gis ma gruppoitalianoscreening mammografico

OSSERVATORIO NAZIONALE SCREENING

CONVEGNO NAZIONALE
GISMa 2010

BOLOGNA, 5-6 maggio 2010
Relais Bellaria Hotel & Congressi

Gruppi a rischio aumentato
Inquadramento teorico

Antonio Russo
Servizio di Epidemiologia e Biostatistica
A.O. Ospedale San Carlo Borromeo - Milano

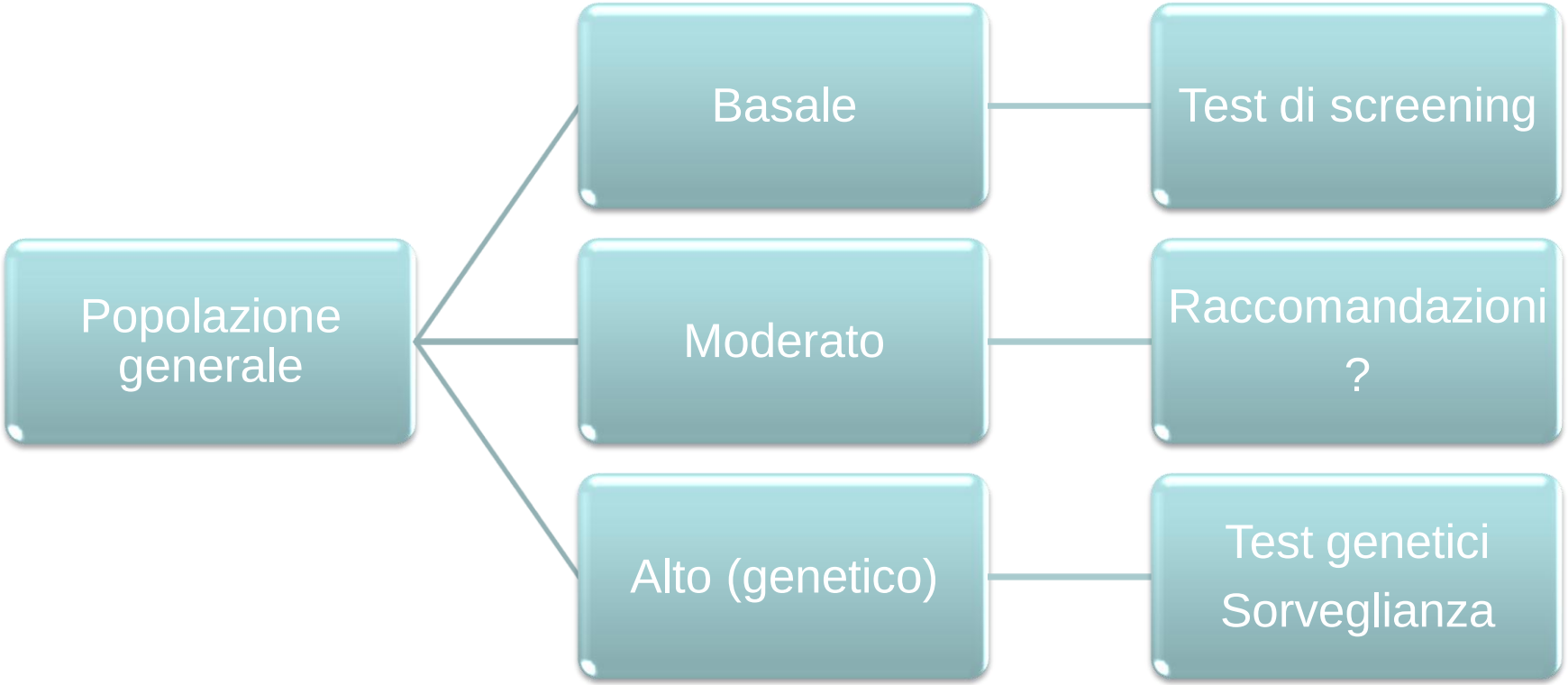
OSPEDALE SAN CARLO BORROMEO
AZIENDA OSPEDALIERA

“dalla diversità dei collettivi alla classificazione dei singoli”

Modelli predittivi

- conosciamo le associazioni principali, i meccanismi biologici alla base della malattia, abbiamo molti dati disponibili
- le risorse allocate sono molte in assoluto ma non sufficienti per tutta la popolazione
- Siamo convinti che intervenire prima sia meglio che mettere in “lista d’attesa poi”
- Per incrementare efficacia ed efficienza del sistema è comprensibile focalizzarsi sui soggetti a potenziale alto rischio

Modelli predittivi



Modello predittivo

- ***Definizione***: Un procedimento che utilizza i dati e la conoscenza disponibili per identificare persone che risultano a "rischio" che probabilmente necessiteranno di un utilizzo dei servizi sanitari superiore / diverso;

- Informazione relativa al tempo *t è utilizzata per* predire *t+k*

Applicazione dei modelli di predizione del rischio assoluto

- **A livello di popolazione**:
  - Stimare il disease burden
  - Stimare l'impatto della modificazione della distribuzione dei fattori di rischio nella popolazione generale
  - Pianificare studi di intervento
- **A livello individuale**:
  - Decisione clinica:
    - Modificazione dei fattori di rischio noti (dieta, esercizio fisico)
    - Valutazione di benefici / rischi di un intervento (es. Chemioprevenzione)
  - Raccomandazioni di screening

Cosa stimano i modelli di predizione del rischio

Rischio assoluto

- **Stimano la probabilità di sviluppare un cancro in un periodo di tempo definito**

Suscettibilità genetica

- **Stimano la probabilità di identificare una mutazione a carico di un gene di suscettibilità in una famiglia/individuo**

Elenco dei modelli di predizione di rischio per il tumore della mammella pubblicati

Rischio assoluto

- Ottman, 1983
- Anderson, 1985
- Gail, 1989
- Taplin, 1990
- Claus, 1993
- Rosner, 1996
- Colditz, 2000
- Gilpin, 2000
- Ueda, 2003
- Fisher, 2003
- Tyrer, 2004
- Barlow, 2006
- Chen, 2006
- Tice, 2008

Predizione di mutazione

- Couch, 1997
- Sattuck-Eidens, 1997
- Parmigiani, 1998
- Franck, 1998
- Hattge, 1999
- Vahteristo, 2001
- Berry, 2002
- Antoniou, 2002
- De la Hoya, 2002
- Apicella, 2003
- Jonker, 2003

VALUTAZIONE

Calibrazione

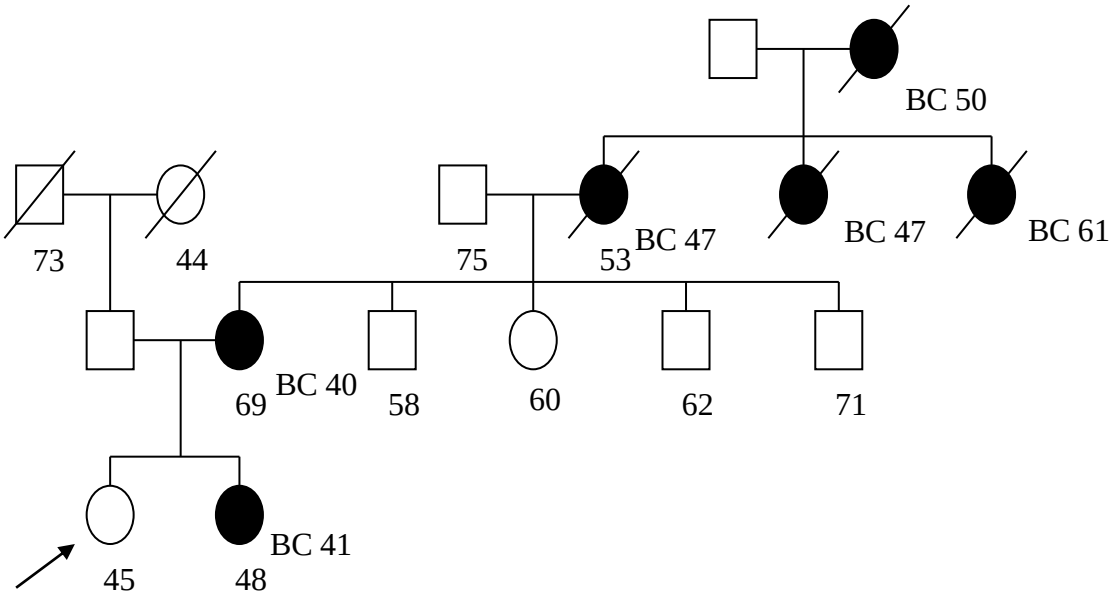
- Capacità di un modello di predire l'incidenza di malattia in un gruppo di individui

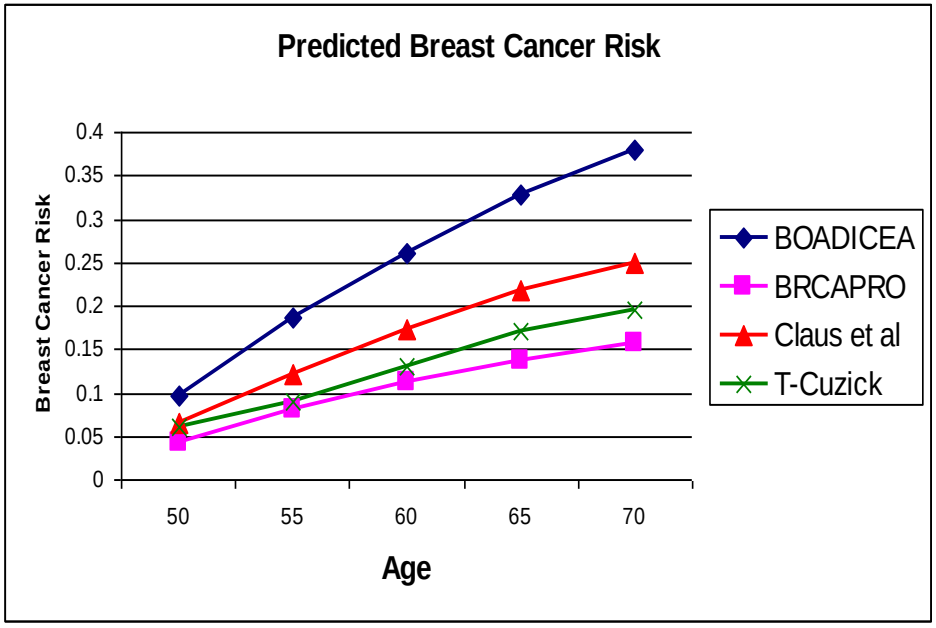
Discriminatory Accuracy

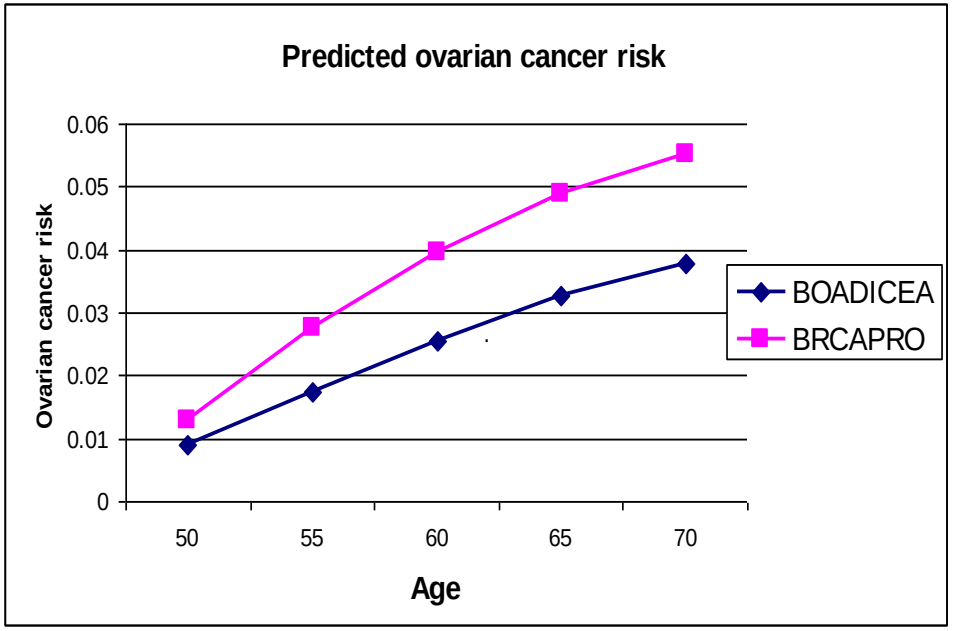
- Misura la capacità di un modello di discriminare chi svilupperà la malattia da chi non la svilupperà

