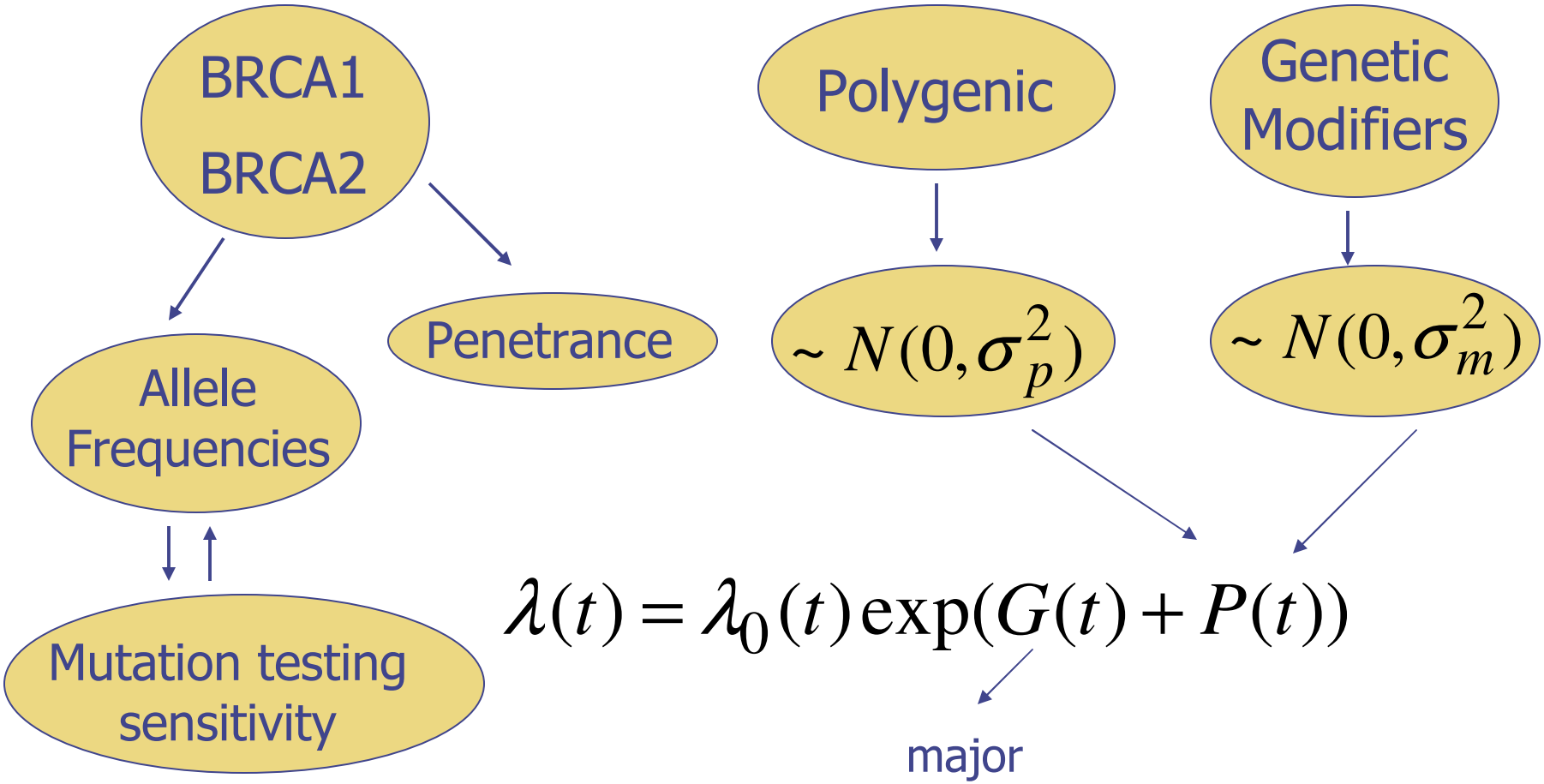
Updating - current data – number of families

