National Cancer Institute

Absolute Risk: Clinical Applications and Controversies

Biopharmaceutical Applied Statistics Symposium, XIV
November 5, 2007

Mitchell Gail

Biostatistics Branch
Division of Cancer Epidemiology and Genetics

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Overview

- Definition and example of absolute risk model
- Applications
- General criteria for assessing risk models
- Loss function approach tailored for specific problems
- Conclusions

Relative Risk for Breast Cancer

age 40

Menarche age 14	baseline risk
Nulliparous	increased risk
No biopsies	baseline risk
Mother had breast cancer	increased risk

Relative risk = 2.76 compared to a 40 year old woman with all risk factors at baseline.

Absolute Risk for Breast Cancer Computed from Gail et al., JNCI, 1989

age 40

Menarche age 14	baseline risk
Nulliparous	increased risk
No biopsies	baseline risk
Mother had breast cancer	increased risk

What is the chance that this woman will be diagnosed with breast cancer in the next 30 years? 0.116 (11.6%)

Absolute ("Crude") and "Pure" Risk in 1000 60-Year Old Women

Age at Start of Interval	# At Risk	# Incident Breast Cancer	# Deaths from Other Causes
60	1000	17	44
65	939	20	63
70	856	22	89
75	745	. . . .	. . . .

Absolute risk of breast cancer to age 75 =
(17+20+22)/1000 = 5.9%

"Pure" risk = 1- (1-17/1000)(1-20/939)(1-22/856)
= 6.3%

Absolute Risk Calculation for Woman with Risk Factors X

$$\int_a^{a+\tau} h_1(t)\,rr(t;x)\exp\left[-\int_a^t \{h_1(u)\,rr(u;x)+h_2(u)\}\,du\right]dt$$

$h_1(t)$ is baseline hazard of breast cancer incidence

$h_2(t)$ is mortality hazard from competing risks

$rr(t;x)=\exp\{\beta^T x(t)\}$ is relative risk of breast cancer for covariates $x(t)$

Absolute Risk Depends on

- Age
- Age Interval at Risk
- Risk Factors
- Competing Risks

Advantages of Cause-Specific Relative Risk Model for Covariates

- **Familiar interpretation** of cause-specific relative risks
- **Standard survival methods** for estimation with cohort data
- Possible to use **different data sources:**
  - **Relative risks** from case-control or case-cohort data
  - **Baseline hazard $h_1(t)$** from SEER data via

    $$h_1(t) = h^*_1(t)\,\{1-AR(t)\},$$

    where $h^*_1(t)$ is the incidence rate in SEER
- For alternative modeling, see Fine and Gray (JASA, 1999)

Uses of Absolute Risk

- Counseling patients
- Comparing risks and benefits of interventions such as tamoxifen
- Designing clinical trials
- Assessing the burden of disease in populations

Example of Use of Risk Model: Weighing the Risks and Benefits of Tamoxifen

Gail, Costantino, Bryant, Croyle, Freedman, Helzlsouer, Vogel, JNCI 1999; 91:1829-46.

TAMOXIFEN EFFECTS ON LIFE-THREATENING EVENTS

	RR	(95% CI)
INVASIVE BREAST CANCER	**0.51**	(0.39 -.66)
HIP FRACTURE	**0.55**	(0.25 -1.1)
ENDOMETRIAL CANCER		
<50	**2.5**	(1.4 -5.0)
50+	**4.0**	(1.7-11)
STROKE	**1.6**	(0.9 -2.8)
PULMONARY EMBOLUS	**3.0**	(1.2 -9.3)

Fisher et al, JNCI, 1998

TAMOXIFEN EFFECTS ON SEVERE AND OTHER EVENTS

	RR	(95% CI)
SEVERE EVENTS		
In Situ BREAST CA	**0.50**	(0.33-0.77)
DEEP VEIN THROMB.	**1.60**	(0.91-2.86)
OTHER EVENTS		
COLLES' FRACTURE	**0.61**	(0.29-1.23)
SPINE FRACTURE	**0.74**	(0.41-1.32)
CATARACTS	**1.14**	(1.01-1.29)

10,000 40-YEAR- OLD WHITE WOMEN WITH UTERI. 5-YEAR RISK OF INVASIVE BREAST CANCER 2%.