Generalizzabilità

- Capacità di fornire una predizione in un campione indipendente
  - Riproducibilità
    - Su una popolazione identica
  - Trasportabilità
    - Su popolazioni differenti o campioni raccolti in maniera differente

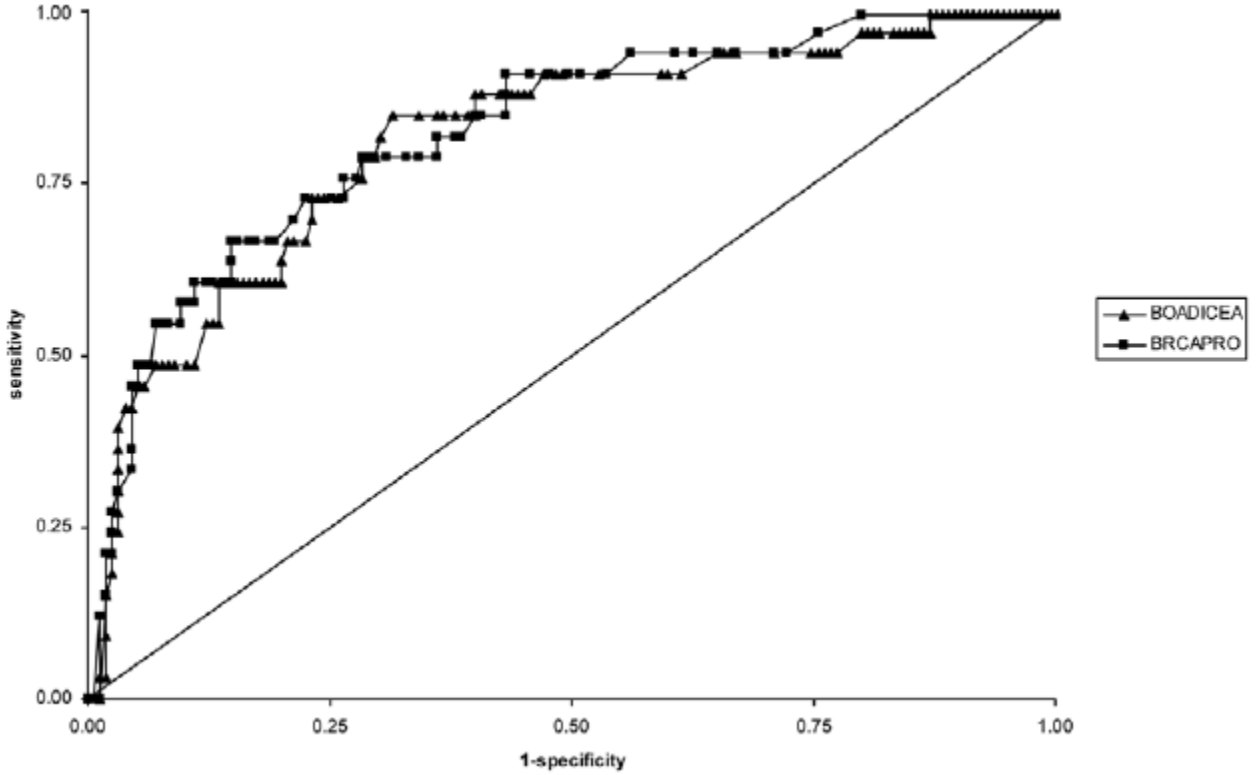

BC 50
73
44
75
53
BC 47
BC 47
BC 61
69
BC 40
58
60
62
71
BC 41
45
48


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

BRCA1 and *BRCA2* mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families

Antonis C Antoniou[1], Francine Durocher[2], Paula Smith[1], Jacques Simard[2], INHERIT BRCAs program members[3] and Douglas F Easton[1]



The ROC curves under BOADICEA using the full pedigrees and under BRCAPRO are shown in Fig. 2. The area under the curve was 83% (95% CI 75–91%) under BRCAPRO and slightly lower, at 81% (95% CI 73–90%), under BOADICEA.

BRCA Mutation Probability Models

Print

Quit

BRCA1	Individual	Family
U. Penn	0,032	0,032
Myriad I	0,111	0,111
Myriad II	0,282	0,282
BRCAPRO	0,493	

BRCA2	Individual	Family
Myriad II	0,116	0,116
BRCAPRO	0,354	

*BRCA**	Individual	Family
Myriad II	0,400	0,400
BRCAPRO	0,846	

Pedigree Information

Ashkenazi family: **No**
Number of family members: **20**
Number with breast cancer only: **9**
Number with ovarian cancer only: **0**
Number with both breast and ovarian cancer: **0**
Number with bilateral breast cancer: **0**
Mean age breast cancer: **50**
Mean age ovarian cancer: #

*Either *BRCA1* or *BRCA2*

Values expressed as probabilities, not percents
means no calculation possible

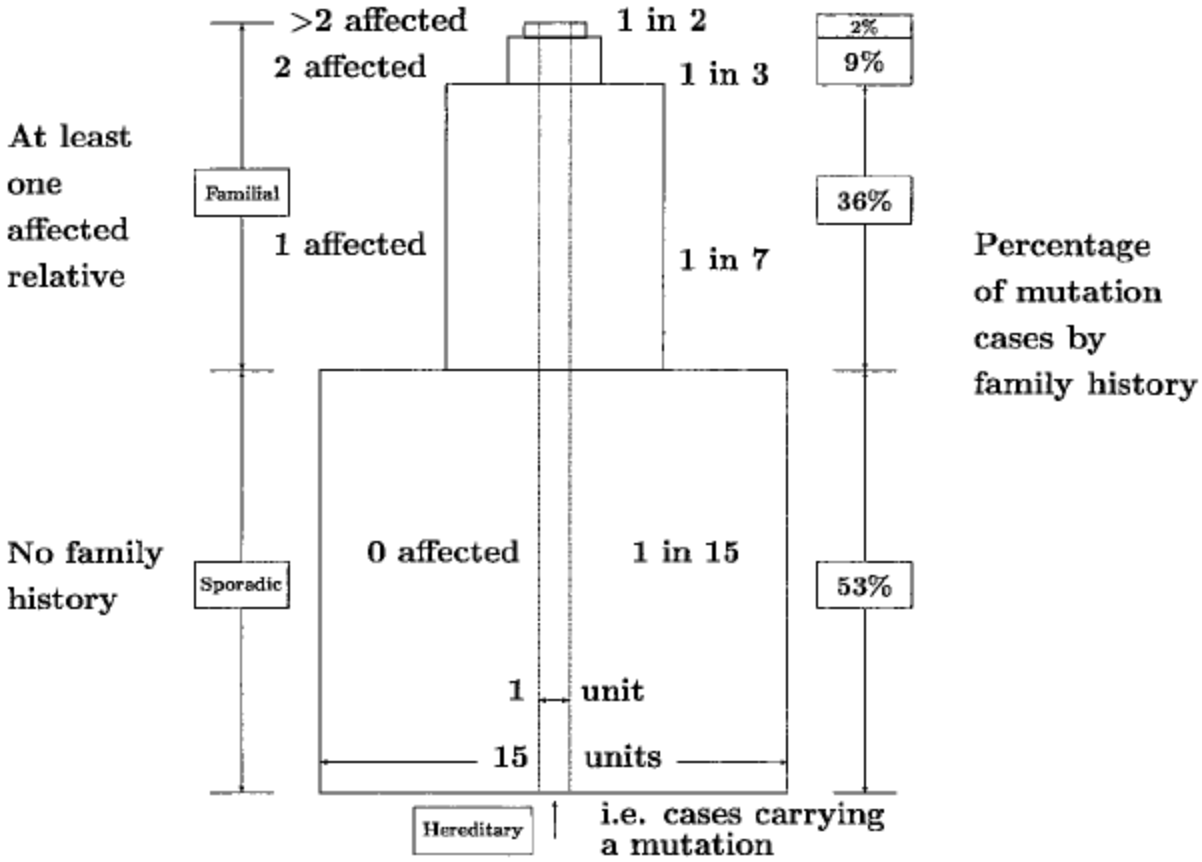
Why Are the Majority of Hereditary Cases of Early-Onset Breast Cancer Sporadic? A Simulation Study[1]

Jisheng Cui and John L. Hopper[2]

Centre for Genetic Epidemiology, The University of Melbourne, Carlton, Victoria 3053, Australia

Cancer Epidemiology, Biomarkers & Prevention

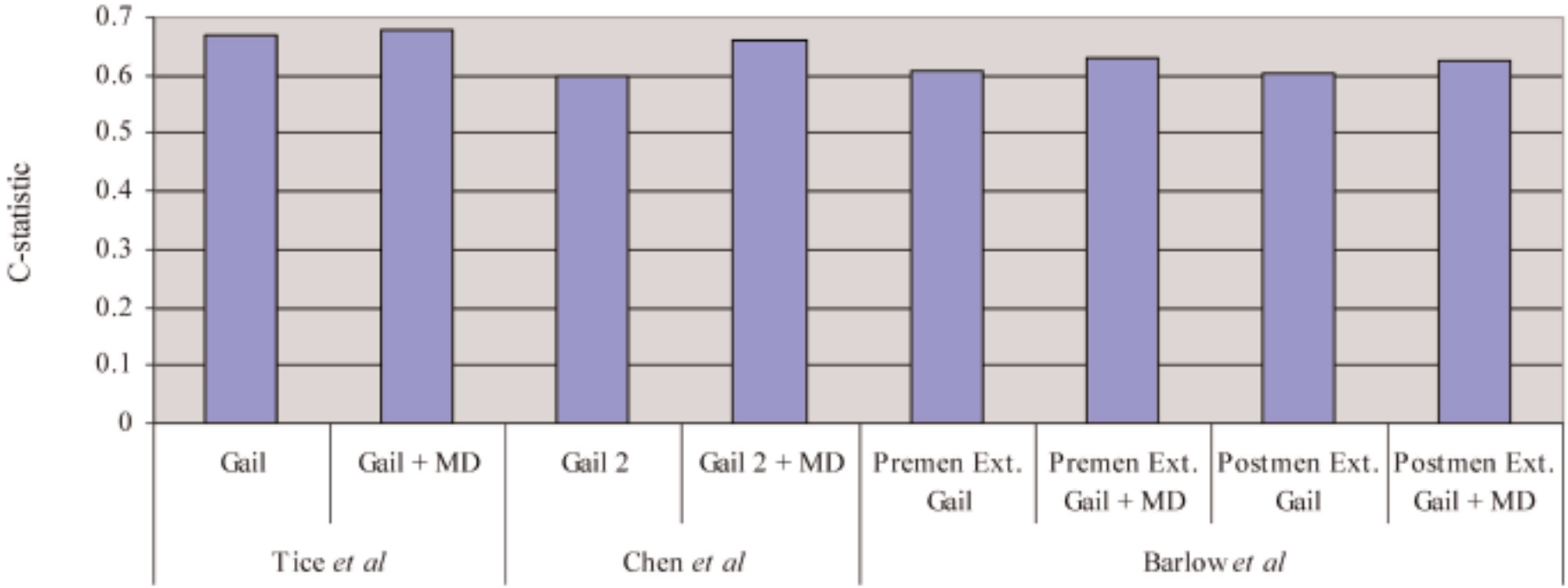
Vol. 9, 805–812, August 2000



Breast Cancer Risk Assessment Tool (BCRAT)