Study	Index mutation status BRCA1	BRCA2	Non-carriers	Total
ABC	8	15	1461	1484
UK[1]	16	14	587	617
Manchester[2]	9	7	83	99
B Families	21	18	117	156
Meta-analysis[3]	247	182	NA	429
Total	301	236	2248	2785

[1] Peto et al, JNCI (1999)
[2] Lalloo et al, Lancet (2003)
[3] Antoniou et al, AJHG (2003)

} Population based studies

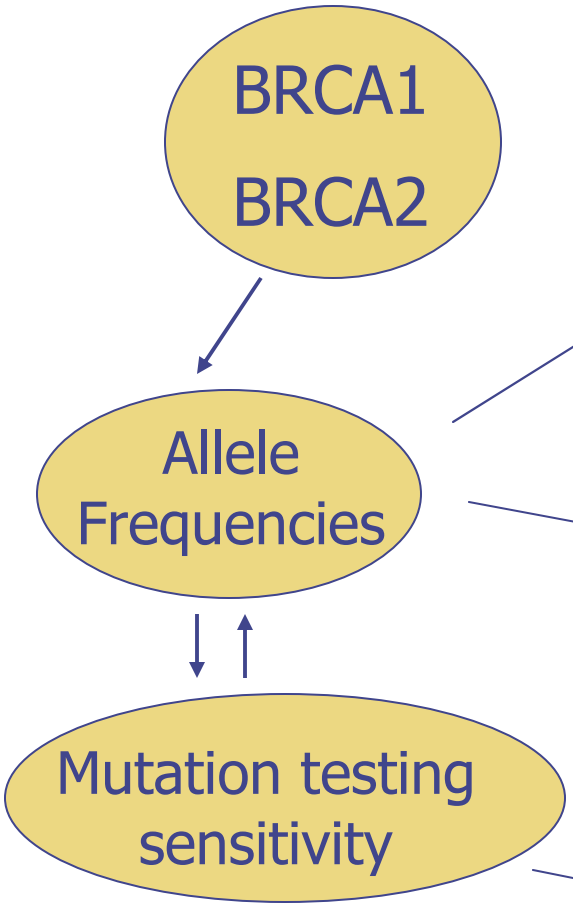
Model components



Birth cohort effect: <1920,1920-29, 1930-39, 1940-49, 1950+

All effects estimated simultaneously.

