On Criteria for Evaluating Risk Prediction Models for Public Health Applications

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Motivation: Absolute Risk for Cancer Incidence

$$r(x,a,\tau) = P(T \le a+\tau, cause = C \mid T > a; x)$$

$$= \int_a^{a+\tau} h_C(t,x) \exp\left[-\int_a^t \left\{ h_C(u,x) + h_D(u,x) \right\} du \right] dt$$

T - event time
X - individual risk or protective factors
a - age
τ - length of projection
$h_C(t,x)$ – cancer hazard at age t
$h_D(t,x)$ - mortality hazard from competing risks

Combine Data from Different Sources to Estimate Absolute Risk

model $h_c(t,x) = h_{c0}(t)rr(\beta_c x)$

Cohort, nested case-control, case cohort , case-control data

Cancer Registries

Estimate **relative risk,** $rr(\beta_c x)$ and **attributable risk,** $AR(x)$

$h_{c0}^*(t)$, composite cancer hazard (age spec.)

$$\hat{h}_c(t,x) = h_{c0}^*(t)(1-AR_c)rr(\beta_c x)$$

$$\hat{r}(x,a,\tau) = \int_a^{a+\tau} \hat{h}_C(t,x)\exp\left[-\int_a^t \left\{\hat{h}_C(u,x)+\hat{h}_D(u,x)\right\}du\right]dt$$

Absolute Risk Models for Endometrial and Breast Cancers

We combined data on white non-Hispanic women ages 50+ from two large cohorts to estimate **relative risks** for endometrial and breast cancers

Outcome	Combined cohort size	Total # cases
Endometrial cancer	157,755	**1,656**
Breast cancer	256,522	**8,160**

Relative Risk Estimates

Variable	Endometrial Cancer	Breast Cancer
	RR (95%CIs)	RR (95%CIs)
BMI (<25, 25-<30, 30-<35, 35-<40, 40+)	1.72* (1.65-1.80)	X
Oral contraceptive use (1+ year , <1 year)	1.44(1.28-1.61)	
Menopausal hormone therapy use (never, <10 years, 10+ years)	X	1.40 (1.32-1.49)
Parity (3+, 1-2, 0)	X	X
Family history of breast or ovarian cancer		1.39 (1.32-1.47)
Benign breast disease/biopsy (no/yes)		1.40 (1.33-1.48)
Smoking Never compared to current	1.47 (1.22-1.78)	
Former compared to current	X	
Age first life birth	X	X
Alcohol consumption		X
Age at menopause		X

Absolute Risk Estimates: two 50 year old non-smoking women without history of benign breast disease

	Woman 1	Woman 2
Oral contraceptive use	no	yes
Age at first birth	25	39
# of life births	3	1
BMI, kg/m^2	24	40
Menopausal	no	yes
Alcohol consumption (drinks/day)	0	>1
Family history breast/ovarian cancer	no	yes
HRT use+ duration>1 year	no	yes
10 year absolute breast cancer risk estimate	**1.83%**	**6.83%**
10 year absolute endometrial cancer risk estimate	**0.40%**	**5.91%**

External Validation: Independent Population for Assessment of Model Performance

Assume population of N individuals followed over time period t (cohort data)

Observe disease outcome at end of follow-up

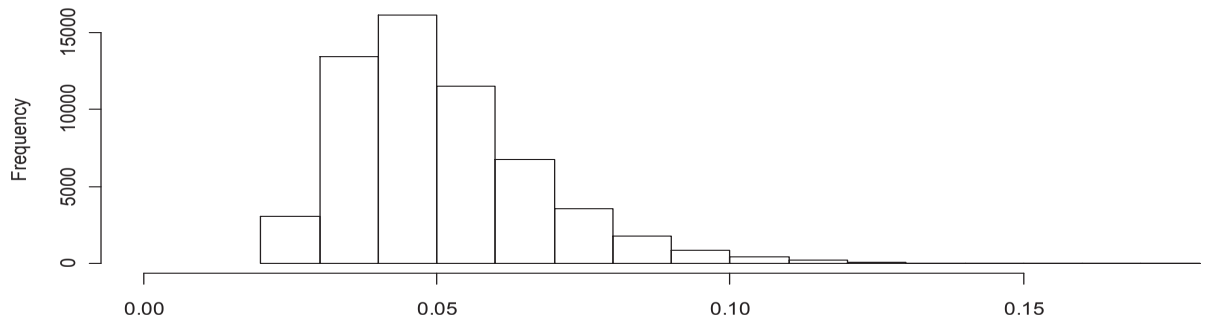
$$Y_i = \begin{cases} 1, & \text{if ith woman develops event during } t \\ 0, & \text{otherwise} \end{cases}$$