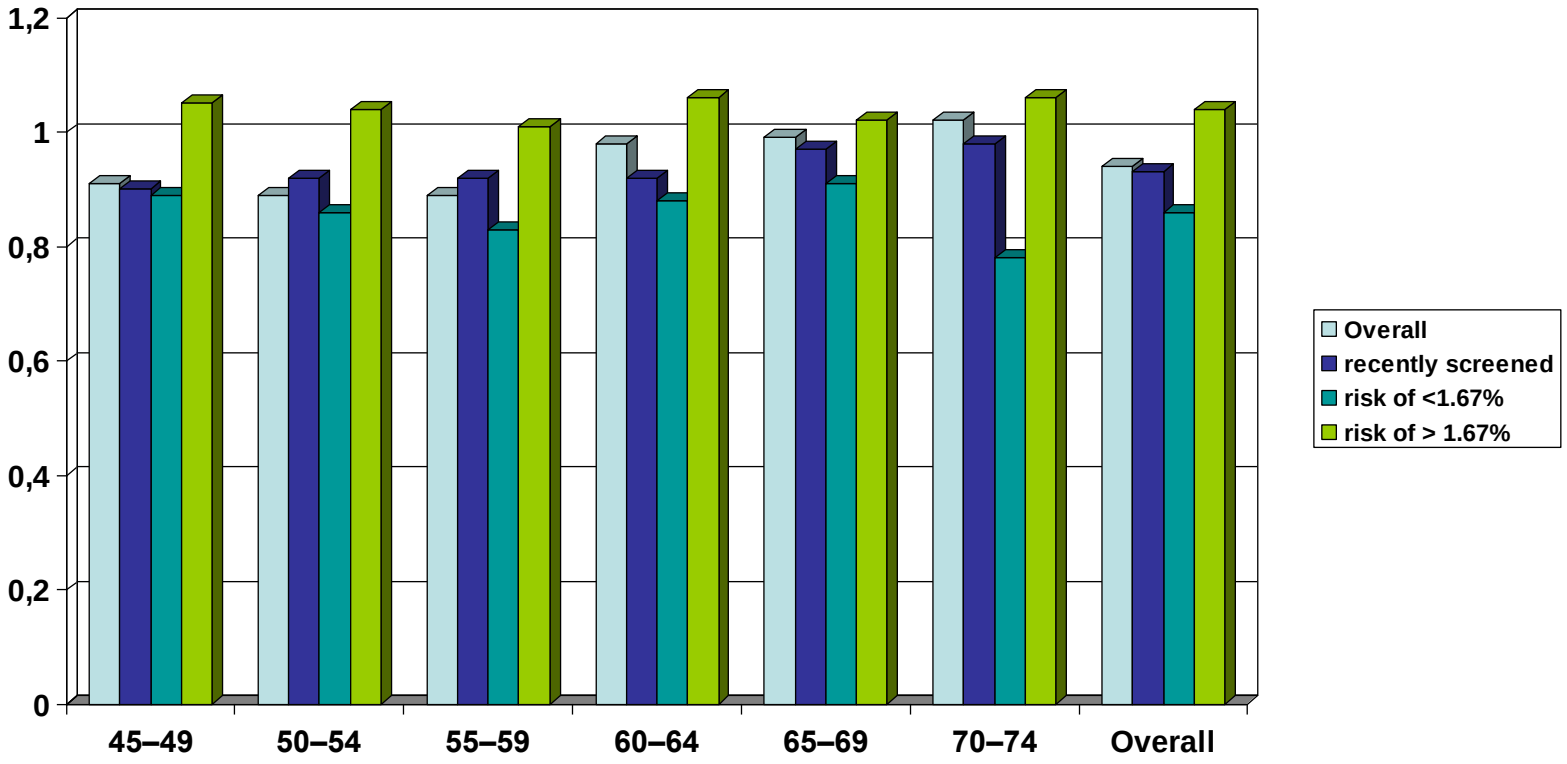
- The NCI's BCRAT or "Gail Model 2"
  - Risk factors in BCRAT
    - Age
    - Age at first live birth
    - Age at menarche
    - Number of mother/sisters with breast cancer
    - Number of previous benign breast biopsies and whether atypical hyperplasia present on any

Gain in C-statistic in three breast cancer risk prediction models with the addition of mammographic density



Mammographic density, breast cancer risk and risk prediction.
Breast Cancer Research 2007, 9:217 (20 December 2007)

Ratios of expected (E) and observed (O) number of breast cancer cases in the Nurses' Health Study (NHS) based on 5-year risk prediction of Gail



Rockhill et al, JNCI 2001

Model, first author, year (reference)	No. of subjects	Age, y; % race or nationality	Risk factors included in the final model	No. of patients with breast cancer	Calibration, E/O (95% CI)	Discrimination, *c*-statistic (95% CI)
Models with only risk factors						
Gail (original) model						
Gail, 1989 (7)	5998	Median = 55–60; 100% white	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	2852	NR	NR
Spiegelman, 1994 (8)	115 172	Median = 45–49; 98% white	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	2396	1.33 (1.28 to 1.39)	NR
Costantino, 1999 (9)	5969	Median = 50–59; 100% white	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	204	0.84 (0.73 to 0.97)	NR
Gail model 2 (BCPT)						
Costantino, 1999 (9)	5969, with Gail risk >1.66%	Median = 50–59; 100% white	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	204	1.03 (0.88 to 1.21)	NR
Rockhill, 2001 (10)	82 109	Median = 55–59; 100% white	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	1354	0.94 (0.89 to 0.99)	0.58 (0.56 to 0.60)
Tice, 2005 (11)	6904	Median = 43; 71% white, 11% black, 11% Asian, 5% Hispanic, 2% other	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	400	NR	0.62 (NR)
Novotny, 2006 (12)	14 566†	Median = 57; 100% Czech	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	2299	NR; estimated >2 from data in text	NR
Decarli, 2006 (13)	10 381	Median = 50–59; 100% Italian	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	194	0.93 (0.81 to 1.08)	0.59 (0.55 to 0.63)
Chlebowski, 2007 (23)	147 916	Mean = 63; 83% white, 9% black, 3% Asian, 4% Hispanic, <1% American Indian	Age, race, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	3236	0.79 (NR, $P < .001$)	0.58 (0.56 to 0.60)
Claus model						
Claus, 1990–1991 (14–16)	9418	Range = 20–54; 100% white	Age, first-degree relatives with BC, second-degree relatives with BC, age at each BC diagnosis	4730	NR	NR
Rosner and Colditz model 1						
Rosner, 1996 (17)	89 132	Age, NR; race, NR but ~98% white‡	Age, age at menarche, age at birth of first child, age at menopause, parity	2249	NR	NR
Rockhill, 2003 (18)	45 210	Mean = 58; race, NR but ~98% white‡	Age, age at menarche, age at birth of first child, age at menopause, parity	757	1.00 (0.93 to 1.07)	0.57 (0.55 to 0.59)
Rosner and Colditz model 2						
Colditz, 2000 (19)	58 520	Range = 30–55; race, NR but ~98% white‡	Age, age at menarche, age at birth of first child, age at menopause, parity, age at oophorectomy, current HT, years ET, years EPT, height, BMI, benign breast disease	1761	NR	NR

J Natl Cancer Inst 2009;101: 384 – 398

Model, first author, year (reference)	No. of subjects	Age, y; % race or nationality	Risk factors included in the final model	No. of patients with breast cancer	Calibration, E/O (95% CI)	Discrimination, *c*-statistic (95% CI)
Rockhill, 2003 (18)	45 210	Mean = 58; race, NR but ~98% white‡	Age, age at menarche, age at birth of first child, age at menopause, parity, age at oophorectomy, current HT, years ET, years EPT, height, BMI, benign breast disease	757	1.01 (0.94 to 1.09)	0.63 (0.62 to 0.66)
Ueda model						
Ueda, 2003 (20)	806	Age, NR; 100% Japanese	Age, age at menarche, age at birth of first child, age at menopause, first-degree relatives, BMI	376	NR	NR
CARE model						
Gail, 2007 (21)	3254	Age, NR; 100% black	Age, first-degree relatives with BC, age at menarche, age at birth of first child, breast biopsy, atypical hyperplasia	1607	1.08 (0.97 to 1.20)	0.56 (0.54 to 0.58)
WHI model						
Chlebowski, 2007 (23)	147 092 postmenopausal women; cases limited to estrogen receptor–positive BC	Mean = 63; 83% white, 9% black, 3% Asian, 4% Hispanic, <1% American Indian	Age, first-degree relatives with BC, breast biopsy	2412	NR	0.58 (0.56 to 0.60)
Risk factors plus breast density						
Barlow, 2006§ (24)						
Premenopausal	141 991	Median = 45–49; 86% white, 6% black, 6% Asian, 1% American Indian, 1% other	Age, first-degree relatives with BC, breast biopsies, BI-RADS breast density	432	1.00 (NR)	0.63 (0.62 to 0.64)
Postmenopausal	410 355	Median = 60–64; 87% white, 6% black, 5% Asian, 1% American Indian, 1% other	Age, race, Hispanic, first-degree relatives with BC, breast biopsies, age at birth of first child, oophorectomy, current HT, BMI, BI-RADS breast density	2303	1.01 (NR)	0.62 (0.62 to 0.63)
Chen model						
Chen, 2006 (22)	2891	Age, NR; 100% white	Age, race, age at birth of first child, first-degree relatives with BC, breast biopsies, atypical hyperplasia, weight, % breast density	1235	NR	0.64 (NR)
Tice model						
Tice, 2008 (25)	629 229	Mean = 53.4; 71% white, 7% black, 3% Asian, 8% Hispanic, 11% other	Age, race, first-degree relatives with BC, breast biopsies, BI-RADS breast density	8784	1.01 (0.99 to 1.03)	0.66 (0.65 to 0.66)

J Natl Cancer Inst 2009;101: 384 – 398

Revisions in the Risk-Based Breast Cancer Screening Program at Group Health Cooperative

1990

Stephen H. Taplin, MD, MPH,* Robert S. Thompson, MD,*
Fernne Schnitzer, MEd,† Carolyn Anderman, MPH,*
and Virginia Immanuel, MPH*

TABLE 2. Revised Risk Algorithm

Mammography frequency	Risk level	Risk level criteria	Minor risk factor
Yearly	1	Previous breast cancer or atypia on biopsy; at least two first-degree relatives with breast cancer	Second-degree relative with breast cancer; menarche age ≤10 yr or menopause ≥55 yr or both; nulliparity or first live birth ≥30 yr; previous negative breast biopsy × 1
Every 2 yr	2	One first-degree relative with breast cancer; age ≥50 yr and ≥2 MRFs	
Every 3 yr	3	Age < 50 yr and ≥1 MRF; age ≥50 yr and ≤1 MRF	
Not recommended	4	Age < 50 yr and no MRF	

First-degree relative: mother, sister, daughter.
Second-degree relative: grandmother, aunt.
MRF: minor risk factors.

Risk level criteria: women must meet one or more of the criteria to be included in a risk level.

Cancer 66:812–818, 1990.