Model components - Results

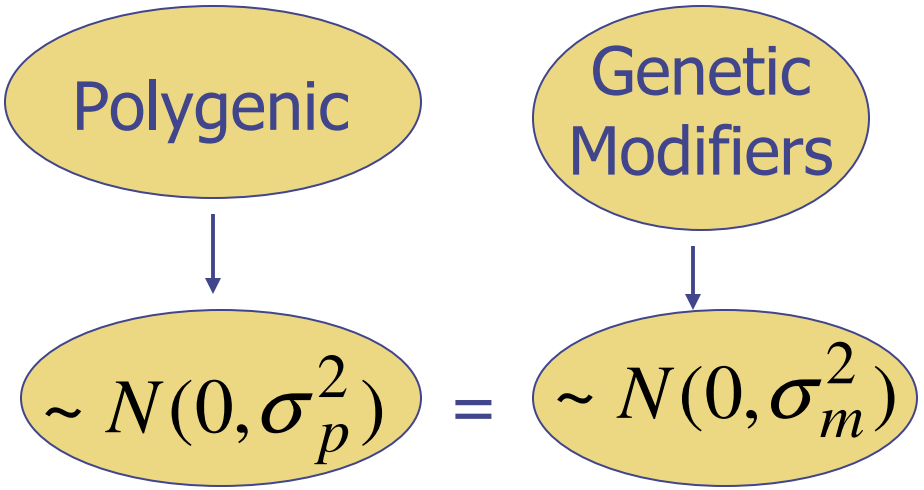


BRCA1: 0.06% (0.04-0.10%),
carriers: 0.12%

BRCA2:0.10% (0.07-0.15%)
carriers: 0.2%

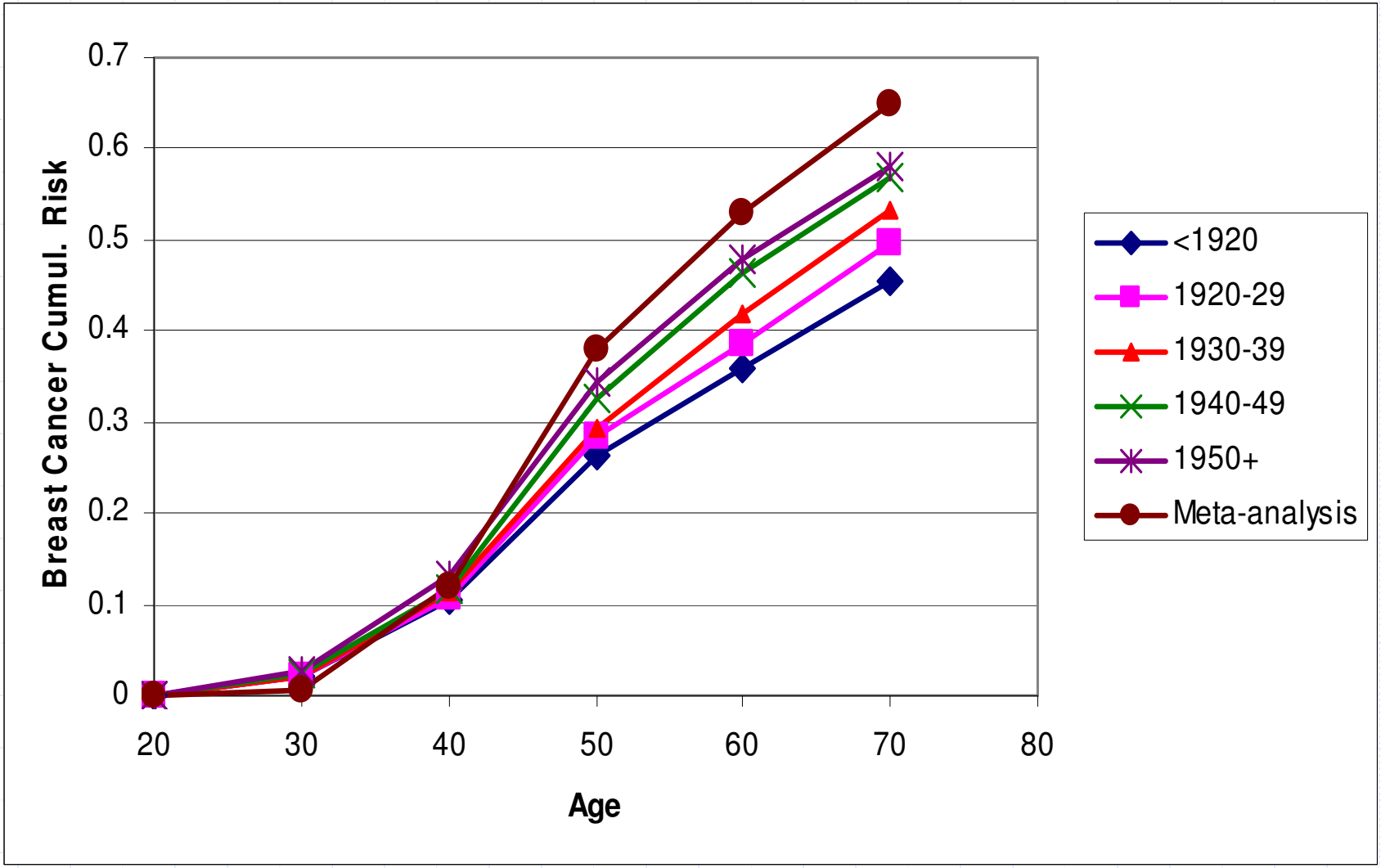
BRCA1: 70%
BRCA2: 80%

Model components - Results



Age	σ^2
20	3.6
30	3.2
40	2.3
50	1.9
60	1.3
70	0.7

BRCA1 "average" cumulative risk by birth cohort



Predicted Familial Relative Risks (affected mother)