	BASELINE	PREVENTED BY TAMOXIFEN
LIFE-THREATENING		
INVASIVE BREAST CA	200	97
HIP FRACTURE	2	1
ENDOMETRIAL CA	10	-16
STROKE	22	- 13
PUL. EMBOLUS	7	-15
		net prevented 54
SEVERE EVENTS		
IN SITU BREAST CA	106	53
DEEP VEIN THROMBOSIS	24	-15
		net prevented 38

NET BENEFIT INDEX* FOR 10,000 WOMEN WITH UTERI OVER 5 YEARS

INVASIVE BREAST CA RISK (5 YEARS)	WHITE		BLACK	
	40-49	50-59	40-49	50-59
2%	73	-75	14	-187
4%	196	38	137	-74
6%	318	149	259	37

***Net number of life-threatening events prevented plus half the net number of severe events prevented**

Model Assessment Based on Population of N Subjects

- Y_i=1 if cancer develops in time specified interval, 0 otherwise, i=1,2,…N
- X_i are covariates for subject i
- $r(X_i)$ is previously developed absolute risk model designed to estimate $P(Y_i = 1)$
- π_i is the true $P(Y_i=1)$

Gail and Pfeiffer, Biostatistics, 2005

Some standard criteria for evaluating the performance of risk models

- **Calibration:** Are estimates r(x) of π unbiased?
- **Discrimination:** How different are the distributions of risk among individuals who do and do not develop the disease (concordance or AUC)?
- **Accuracy:** How well does model categorize individuals (PPV, NPV, Proportion Correctly Classified)?

Assessing Model Calibration

Goodness-of-fit criteria based on comparing observed (O) with expected (E) number of events overall and in subgroups A_1, A_2,… of the population