Exact age procedure

1998

Età	*FFR*
40	2.45
41	2.15
42	1.89
43	1.67
44	1.49
45	1.32
46	1.20
47	1.11
48	1.06
49	1.02
50	1.00

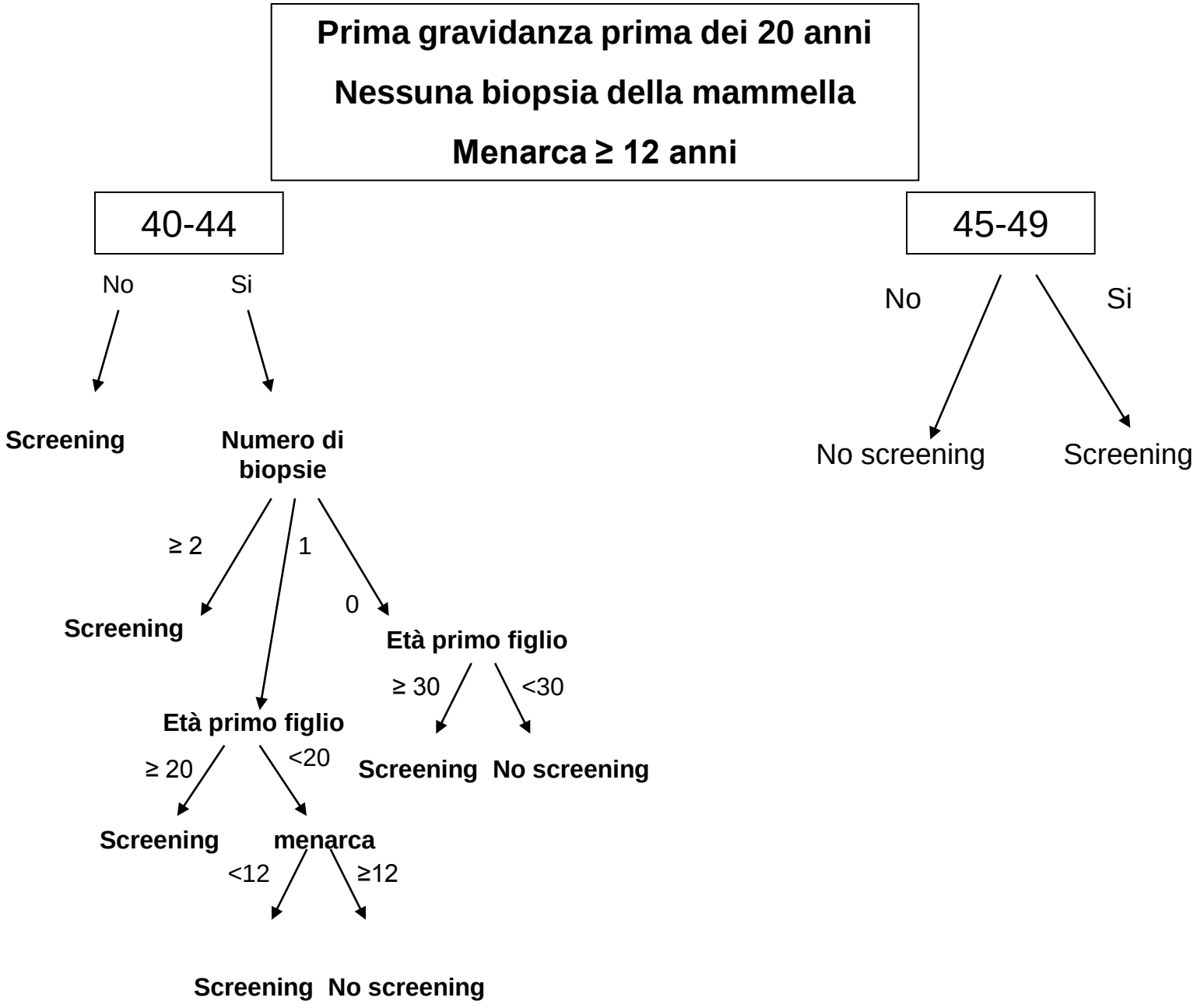
Donna nullipara, 44 anni, menarca 12 anni senza biopsie mammarie

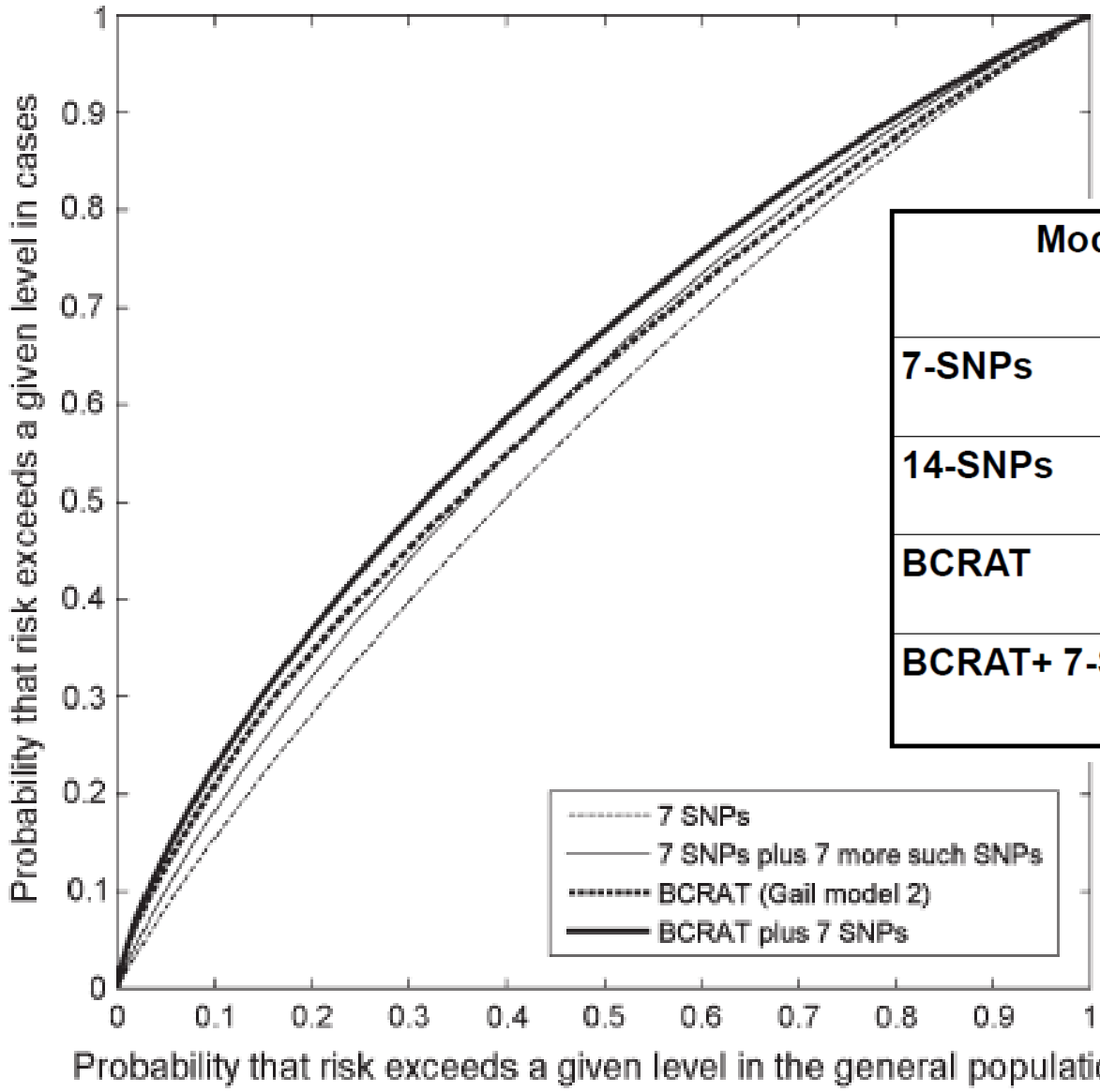
1.099 x 1.000 x 1.548 = 1.701

Screening

Fattore	**RR**
Età al menarca	
≥ 13	1.000
12-13	1.099
< 12	1.207
N. biopsie	
0	1.000
1	1.698
Età al primo figlio	
<20	1.000
20-25	1.244
26-29	1.548
≥ 30	1.927

Grouped age procedure 1998





Model	Age-specific AUC
7-SNPs	0.574
14-SNPs	0.604
BCRAT	0.607
BCRAT+ 7-SNPS	0.632

Discriminatory Accuracy from Single-Nucleotide Polymorphisms in Models to Predict Breast Cancer Risk.
J Natl Cancer Inst. 2008 July 16; 100(14): 1037–1041

A breast cancer prediction model incorporating familial and personal risk factors

Jonathan Tyrer, Stephen W. Duffy and Jack Cuzick*,†

Department of Epidemiology, Mathematics and Statistics, Cancer Research U.K., Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, U.K.

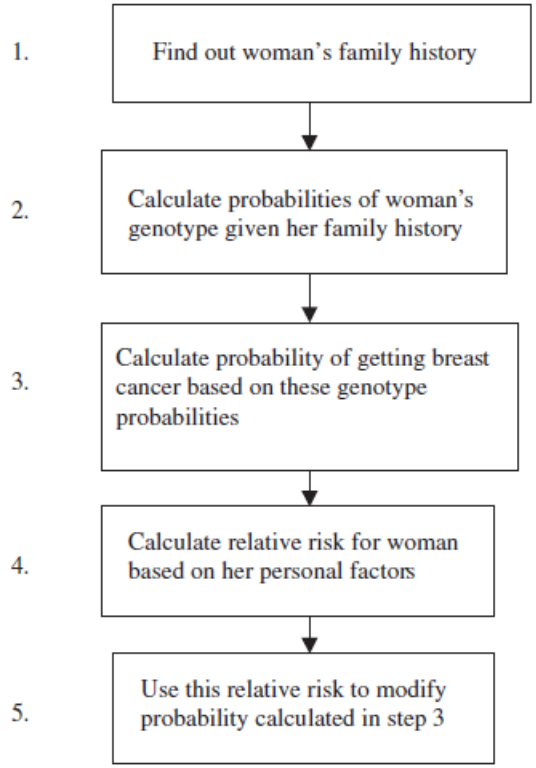


Table VII. Risk factors included in the risk calculation, with their effects as observed in the population.

Factor	Effect
Age at menarche	Risk decreases with increased age at menarche
Parity	Risk is generally less for parous women
Age at first childbirth (if parous)	Risk increases for later age at first childbirth
Age at menopause (if postmenopausal)	Risk increases for a later age at menopause
Atypical hyperplasia	A four-fold increase in risk if present
Lobular carcinoma *in situ*	An eight-fold increase in risk if present
Height	Risk increases with increased height
BMI	Risk increases for post-menopausal women with increased BMI

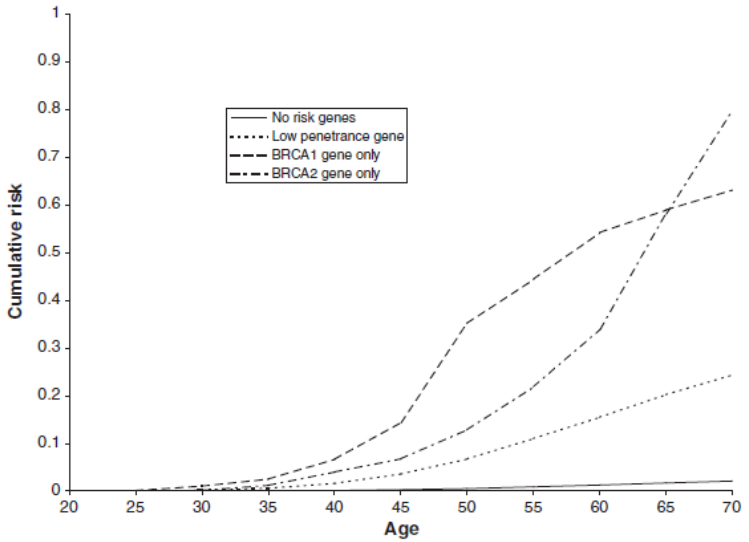
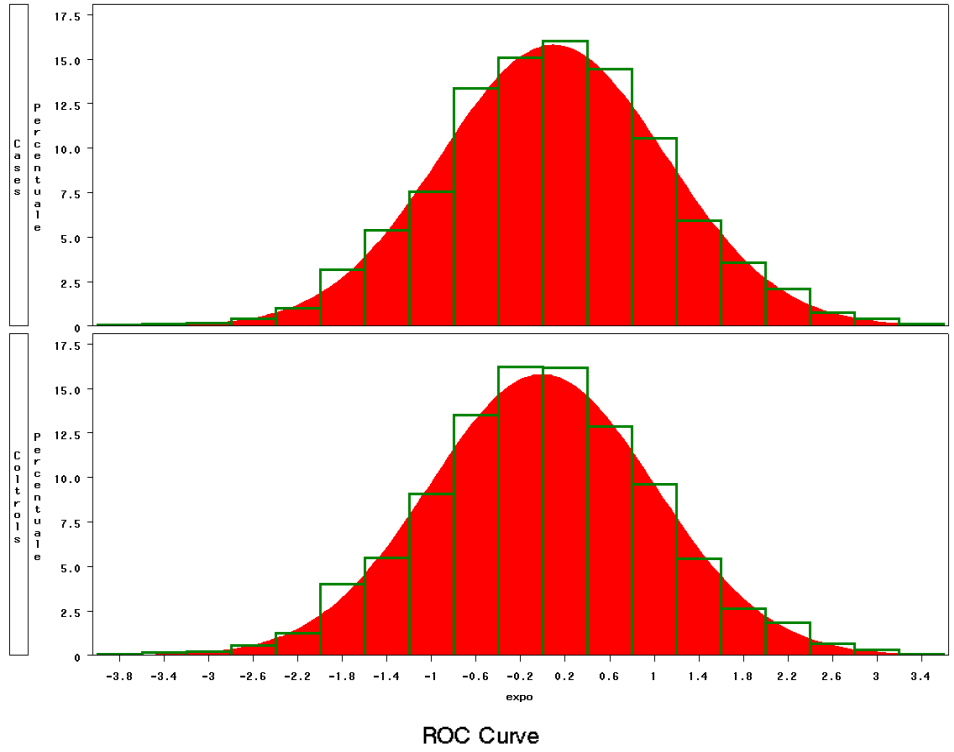