Age	BOADICEA	Claus et al[1]	Observed[2]
25	6.8	10.3	
30	3.9	6.1	5.7
35	3.4	5.6	
40	2.6	2.3	2.0
45	2.3	2.0	
50	1.9	1.5	1.6
55	1.7	1.4	
60	1.5	1.1	
65	1.4	1.1	1.4
70	1.3	1.0	

[1] Claus et al AJHG (1991)
[2] Collaborative group on hormonal factors in breast cancer. Lancet (2001)

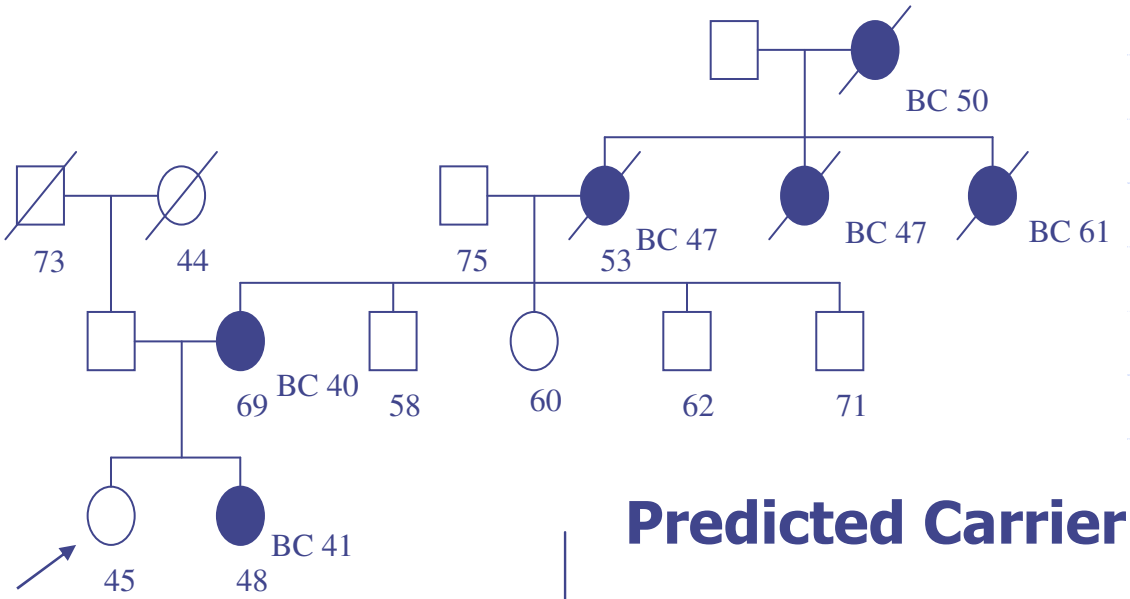
Predicted BRCA1/2 carrier frequency (%) among unselected breast cancer cases