$$O_k = \sum_{i=1}^{N} Y_i I(X_i \in A_k)$$

$$E_k = \sum_{i=1}^{N} r(X_i) I(X_i \in A_k)$$

If r is well calibrated, O_k has mean E_k

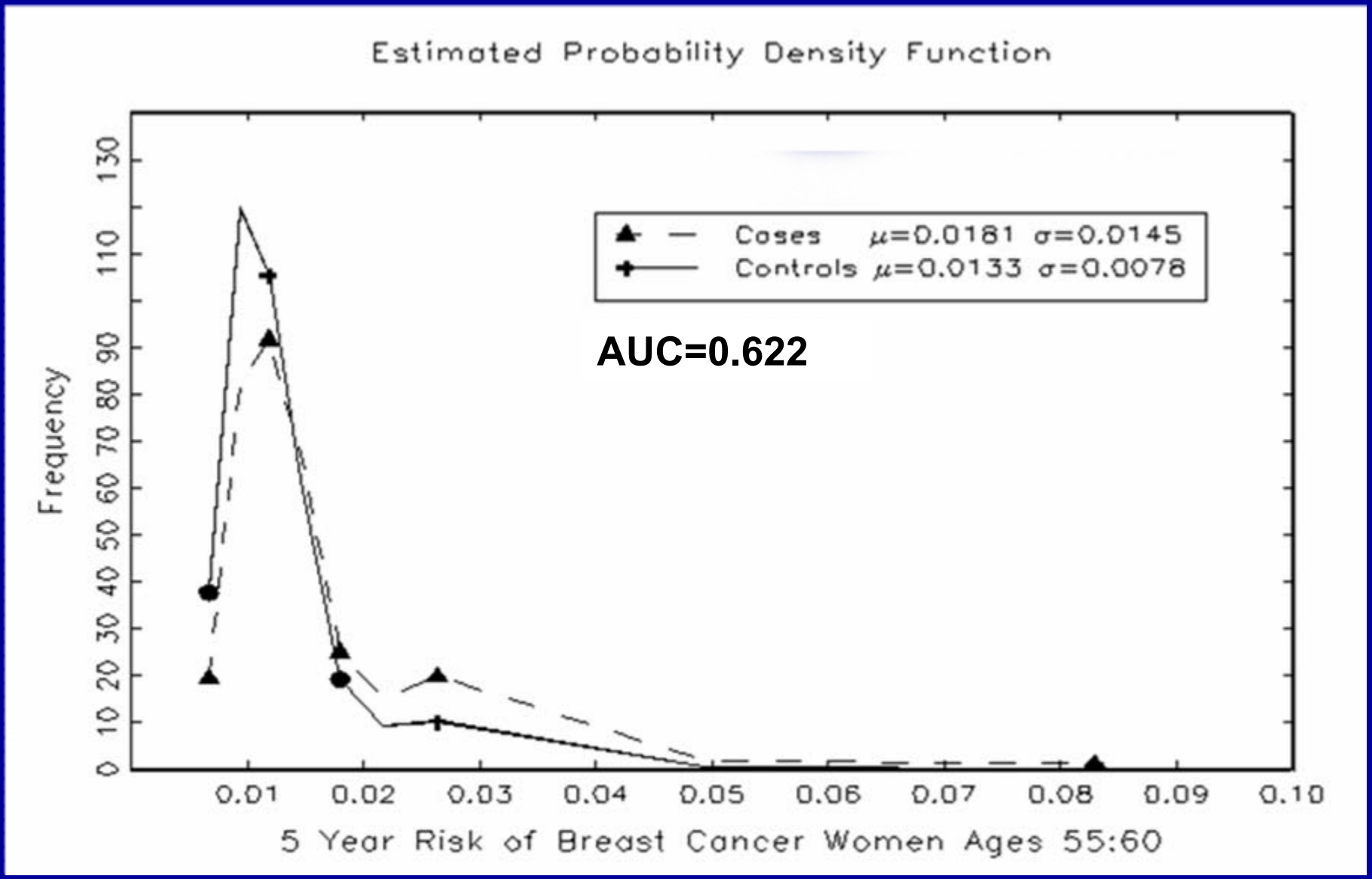
Calibration of the Gail Model in the Breast Cancer Prevention Trial (Costantino et al, 1999)

Age Group	# women	O	E	E/O
<=49	2332	60	55.9	0.9
50-59	1807	43	48.4	1.1
>=60	1830	52	54.7	1.1
All ages	5969	155	159.0	1.0

Modest Discriminatory Power

Rockhill et al., JNCI 2000

Distribution of breast cancer risk among cases and controls derived from National Health Interview Survey Data



Distribution of r(X) in the Population

Let the set of risk factors X have distribution $G_x(x)$.

The induced distribution of r(X) is:

$$F(r) = \int_{\{x:\, r(x) \le r\}} dG_x(x)$$

Distributions of Risk, r, in Random Samples of Cases and Controls

$$F_{case}(r^*) = P(r \le r^* \mid Y = 1)$$

$$= \frac{1}{\mu}\int_0^{r^*} r\,dF(r)$$

$$F_{control}(r^*) = P(r \le r^* \mid Y = 0) = \frac{1}{1-\mu}\int_0^{r^*} (1-r)\,dF(r)$$