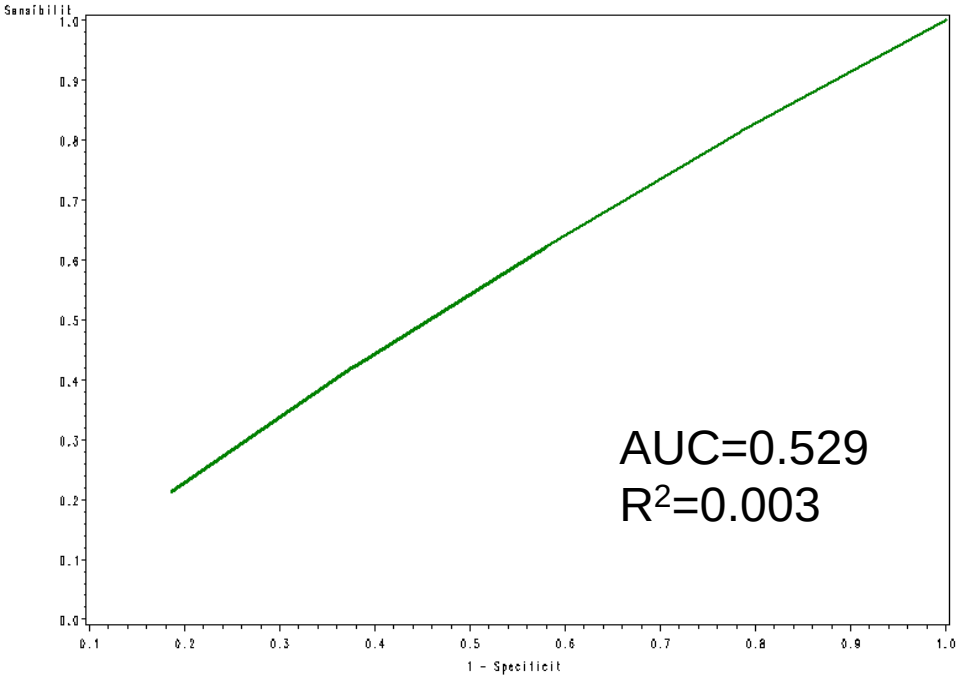
Figure 5. Cumulative risk of breast cancer by age and hypothetical gene status.

STATISTICS IN MEDICINE
Statist. Med. 2004; **23**:1111–1130 (DOI: 10.1002/sim.1668)



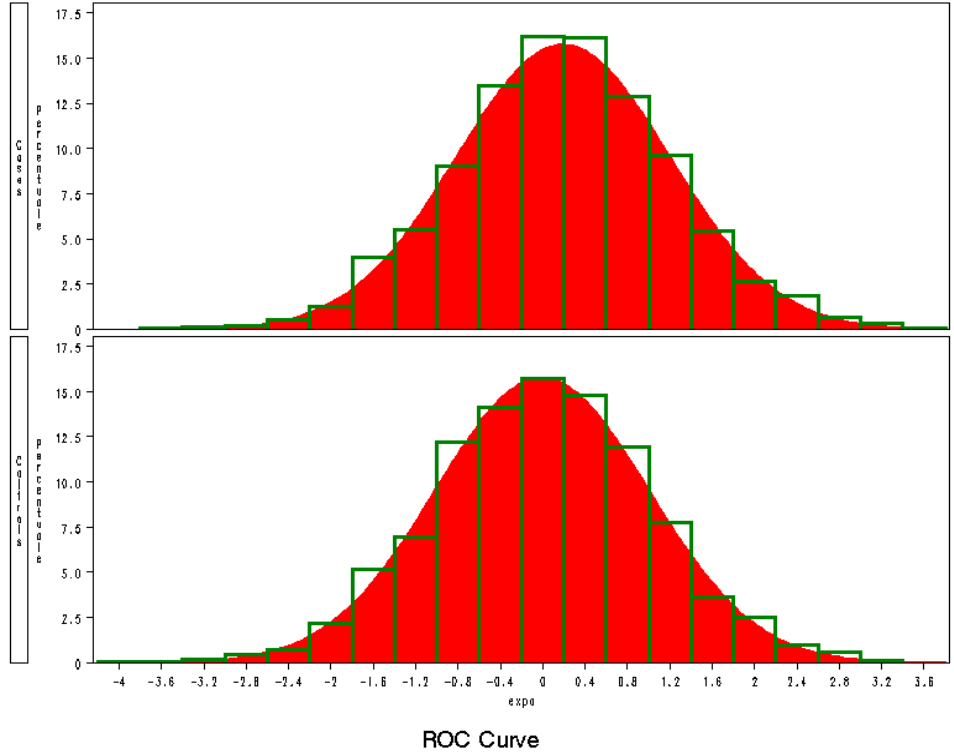
Quintile	OR	95% CI	
II	1.094	0.899	1.332
III	1.150	0.945	1.400
IV	1.265	1.039	1.539
V	1.330	1.093	1.618

$$RR_{1\text{-}5} = 1.3$$



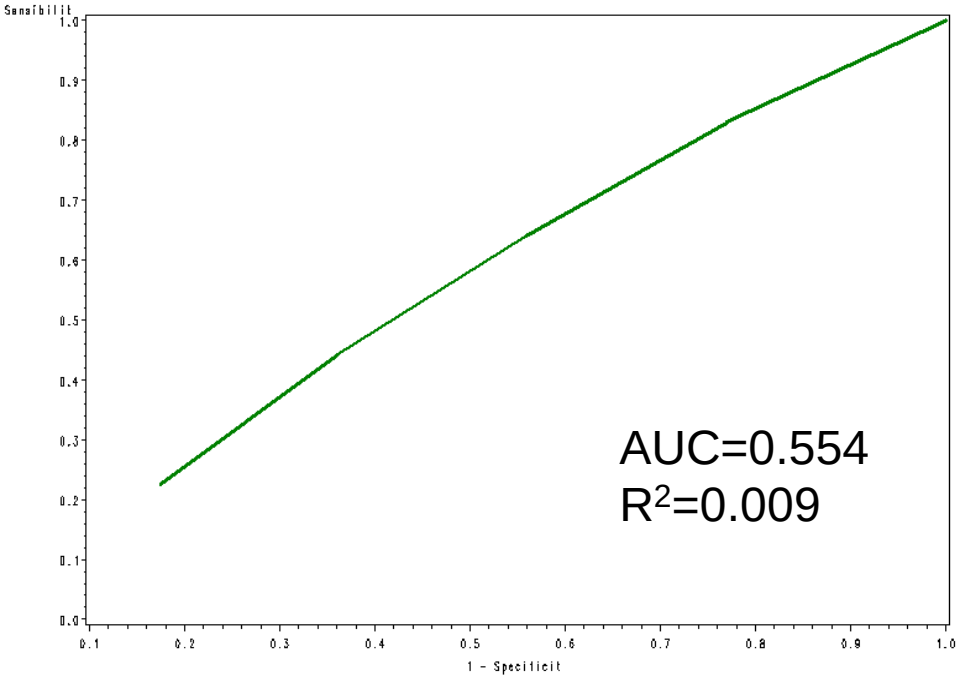
Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	370	370.06	430	429.94
II	800	388	388.00	412	412.00
III	800	398	398.00	402	402.00
IV	800	417	416.99	383	383.01
V	800	427	426.96	373	373.04

Brier-score=0.249



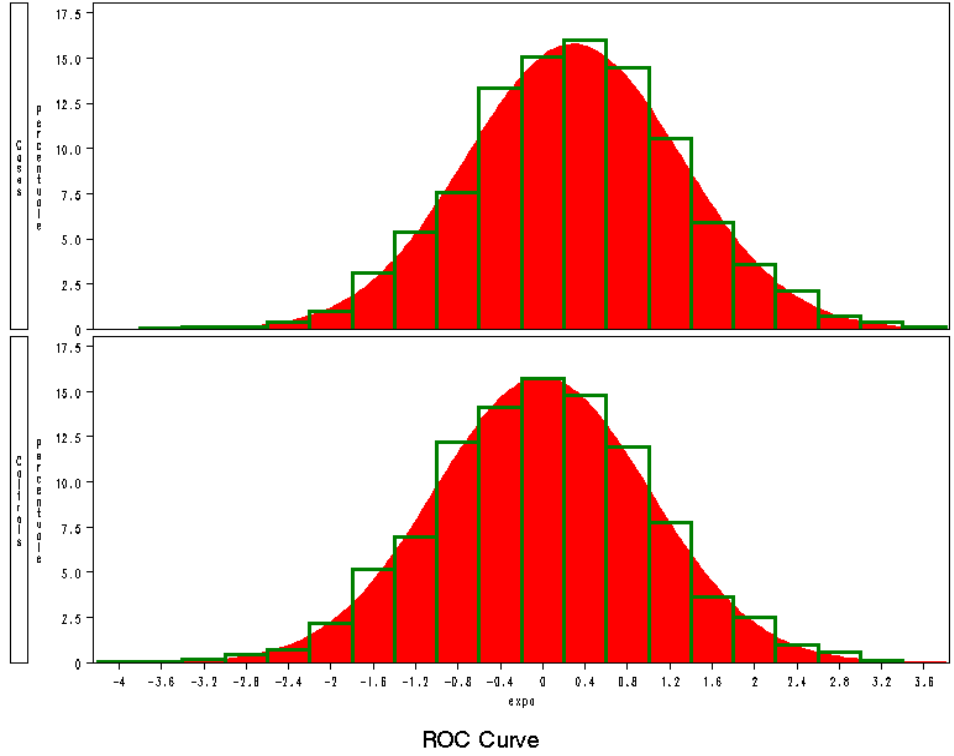
Quintile	OR	95% CI	
II	1.218	1.000	1.484
III	1.353	1.111	1.648
IV	1.580	1.297	1.925
V	1.739	1.427	2.120

$$RR_{1\text{-}5} = 1.7$$



Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	340	340.00	460	460.00
II	800	379	379.00	421	421.00
III	800	400	400.00	400	400.00
IV	800	431	431.00	369	369.00
V	800	450	450.00	350	350.00