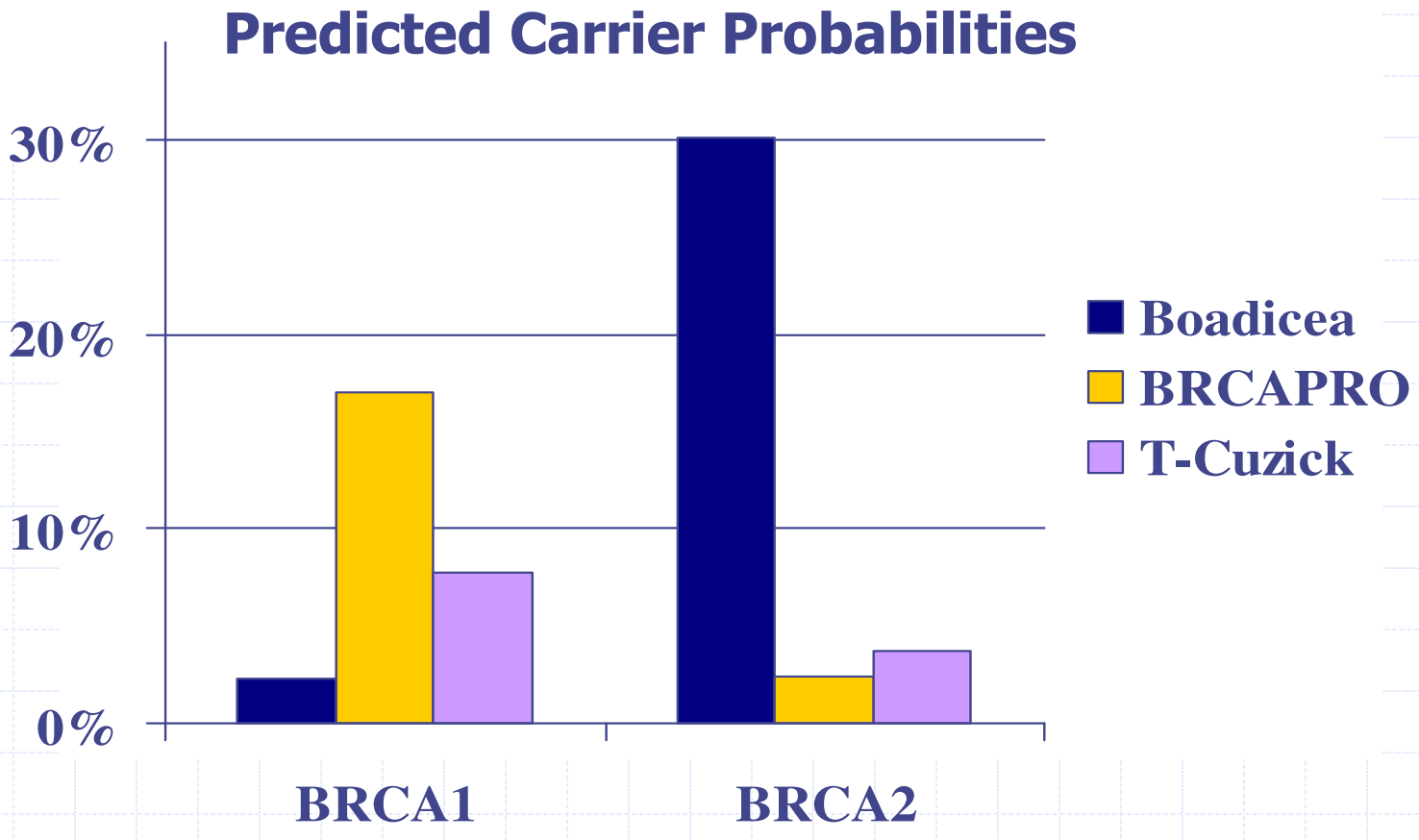
Age dx	BRCA1	BRCA2
30	3.3 (5.5)*	2.8 (0.8)
40	2.2 (2.9)	2.0 (0.2)
50	0.7 (1.2)	1.6 (0.4)
60	0.5 (0.3)	1.2 (0.3)
70	0.4 (0.0)	1.0 (0.1)