$$\text{with } \mu = \int_0^1 r\,dF(r)$$

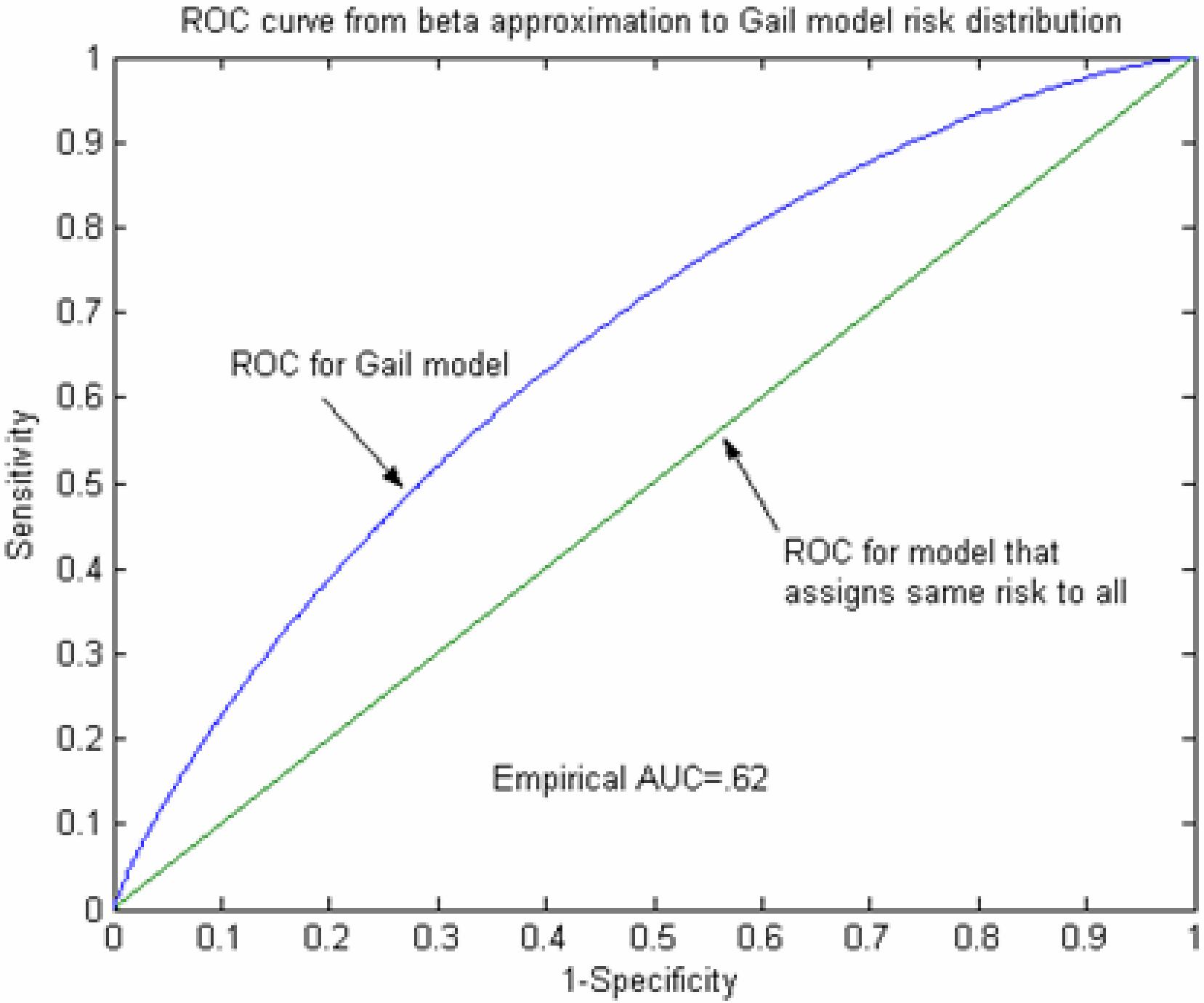
Sensitivity and specificity of decision rule δ=1 if r≥r* and δ=0 otherwise

$$\text{sens}(r^*) = P(\delta = 1 \mid Y = 1) = P(r \geq r^* \mid Y = 1)$$

$$= 1 - F_{case}(r^{*-})$$

$$\text{spec}(r^*) = P(\delta = 0 \mid Y = 0) = P(r < r^* \mid Y = 0)$$

$$= F_{control}(r^{*-})$$


ROC curve from beta approximation to Gail model risk distribution
Sensitivity
1-Specificity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
ROC for Gail model
ROC for model that
assigns same risk to all
Empirical AUC=.62

Comments on Area Under ROC (AUC)

- Can be estimated from case-control data
- Hard to increase
  - Incorporation of mammographic density, a strong risk factor, only increases from e.g. 0.60 to 0.66 for 60-64 yrs women (Chen, . . . Gail, JASA, in press)
- Comparable to AUC for age-specific AUC for cardiovascular risk models

Can a model with modest discriminatory value be useful for screening? For deciding whether or not to intervene?