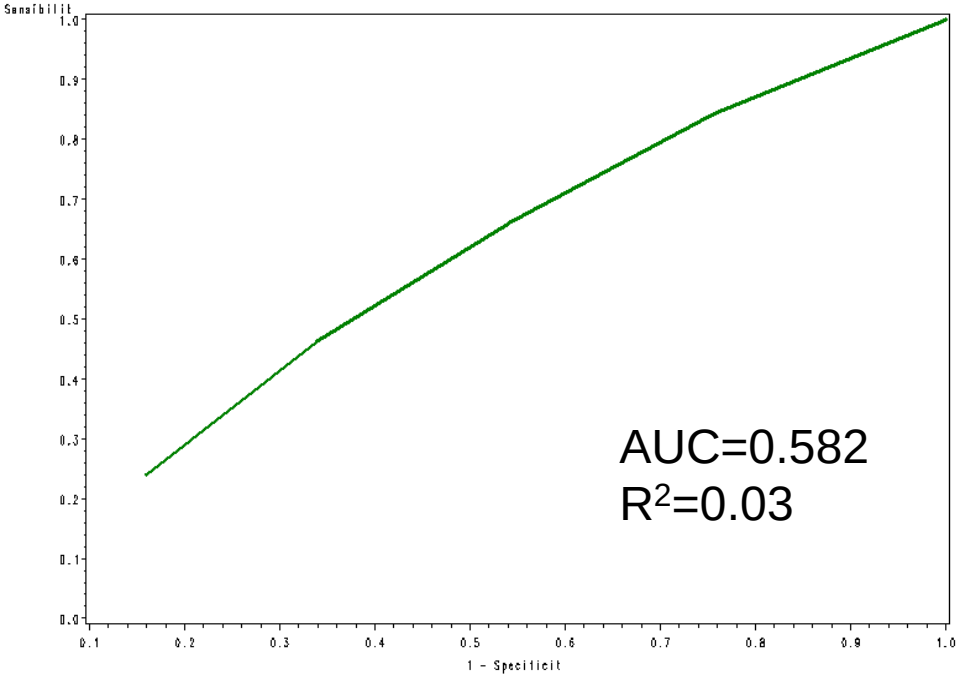
Brier-score=0.248



Quintile	OR	95% CI	
II	1.312	1.075	1.600
III	1.517	1.244	1.850
IV	1.921	1.574	2.343
V	2.322	1.900	2.837

$$RR_{1\text{-}5} = 2.3$$

ROC Curve

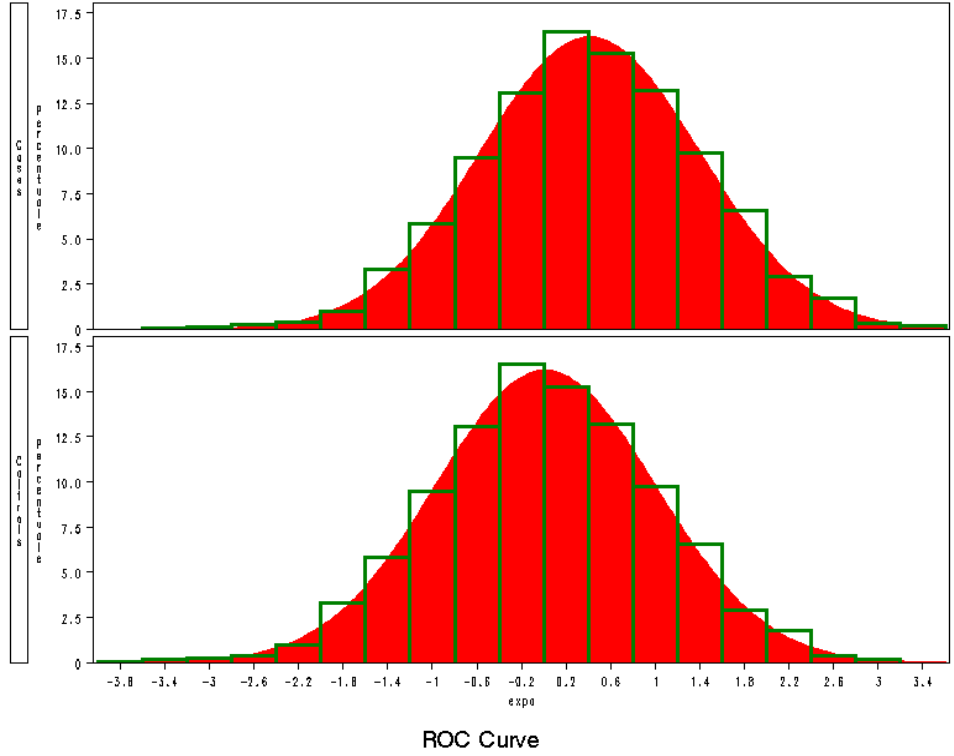


AUC=0.582

R^2=0.03

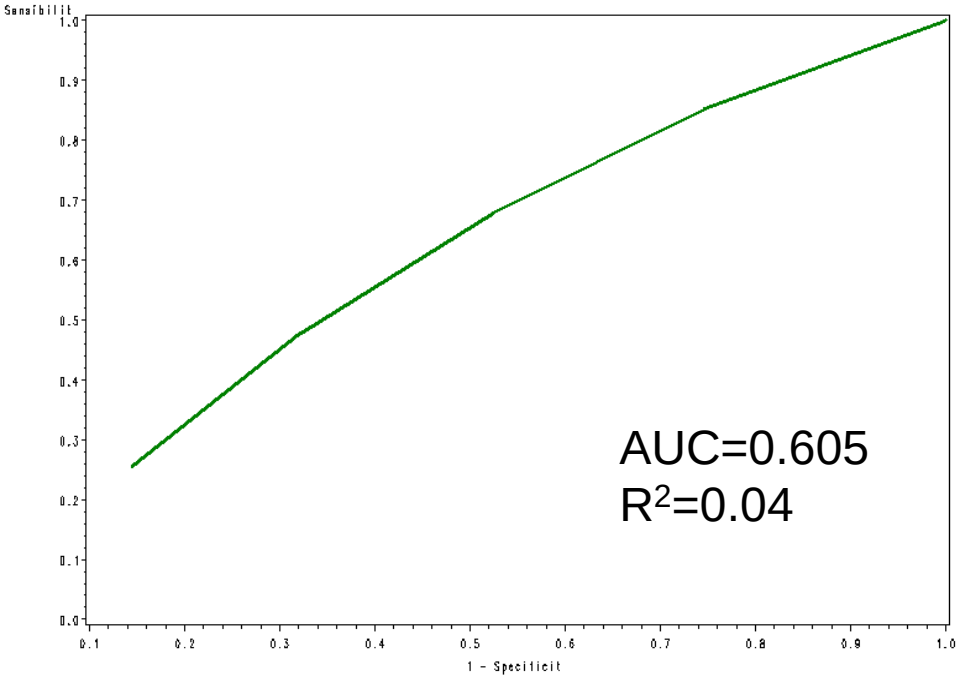
Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	314	314.00	486	486.00
II	800	367	367.00	433	433.00
III	800	396	396.00	404	404.00
IV	800	443	443.00	357	357.00
V	800	480	480.00	320	320.00

Brier-score=0.245



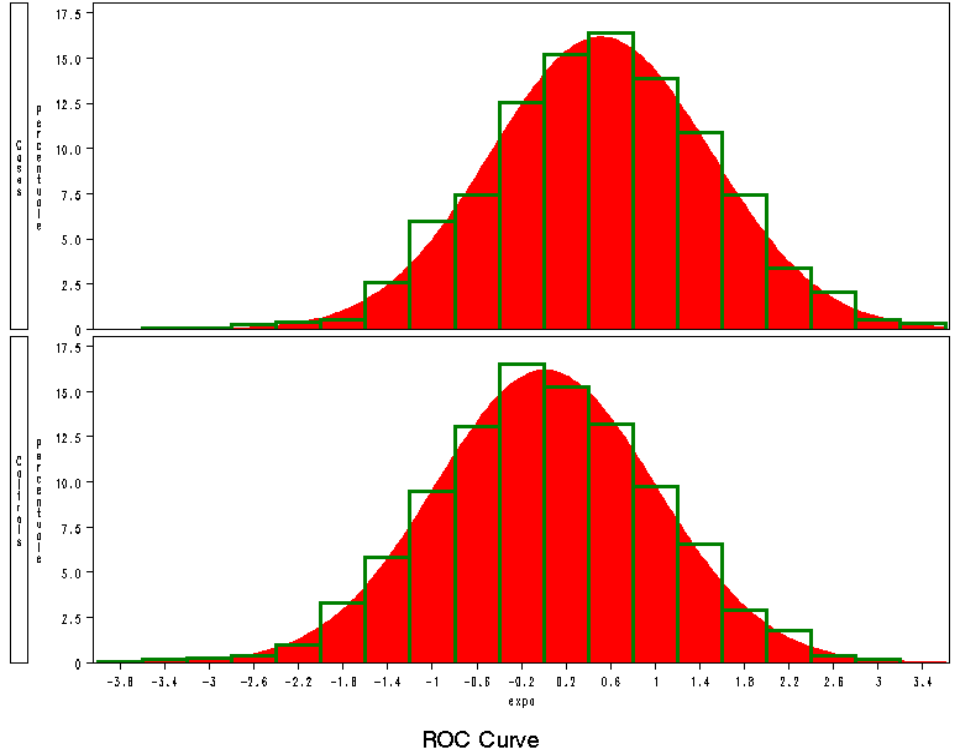
Quintile	OR	95% CI	
II	1.352	1.107	1.652
III	1.712	1.403	2.091
IV	2.157	1.766	2.636
V	3.027	2.469	3.710

$$RR_{1\text{-}5} = 3.0$$



Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	294	294.00	506	506.00
II	800	352	352.00	448	448.00
III	800	399	399.00	401	401.00
IV	800	445	445.00	355	355.00
V	800	510	509.99	290	290.01

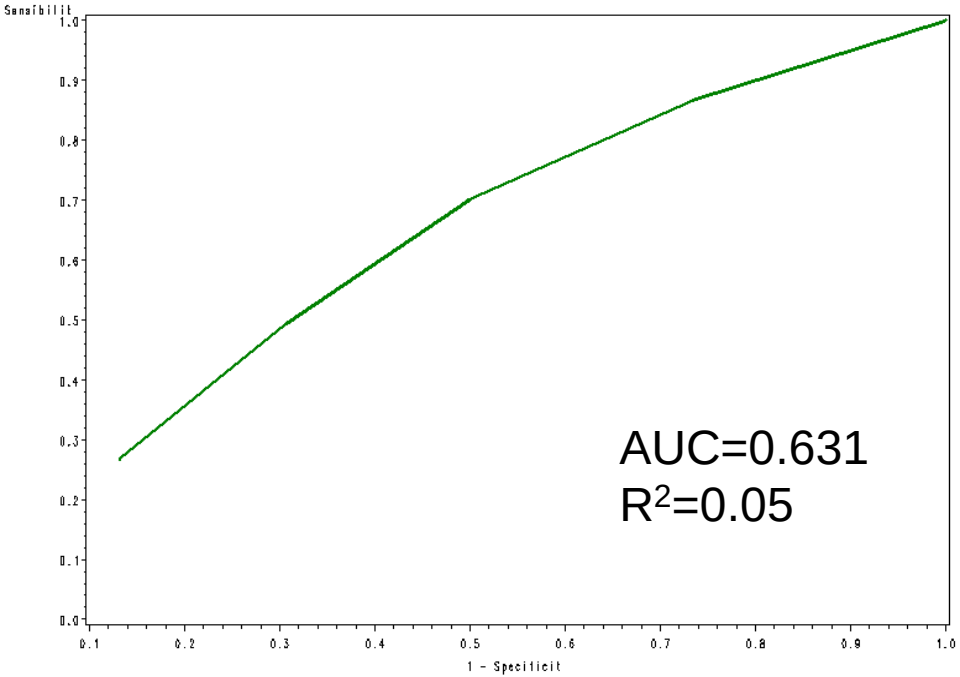
Brier-score=0.240



Quintile	OR	95% CI	
II	1.394	1.137	1.708
III	2.140	1.748	2.618
IV	2.565	2.094	3.141
V	4.029	3.273	4.961