$r(x_i) = \hat{P}(Y = 1 \mid x_i)$ absolute risk estimate for ith person with baseline covariates x_i, including age a over time t

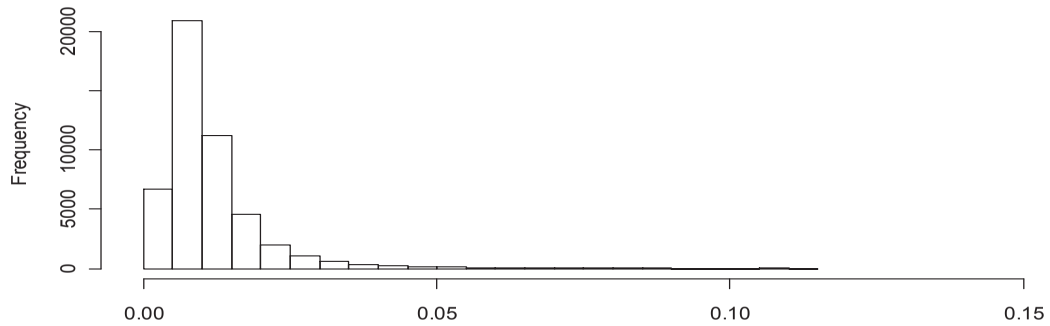
Risk model r known

Risk estimates r have distribution F on $[0, 1]$

Distribution *F* of Risk in Nurses' Health Validation Cohort (N~60,000)



Breast cancer absolute risk estimates



Endometrial cancer absolute risk estimates

Standard Criteria for Evaluating Performance of Risk Prediction Models: Calibration

Assesses model bias

Model r(x) is **well calibrated** if for each x

$$P(Y = 1 \mid r(x) = r) \approx r$$

Then $\mu = E(Y) = P(Y = 1) = \int_0^1 r dF(r) = E(R)$

Model r is unbiased $\left(\text{well calibrated}\right)$ in population if

$$\frac{1}{N}\sum_{i=1}^{N} Y_i \approx \frac{1}{N}\sum_{i=1}^{N} r_i$$

Assess Performance of Models in Nurses' Health Validation Cohort

Ages 51-70 at baseline

Calibration: $O = \sum_{i=1}^{N} Y_i,\ E = \sum_{i=1}^{N} r(X_i)$

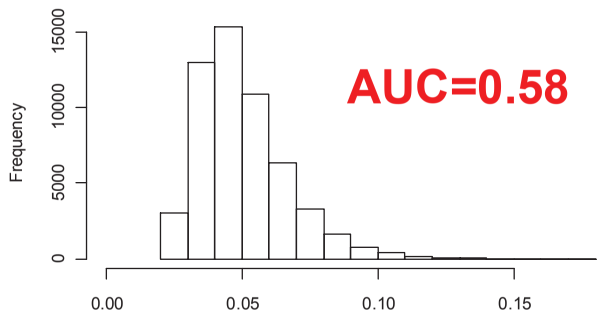
Outcome	# women	O	E	E/O (95%CI)
Breast cancer	57,906	2934	2930	**1.00** (0.96–1.04)
Endometrial cancer	37,241	532	637	**1.20** (1.11-1.29)

Standard Criteria for Evaluating Performance of Risk Prediction Models: Measures of Discrimination

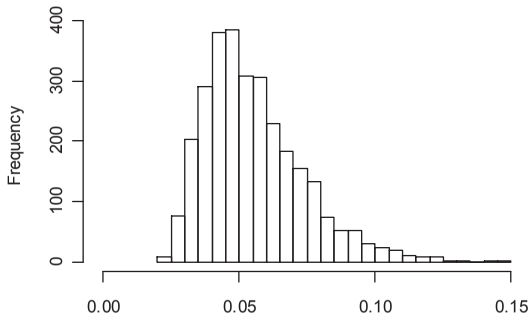
- **Receiver operating characteristic** (ROC) **curve** plots sensitivity (true positive rate) vs. 1 − specificity (false positive rate), for binary classifier as discrimination threshold is varied
- Area under the ROC curve **(AUC) (c-statistic)**

$$AUC=P(r_{Y=1}>r_{Y=0})$$

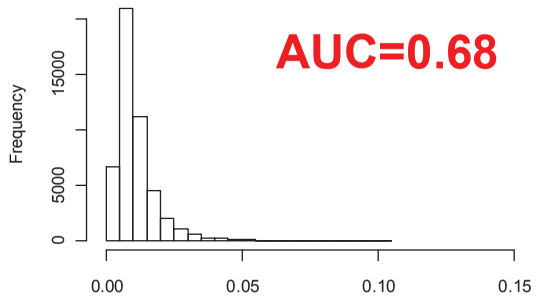
Distribution of risk estimates in independent validation cohort (Nurses' Health Study)