Specific Loss Function-Based Approach to Model Assessment

Two applications:

- Screening
- Weighing risks and benefits of an intervention

Gail and Pfeiffer, Biostatistics 2005

Screening Context

- Screening (no effect on outcomes)
  - Questionnaire given
  - Risk r estimated from questionnaire data
- Recommend colonoscopy ($\delta=1$) if $r \geq r^*$, a threshold

Losses from Using a Risk Model to Decide Whether to Recommend Colonoscopy

Outcome over next 5 Years	No Colonoscopy	Colonoscopy
Y=0 (no cancer)	0 = C_{00}	1 =C_{10}
Y=1 (cancer)	100 = C_{01}	11 = C_{11}

Expected Loss

$$EL = C_{11}P(Y=1,\delta=1) + C_{01}P(Y=1,\delta=0)$$
$$+C_{10}P(Y=0,\delta=1)+C_{00}P(Y=0,\delta=0)$$
$$= C_{11}\int_{r^*}^{1} r\,dF(r) + C_{01}\int_{0}^{r^*} r\,dF(r) + C_{10}\int_{r^*}^{1}(1-r)\,dF(r)$$
$$+C_{00}\int_{0}^{r^*}(1-r)\,dF(r)$$

$$\text{EL}_{\text{Min}} \text{ for } \text{r}^* = \frac{C_{10} - C_{00}}{C_{10} + C_{01} - C_{00} - C_{11}}$$

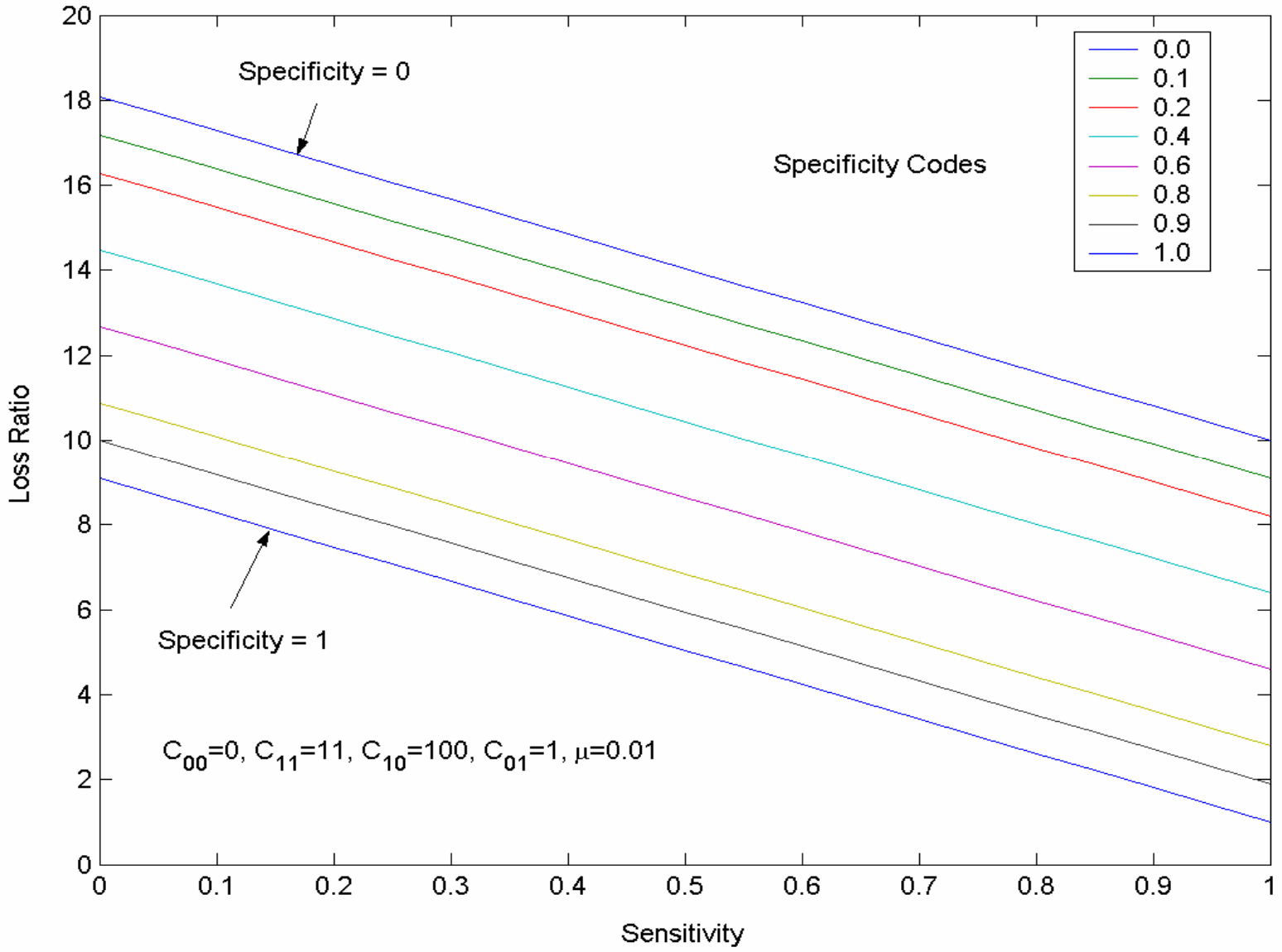
$$EL_{Min} = C_{11}\mu\ \text{sens}(r^*) + C_{01}\mu(1-\text{sens}(r^*)) + C_{10}(1-\mu)(1-\text{spec}(r^*)) + C_{00}(1-\mu)\text{spec}(r^*)$$