$$RR_{1\text{-}5} = 4.0$$

ROC Curve

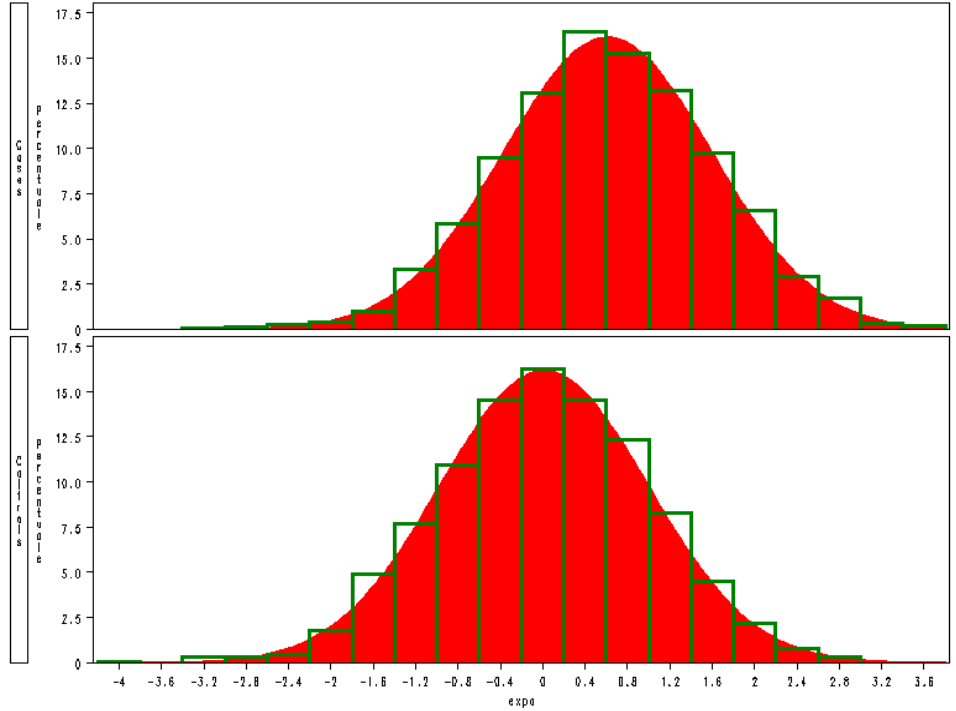


AUC=0.631

R^2=0.05

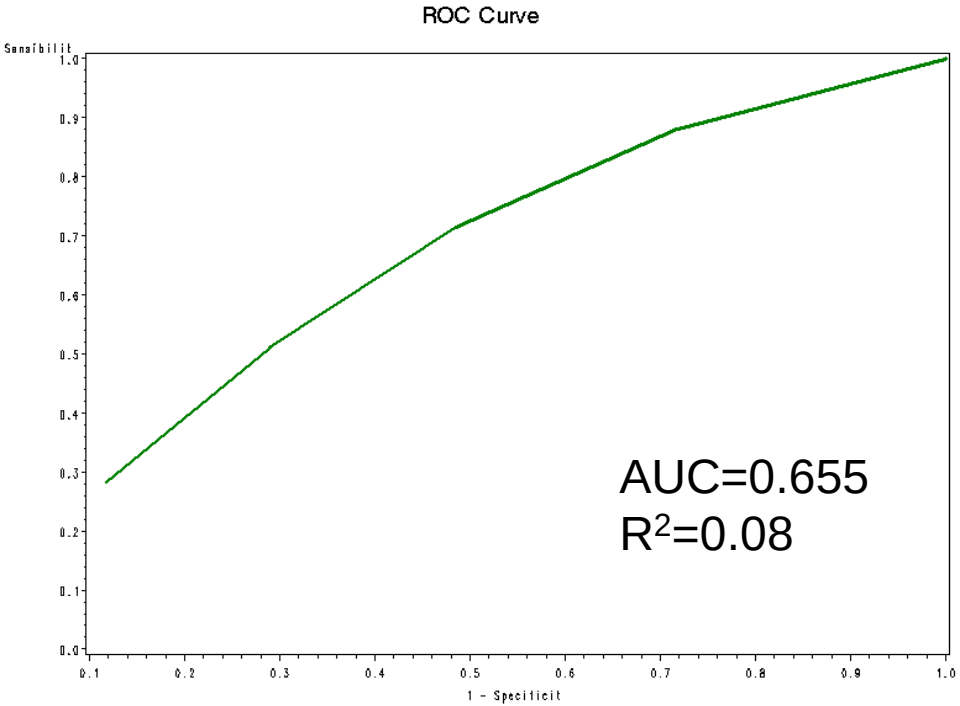
Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	268	268.02	532	531.98
II	800	330	330.00	470	470.00
III	800	415	415.00	385	385.00
IV	800	451	451.00	349	349.00
V	800	536	535.98	264	264.02

Brier-score=0.236



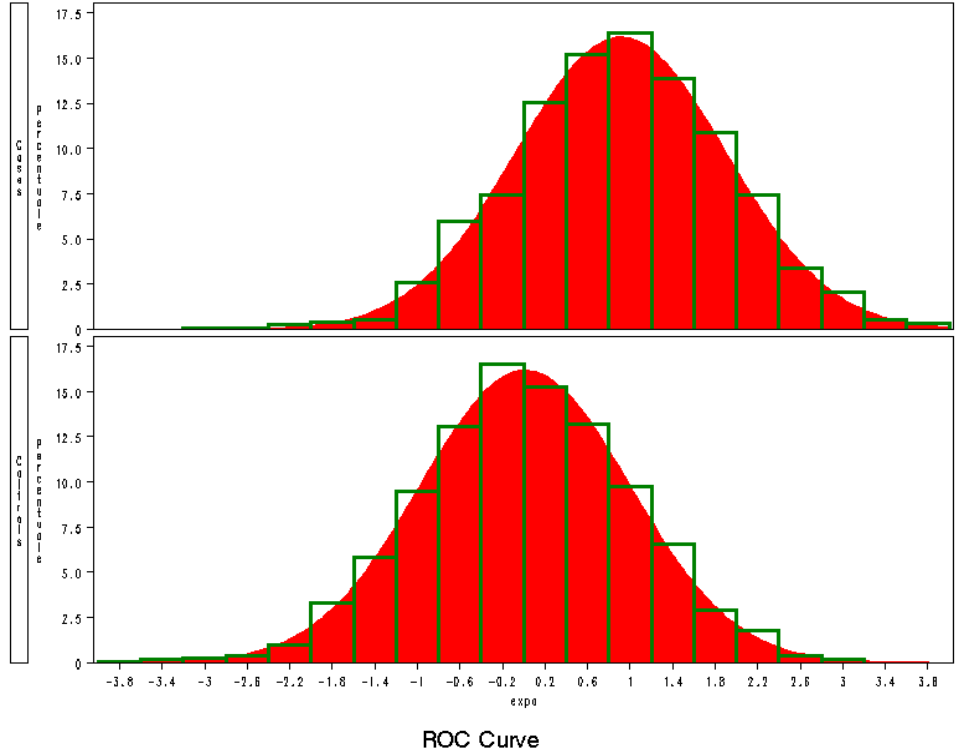
Quintile	OR	95% CI	
II	1.684	1.369	2.070
III	2.458	2.001	3.018
IV	3.130	2.547	3.847
V	5.677	4.580	7.037

$$RR_{1\text{-}5} = 5.7$$



Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	238	238.00	562	562.00
II	800	333	333.00	467	467.00
III	800	408	408.00	392	392.00
IV	800	456	456.00	344	344.00
V	800	565	565.00	235	235.00

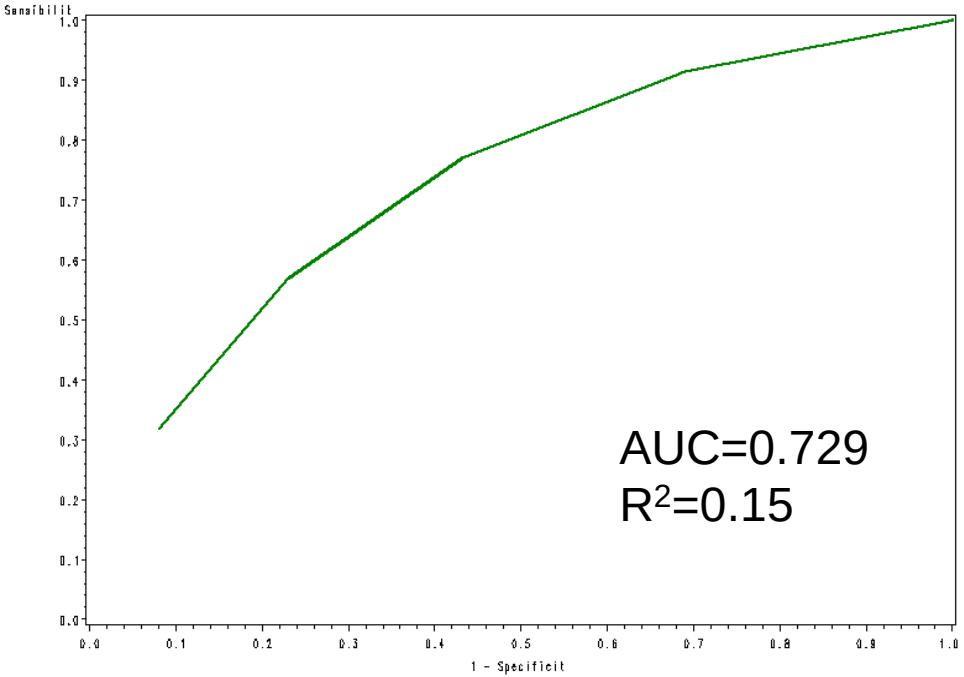
Brier-score=0.231



Quintile	OR	95% CI	
II	2.039	1.633	2.545
III	3.624	2.914	4.507
IV	6.073	4.869	7.575
V	14.27	11.22	18.16

$$RR_{1\text{-}5} = 14.3$$

ROC Curve

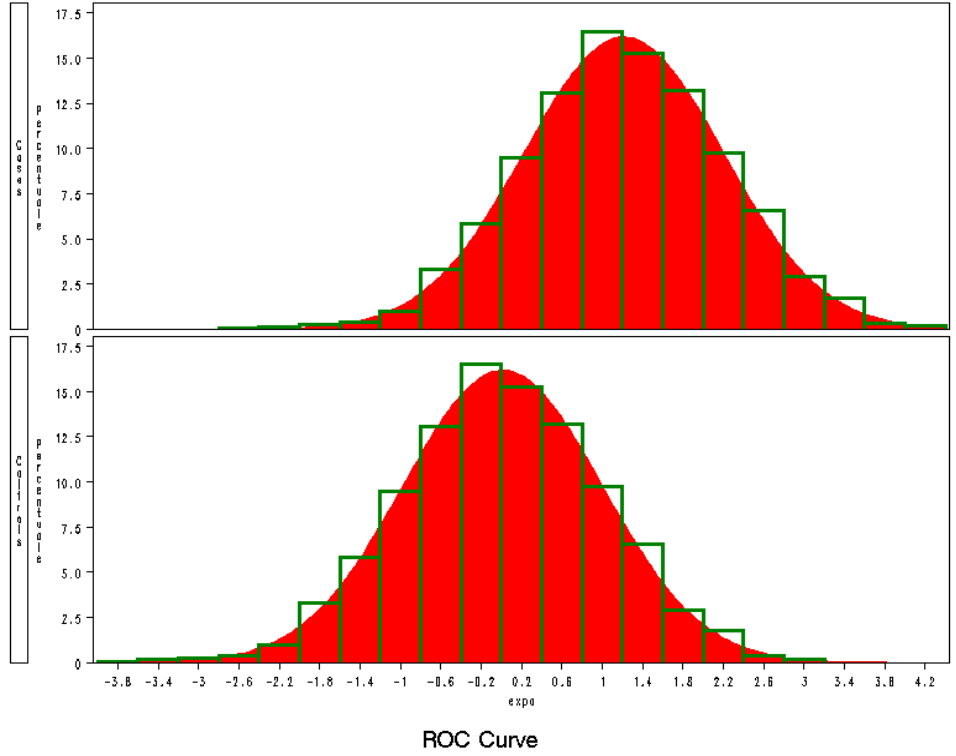


AUC=0.729

R^2=0.15

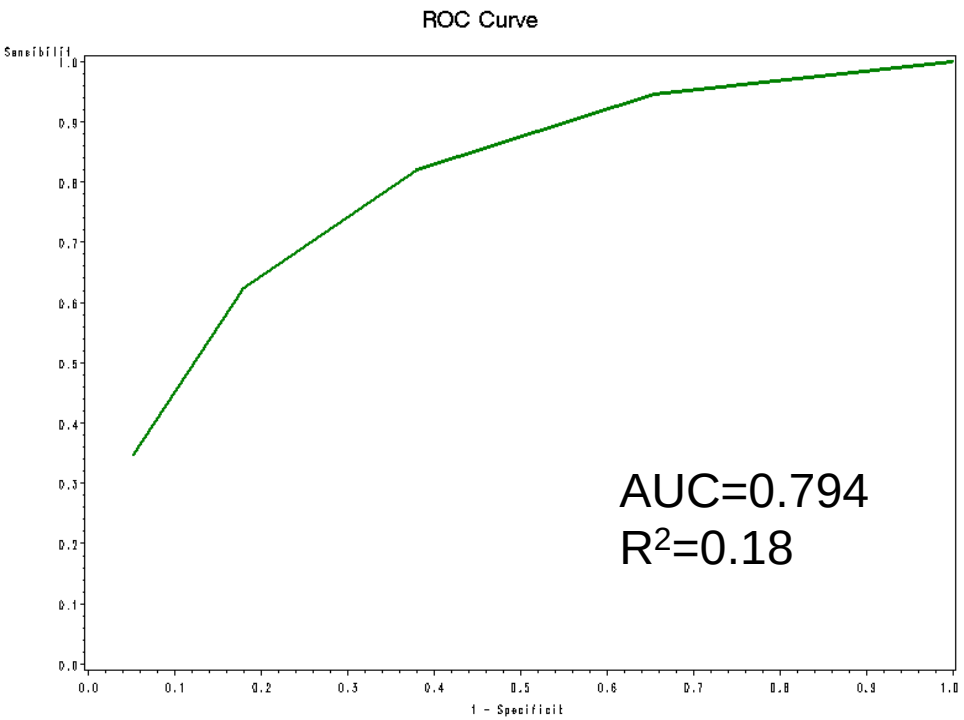
Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	173	173.00	627	627.00
II	800	288	288.00	512	512.00
III	800	400	400.00	400	400.00
IV	800	501	501.00	299	299.00
V	800	638	638.00	162	162.00