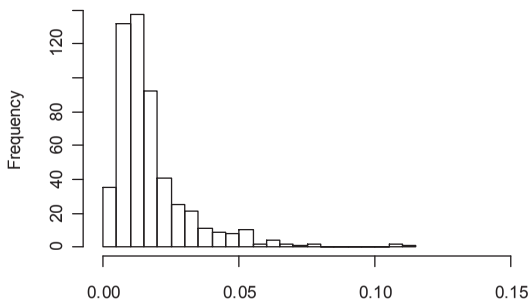
Y=Breast cancer=0



Y=Breast cancer=1



Y=Endometrial Cancer=0



Y=Endometrial Cancer=1

Criteria that Assess Model Performance for Screening Applications

Wish to make **screening recommendations** for population over next five years based on baseline risk assessment from absolute risk model

Compute 5-year cancer risk from model for every woman given baseline covariates X, $r_i = r(X_i)$, i=1,…N

Rank risks from lowest to highest risk: $r_{(1)} \leq r_{(2)} \leq \ldots \leq r_{(N)}$

1. **Proportion of cases followed, PCF(q):** proportion of cases followed-up in screening program that screens proportion *q* of population at highest risk
2. **Proportion needed to follow, PNF(p):** proportion of population at highest risk that needs to get screened so that proportion *p* of future cases will be screened

Distributions of Risk in Cases and Non-cases

$r(x) = \hat{P}(Y = 1 \mid x)$ risk estimate

$F(r^*) = P(r \leq r^*)$ distribution of risk in general population

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$r(x) = \hat{P}(Y = 1 | x)$ risk estimate

$F(r^*) = P(r \le r^*)$ distribution of risk in general population

$G(r^*) = P(r \le r^* | Y = 1)$, distribution of risk in cases

Distributions of Risk in Cases and Non-cases

$r(x) = \hat{P}(Y = 1 | x)$ risk estimate

$F(r^*) = P(r \le r^*)$ distribution of risk in general population

$G(r^*) = P(r \le r^* | Y = 1)$, distribution of risk in cases

$K(r^*) = P(r \le r^* | Y = 0)$, distribution of risk in non-cases

Proportion Cases Followed, PCF(q)

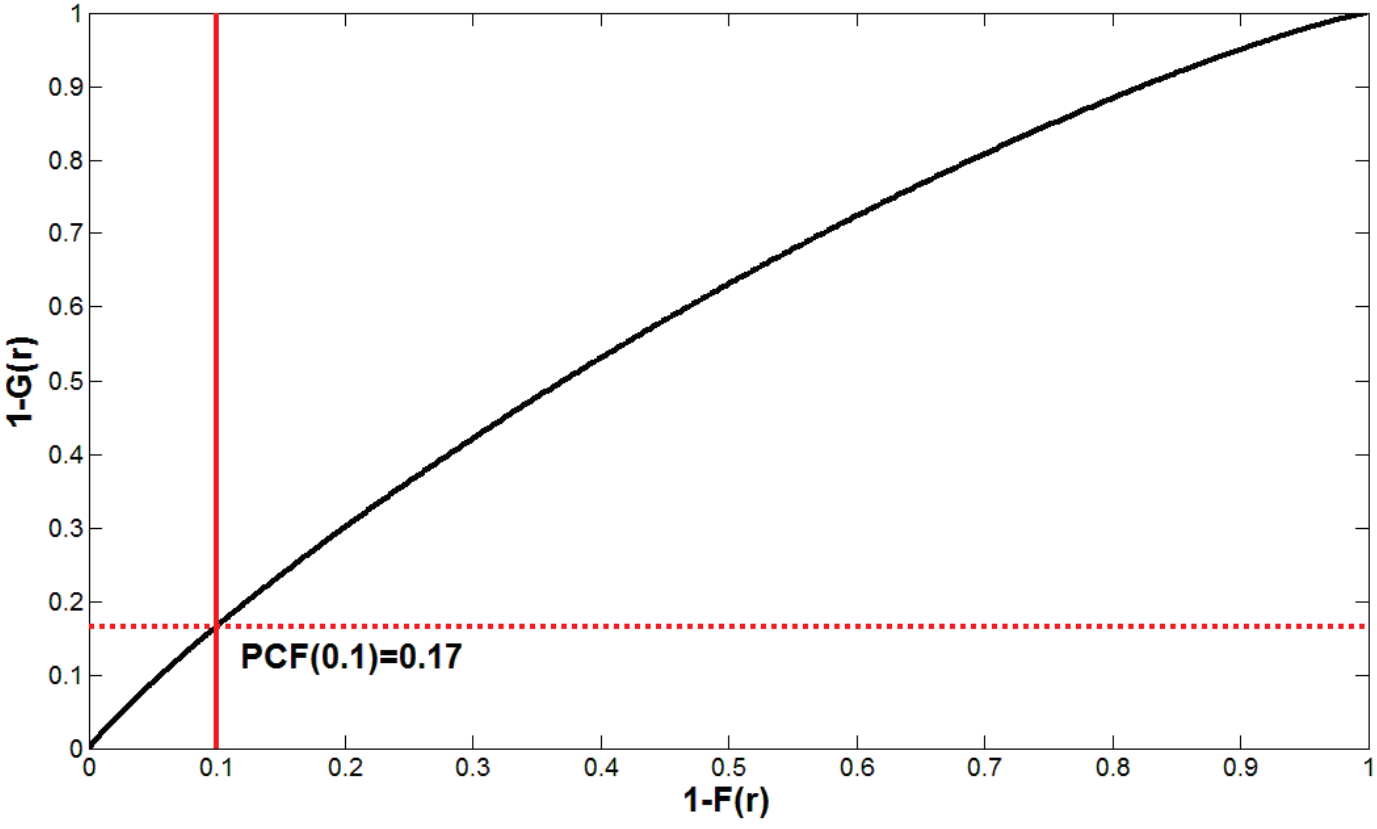
Proportion of cases who are included in proportion *q* of population at highest risk.