A perfect model with sens(r*)=1 and spec(r*)=1 attains expected loss:

$$EL_{perfect} = C_{11}\mu + C_{00}(1-\mu)$$

$$\text{Loss Ratio} = EL_{Min} / EL_{perfect}$$

Loss Ratio vs Sensitivity for Various Specificities



Conclusion for Screening Application

- Losses are large, compared to model with perfect sensitivity and specificity.

- A risk model with sensitivity and specificity of Gail model has loss ratio 6.6 for screening

Decision to Intervene

δ=1 if decide to intervene, δ=0 otherwise.

"Intervention" changes distribution of health outcomes.

Consider two outcomes for tamoxifen intervention:

Y_1=breast cancer

Y_2=stroke

$$P(Y_1=i, Y_2=j \mid \delta=0) \neq P(Y_1=i, Y_2=j \mid \delta=1)$$

Loss function for clinical decision: should woman take Tamoxifen for breast cancer prevention?

	No BC	*BC*	*No Stroke*	*Stroke*
No Tamoxifen	0	1	0	1
Tamoxifen	0	1	0	1

Example: Breast Cancer, Stroke and Intervention by Tamoxifen

STROKE: No covariate model for stroke risk; use average age-specific risk s

$$r_{001}(x) = \mathrm{s},\ r_{101}(x) = 1.6s$$

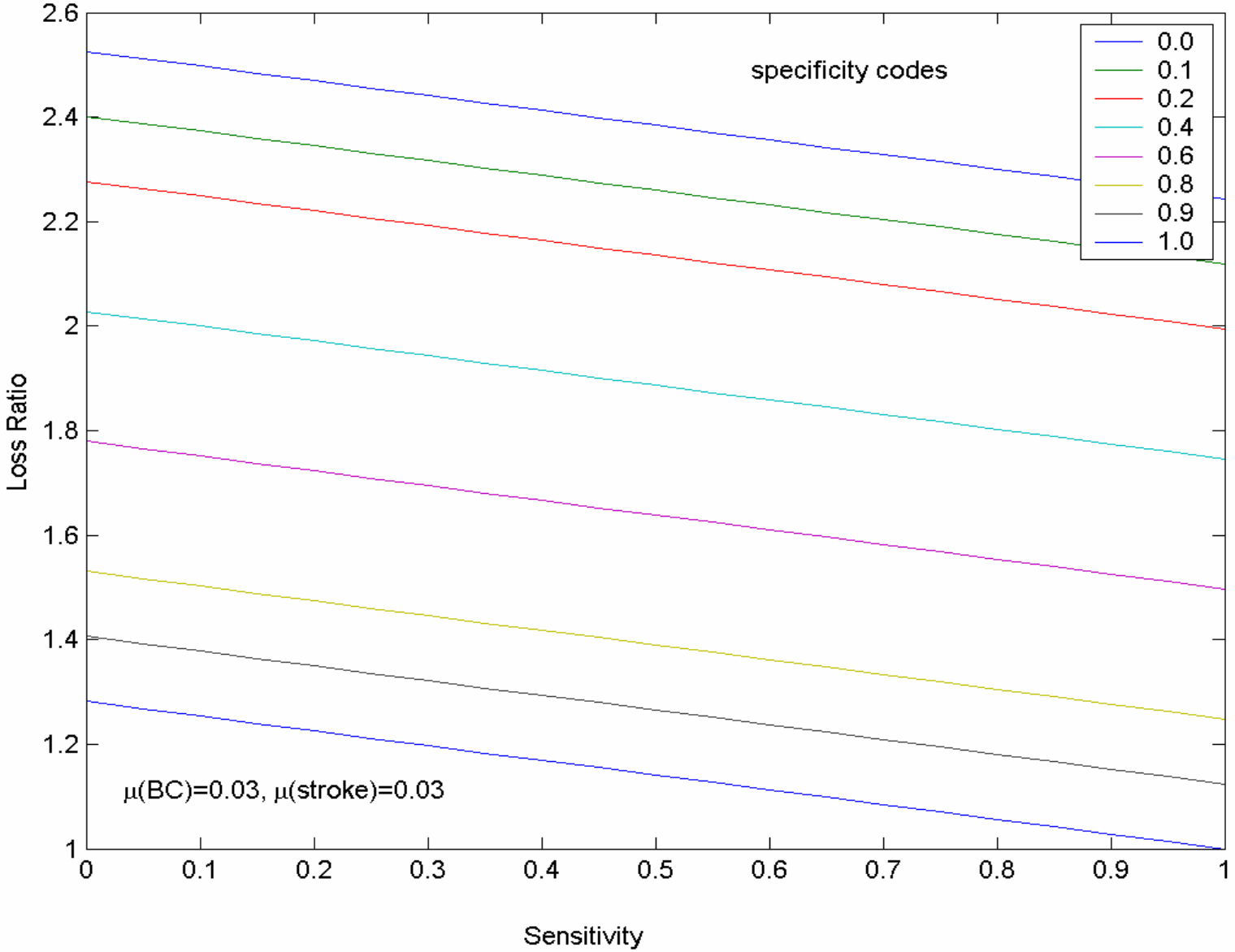
BREAST CANCER:

$$r_{010}(x) = \text{Gail model estimate for breast cancer}$$

$$r_{110}(x) = 0.5 r_{010}(x)$$

$$r_{011}(x) = r_{111}(x) = 0$$

Loss Ratio vs Sensitivity for Various Specificities



Conclusions for Intervention Setting