Brier-score=0.210



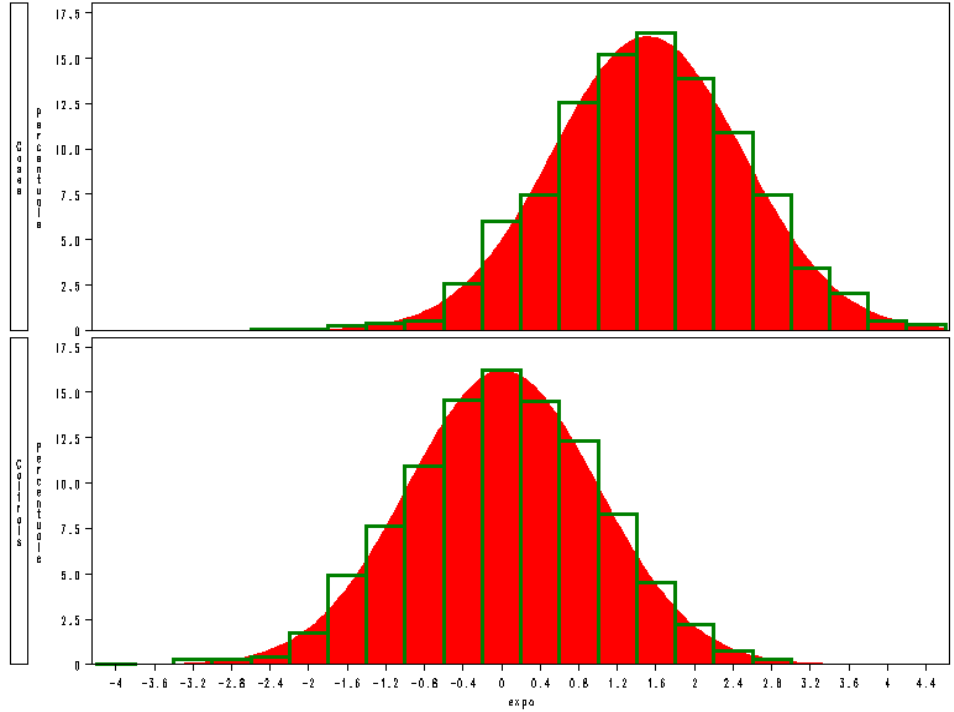
Quintile	OR	95% CI	
II	2.898	2.255	3.726
III	6.214	4.864	7.939
IV	13.79	10.72	17.72
V	42.43	31.79	56.62

$$RR_{1\text{-}5} = 42.4$$



Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	109	109.00	691	691.00
II	800	251	251.00	549	549.00
III	800	396	396.00	404	404.00
IV	800	548	548.00	252	252.00
V	800	696	696.00	104	104.00

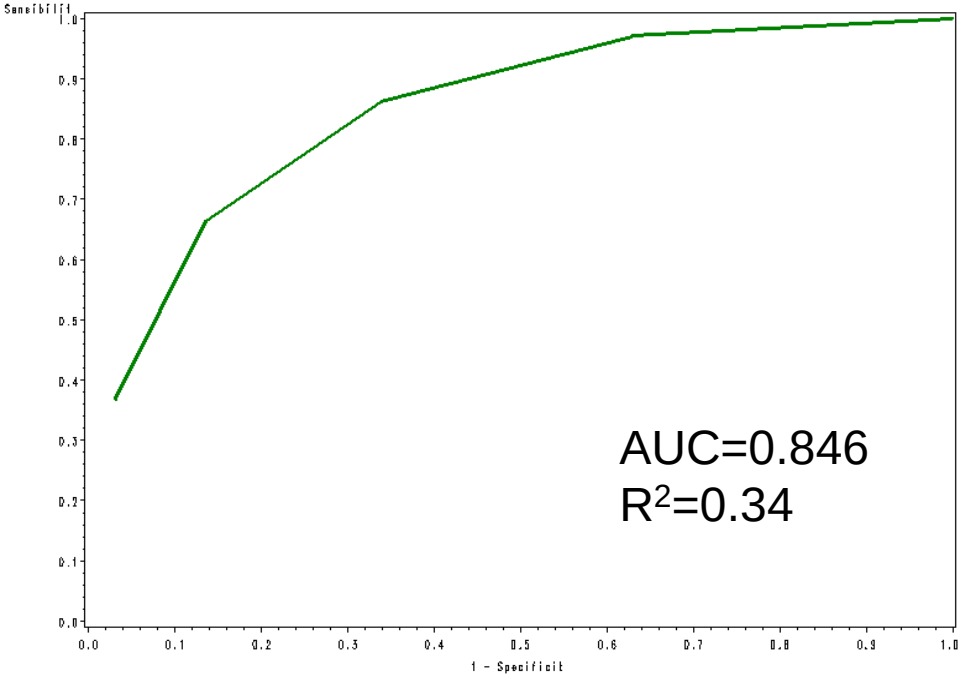
Brier-score=0.185



Quintile	OR	95% CI	
II	4.821	3.539	6.568
III	12.47	9.233	16.86
IV	36.17	26.52	49.33
V	149.6	103.3	216.8

$$RR_{1\text{-}5} = 149.6$$

ROC Curve

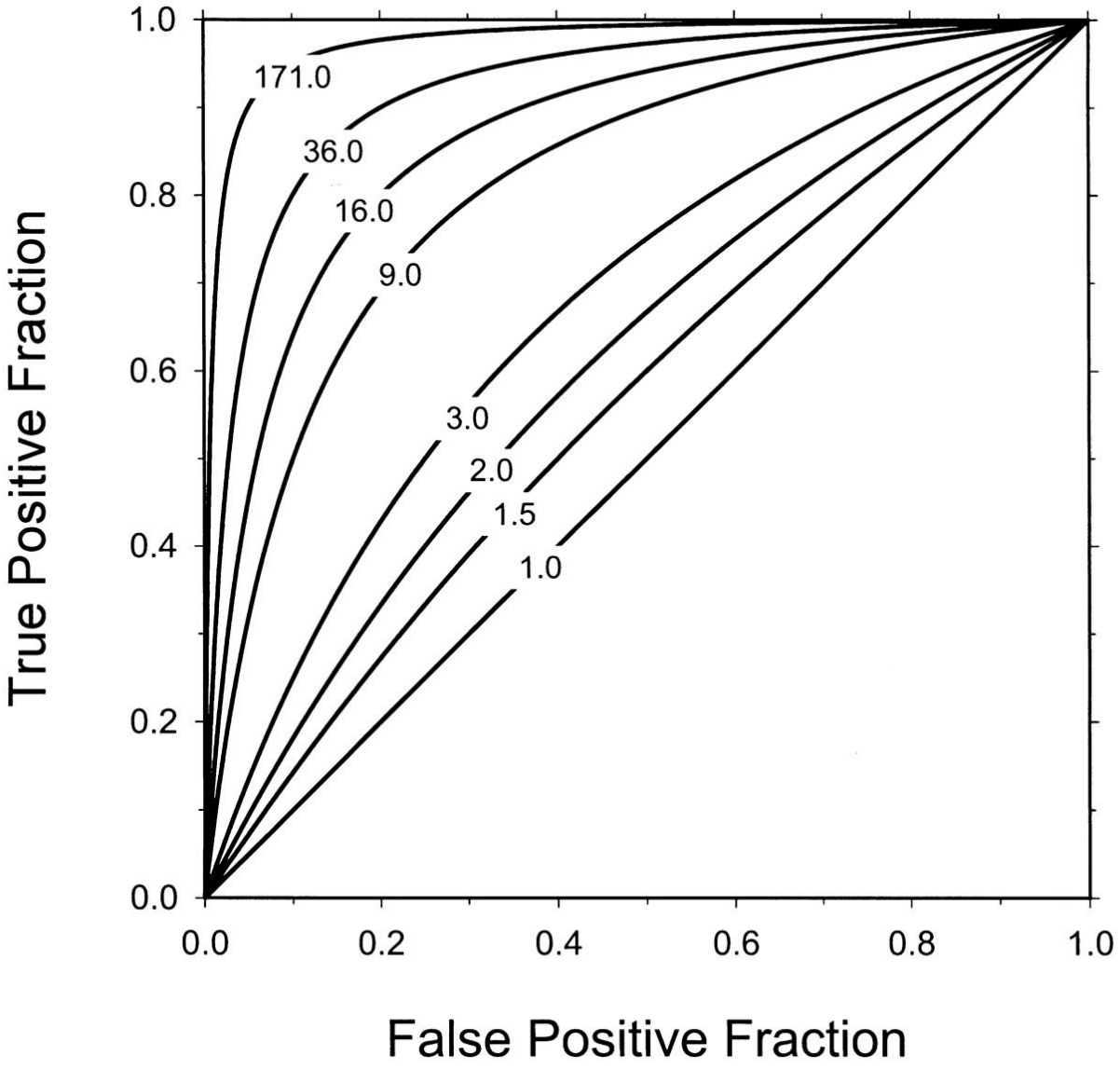


AUC=0.846

R^2=0.34

Quintile	Totale	Casi		Controlli	
		Osservati	Attesi	Osservati	Attesi
I	800	58	58.01	742	741.99
II	800	219	219.00	581	581.00
III	800	395	395.00	405	405.00
IV	800	591	591.00	209	209.00
V	800	737	737.00	63	63.00

Brier-score=0.159


True Positive Fraction
False Positive Fraction
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
171.0
36.0
16.0
9.0
3.0
2.0
1.5
1.0

CONCLUSIONI

- I modelli predittivi esistenti che stimano un rischio assoluto NON possono essere utilizzati a livello di singolo individuo;
- gli screening oncologici possono utilizzare i modelli predittivi esistenti per simulare l'esito di:
  - **nuove strategie preventive** (variazione del test, chemioprevenzione, modificazione dei fattori di rischio)
    - **a livello di popolazione**
- un modello predittivo che stima un rischio assoluto sul soggetto è difficile da ipotizzare …. non abbiamo i fattori di rischio !

- Allora rassegnamoci ad utilizzare il modello di Gail in quanto **è un modello ben calibrato** l'accutarezza **NON** ci interessa

Lo stupido parla del passato, il saggio del presente, il folle del futuro. (Napoleone Bonaparte)

Io evito sempre di fare previsioni in anticipo perche' e' molto meglio fare profezie dopo che l'evento e' gia' avvenuto. (Winston Churchill)

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Grazie dell'attenzione !