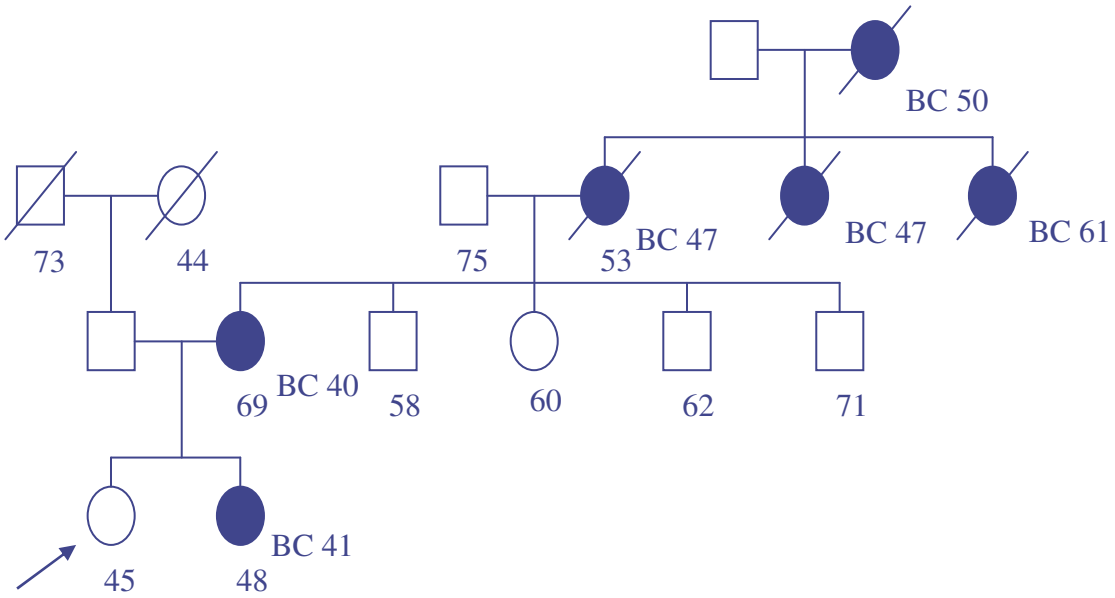
* Predictions by BRCAPRO (CancerGene v3.1)