$F^{-1}(1-q)$: (1-q)th quantile of population distribution *F*

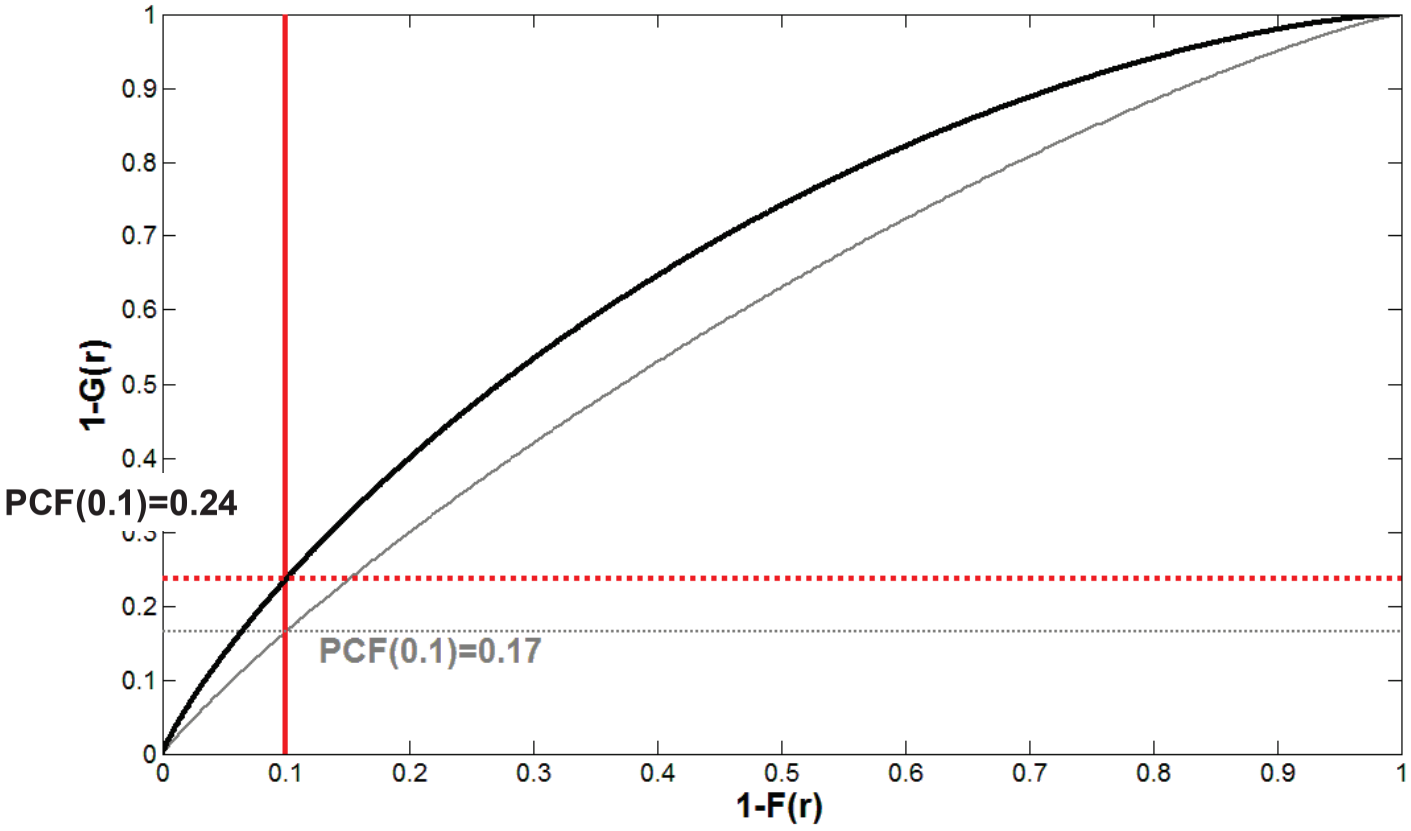
G- distribution of risk in cases

$$PCF(q)=1-G\circ F^{-1}(1-q)$$

PCF, risk distribution *F* in population is Beta(8.5, 161.5) (AUC=0.59)



PCF, risk distribution *F* in population is Beta(2.3, 43.7) (AUC=0.68)



Integrated Proportion of Cases Followed (iPCF)

G- distribution of risk in cases