- For decision regarding intervention with beneficial and adverse effects, very high discriminatory power not needed

- In tamoxifen/breast cancer/stroke example Gail model has a loss ratio of 1.25, compared to breast cancer model with perfect sensitivity and specificity

Summary – Assessment Procedures

- Good calibration of absolute risk models essential
- High discriminatory power needed for screening, but not as important for other decisions
- Loss-function approach for a specific application can be more revealing than general assessment criteria

Summary - Applications

- Well calibrated absolute risk models useful for:
  - counseling
  - weighing risks and benefits of preventive interventions
  - designing prevention trials
  - assessing disease burden in a population
- Applications in newly diagnosed patients
  - .e.g. What is the chance that a 65 year old male just diagnosed with prostate cancer will die of that disease?

References

Gail model

Gail et al. JNCI, 1989

http://www.cancer.gov/bcrisktool/

Validation studies

Costantino et al. JNCI, 1999

Rockhill et al, JNCI, 2001

Gail and Pfeiffer, Biostatistics, 2005

Measuring risk versus benefit

Gail et al, 1999, JNCI, 91: 1829-1846

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Acknowledgements

Jacques Benichou

Jinbo Chen

Andrew Freedman

Barry Graubard

John Mulvihill

David Pee

Ruth Pfeiffer

Catherine Schairer