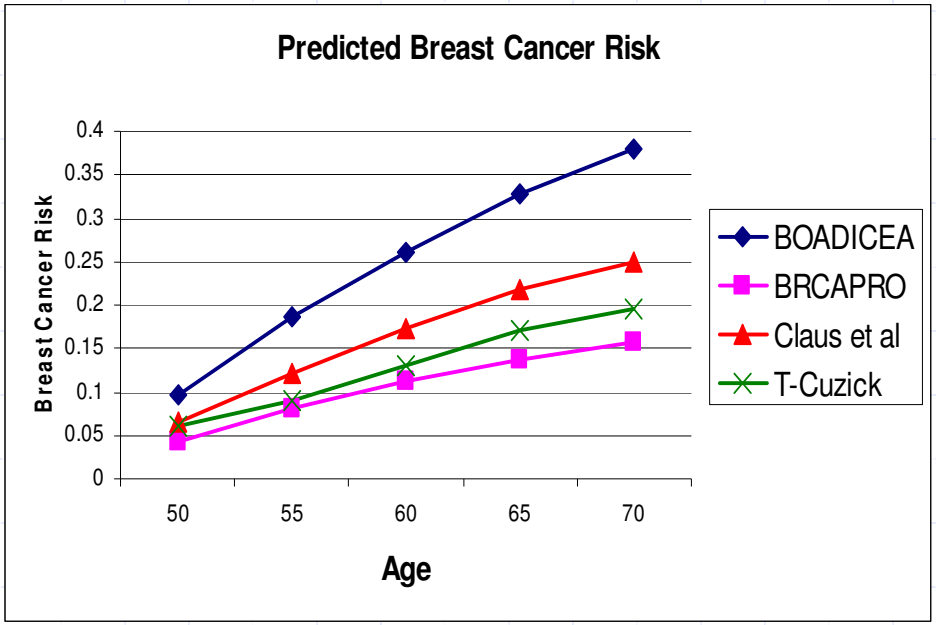
Predicted number of mutations

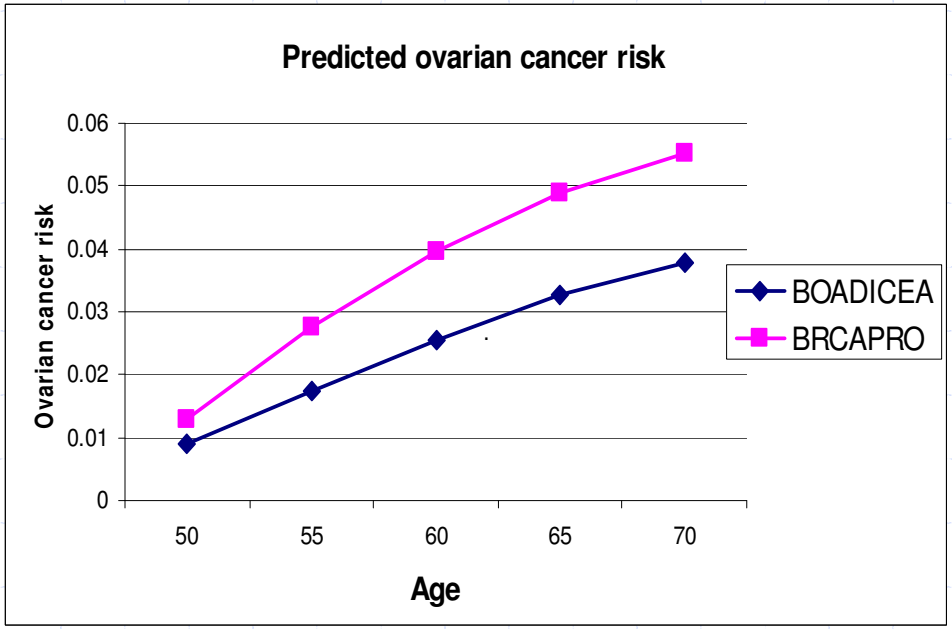
		BRCA1	BRCA2	Non-Carriers
B Families	Observed	21	18	117
	Expected	21.4	16.0	118.6
All	Observed	54	54	2248
	Expected	55.5	53.6	2246.9


BC 50
73
44
75
53
BC 47
BC 47
BC 61
69
BC 40
58
60
62
71
45
48
BC 41


Predicted Carrier Probabilities
30%
20%
10%
0%
BRCA1
BRCA2
Boadicea
BRCAPRO
T-Cuzick


BC 50
73
44
75
53
BC 47
BC 47
BC 61
69
BC 40
58
60
62
71
BC 41
45
48


Predicted Breast Cancer Risk
Breast Cancer Risk
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
50
55
60
65
70
Age
BOADICEA
BRCAPRO
Claus et al
T-Cuzick


Predicted ovarian cancer risk
Ovarian cancer risk
0.06
0.05
0.04
0.03
0.02
0.01
0
50
55
60
65
70
Age
BOADICEA
BRCAPRO

Model Features

- Currently implemented in MENDEL [Lange et al, Gen Epid (1988)].
- Flexible platform for updating the model and incorporating other genetic and environmental effects.
- Aim: Use as the basis for developing a risk assessment package to be used in genetic clinics.

Current/Future Work and Extensions

- Ovarian Cancer modifying effect on BRCA1/2 risks
- Other BRCA1/2 associated cancers (eg prostate, pancreas)/contralateral breast cancer.
- Allowance for other genetic/non-genetic factors (eg CHEK2, parity etc).
- Allele frequencies for other populations.
- **Validation in external datasets.**

Discussion points

- Identify data resources for validation.
- Predictions by different models vary.
- Need to compare the predictions by various models in validation studies.

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Genetic Modification of BC Risk in BRCA1/2 carriers