$PCF(q)=1- G \circ F^{-1}(1-q)$

$$iPCF(q^*)= \int_{q^*}^{1} PCF(q)dq =$$

$$= 1-q^* - \frac{1}{1-q^*} P(R_G \le R_F \mid R_F \in (0, F^{-1}(1-q^*))$$

$$q^* = 0: \; iPCF(0) = P(R_G > R_F)$$

Comparison with ROC curve

F- distribution of risk in population

G- distribution of risk in cases

$$PCF(q)=1-G\circ F^{-1}(1-q)$$

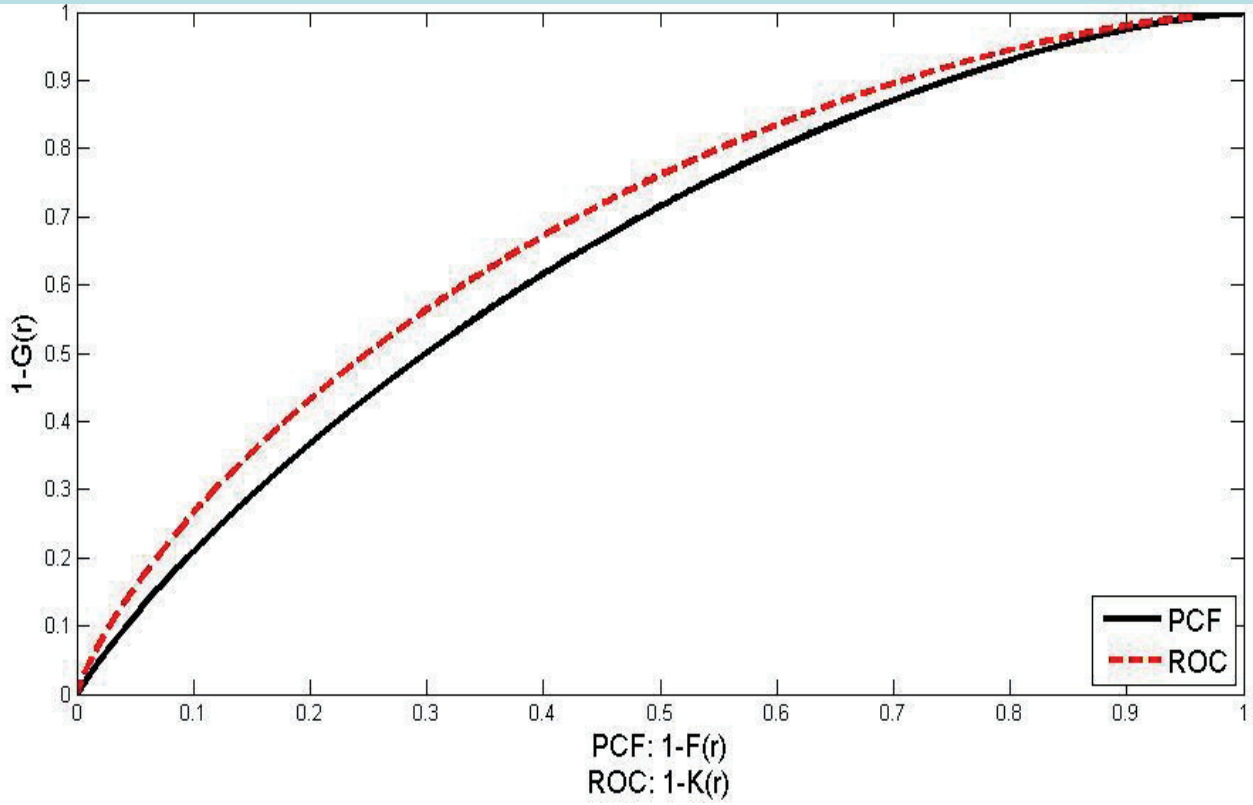
$$iPCF(0)=\int_0^1 PCF(q)dq = P(R_G > R_F)$$

K- distribution of risk in non-cases

$$ROC(q)=1-G\circ K^{-1}(1-q)$$

$$AUC=\int_0^1 ROC(q)dq = P(R_G > R_K)$$

ROC and PCF curves, risk distribution *F* in population is Beta(2.5, 10), AUC=0.69, iPCF=0.66 (mu=0.20)



Proportion Needed to Follow, PNF(p)

Fraction of the general population with highest risks that needs to be screened (followed up) to assure that a given fraction *p* of all cases in population receive screen.

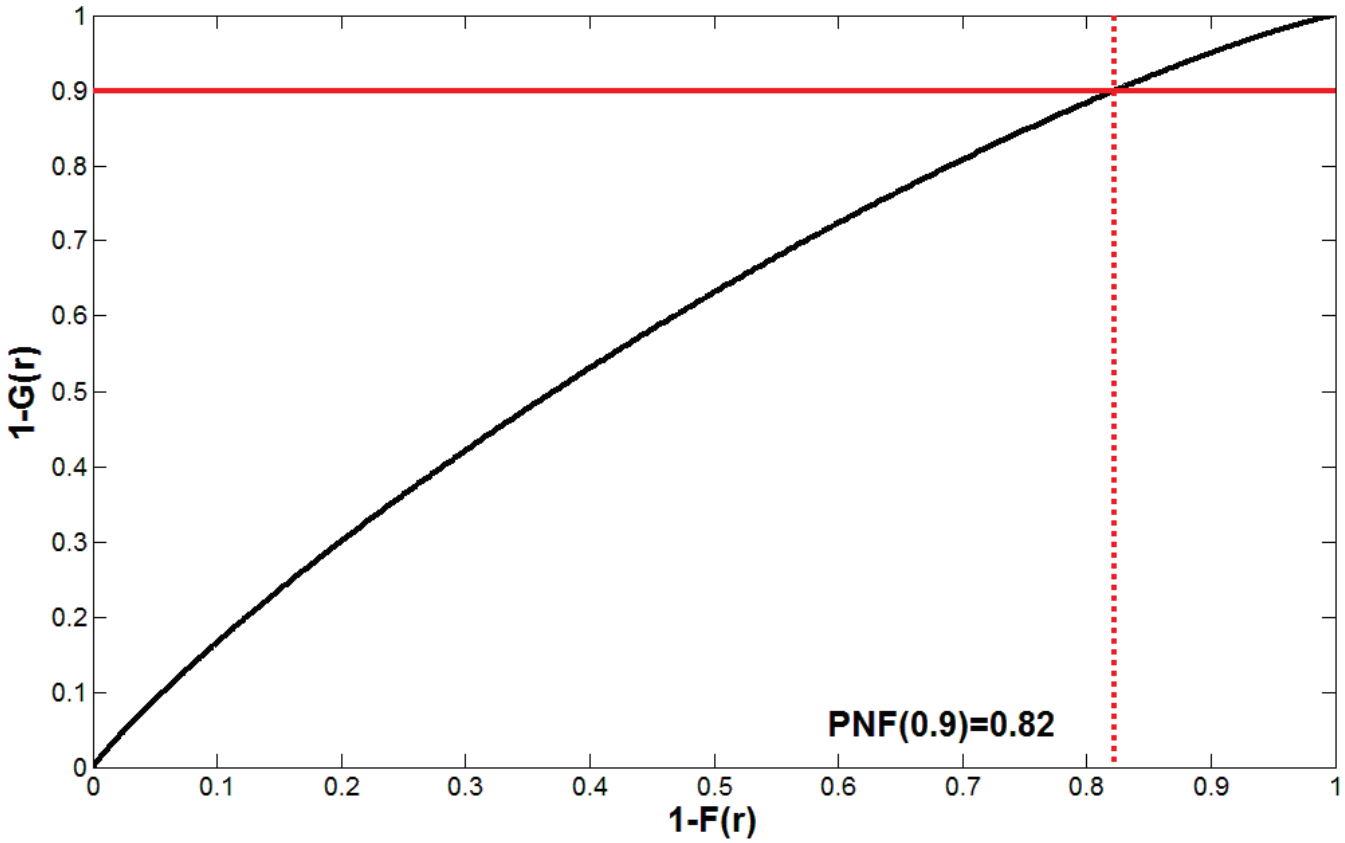
Solve

$$1- G \circ F^{-1}(1-PNF(p)) = p$$

Thus

$$PNF(p) = 1- F \circ G^{-1}(1-p)$$

PNF, risk distribution *F* in population is Beta(8.5, 161.5) (AUC=0.59)



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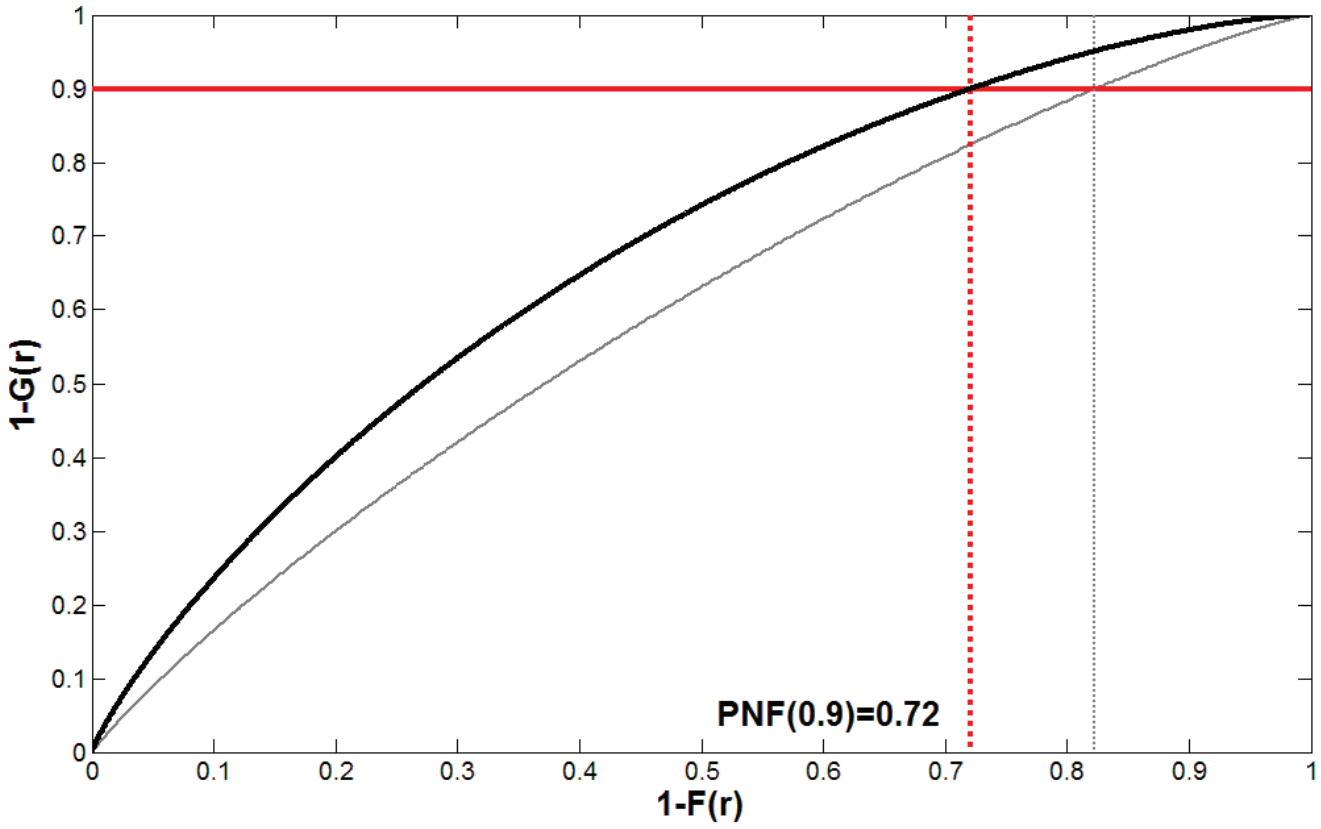

Non-parametric estimates of PCF(q), iPCF, PNF(p), iPNF using three different types of data

- Risks $r_1,\ldots,r_N$ in a **cohort under assumption of a well-calibrated model**
- Risks in **case-control study**, $r_1,\ldots,r_{N0}$ in controls ($Y=0$) and $r_1,\ldots,r_{N1}$ in cases ($Y=1$) with **known disease prevalence μ**
- **Risks and outcomes in a cohort**, $(r_1,Y_1),\ldots,(r_N,Y_N)$

Estimate PCF and PNF under assumption of well calibrated model

If model well calibrated : $P(Y \mid r) \sim r$ and $P(Y=1) = E(R) = \mu$

Distribution of risk in cases

$$G(r^*) = P(R \le r^* \mid Y=1) = \frac{1}{\mu}\int_0^{r^*} r dF(r)$$

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Distribution of risk in cases

$$G(r^*) = P(R \le r^* \mid Y=1) = \frac{1}{\mu}\int_0^{r^*} r dF(r)$$

PCF(q)=1- G $\circ$ F^{-1}(1-q) = $1- \frac{1}{\mu}\int_0^{F^{-1}(1-q)} r dF(r) = 1 - L(1-q)$

where L denotes the *Lorenz curve* for F

Estimate PCF and PNF under assumption of well calibrated model

If model well calibrated : $P(Y \mid r) \sim r$ and $P(Y=1) = E(R) = \mu$

Distribution of risk in cases

$$G(r^*) = P(R \le r^* \mid Y = 1) = \frac{1}{\mu}\int_0^{r^*} r dF(r)$$

$$\text{PCF(q)} = 1 - G \circ F^{-1}(1-q) = 1 - \frac{1}{\mu}\int_0^{F^{-1}(1-q)} r dF(r) = 1 - L(1-q)$$

where L denotes the Lorenz curve for F

$$PNF(p) = 1 - F \circ G^{-1}(1-p) = 1 - L^{-1}(1-p)$$

Non-parametric estimates of $\hat{L}$ and $\hat{L}^{-1}$ provided by Goldie (1977)

Inference

- Derived asymptotic distributions for non-parametric estimates of PCF, iPCF, PNF and iPNF for three designs
  - Observed risks alone under assumption of well calibrated model
  - Case-control data with known disease prevalence
  - Observed risks and outcomes in a population
- Variance estimation:
  - Taylor linearization using influence functions
  - Bootstrap procedure
  - **Estimation under assumption of well calibrated model much more efficient**

PCF and PNF Estimates for Endometrial and Breast Models in Validation Cohort (NHS)

	Breast cancer Model (AUC=0.58)	
q	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$
0.10	**0.17 (0.005)**	**0.17 (0.01)**

PCF and PNF Estimates for Endometrial and Breast Models in Validation Cohort (NHS)

	Breast cancer Model (AUC=0.58)		Endometrial cancer Model (AUC=0.68)	
q	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$
0.10	0.17 (0.005)	0.17 (0.01)	**0.27 (0.02)**	**0.30 (0.03)**

PCF and PNF Estimates for Endometrial and Breast Models in Validation Cohort (NHS)

	Breast cancer Model (AUC=0.58)		Endometrial cancer Model (AUC=0.68)	
q	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$
0.10	0.17 (0.005)	0.17 (0.01)	0.27 (0.02)	0.30 (0.03)
p	$\hat{PNF}_R$	$\hat{PNF}_{(R,Y)}$		
0.90	**0.84 (0.02)**	**0.84 (0.03)**		

PCF and PNF Estimates for Endometrial and Breast Models in Validation Cohort (NHS)

	Breast cancer Model (AUC=0.58)		Endometrial cancer Model (AUC=0.68)	
q	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$	$\hat{PCF}_R$	$\hat{PCF}_{(R,Y)}$
0.10	0.17 (0.005)	0.17 (0.01)	0.27 (0.02)	0.30 (0.03)
p	$\hat{PNF}_R$	$\hat{PNF}_{(R,Y)}$	$\hat{PNF}_R$	$\hat{PNF}_{(R,Y)}$
0.90	0.84 (0.02)	0.84 (0.03)	**0.76 (0.02)**	**0.78 (0.04)**

Summary

- Presented PCF, PNF, and their integrated versions (iPCF and iPNF) for assessing performance of risk prediction models for screening applications
- Presented non-parametric estimates for PCF, iPCF, PNF, iPNF and their asymptotic properties using influence function approach for three different designs
- Developed methods for testing differences between two models evaluated on same independent validation data
- High discriminatory accuracy needed for screening applications on population level

References

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Pfeiffer RM, Gail MH. Two criteria for evaluating risk prediction models. *Biometrics*, 2011

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