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# Using Risk Models for Breast Cancer Prevention

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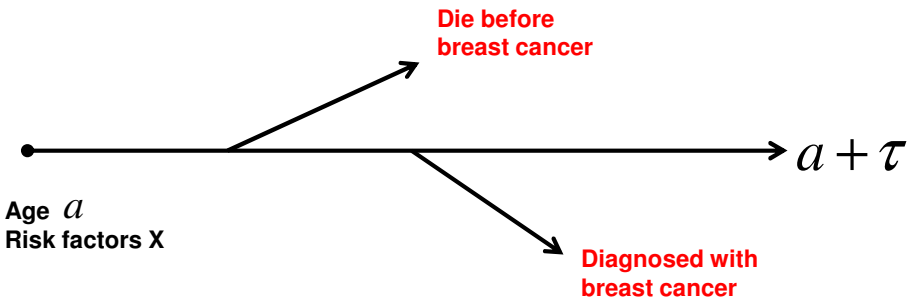
## Overview

- What is absolute risk?
- Counseling
- Cancer prevention in the population
- Do SNPs add much in these applications?

## 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 by age 70? 0.116 (11.6%)




Absolute risk is probability diagnosed with breast cancer in the interval $a$ to $a+\tau$ among women with risk factors X and well at age $a$.

## Using Risk Models to Counsel Women for Early Detection or Prevention

- General perspective on risk
- Formal weighing of risks and benefits

## Should a Woman in her Forties Have Screening Mammography?

- US Prev. Services Task Force (AIM, 2009)
  - "recommends against routine screening mammography in women aged 40 to 49 years."
  - No factors except age and deleterious mutations "conveys a clinically important absolute increased risk for cancer."
  - Decision based instead on "patient context, including the patient's values regarding specific benefits and harms."

## Counter-example

A 40-year old woman is uncertain whether to have screening mammograms. Her mother and sister had breast cancer. Her 5-year absolute risk (1.8%) exceeds that of a 50-year old woman without risk factors (0.6%).

## Women in Their Forties with the Breast Cancer Risk of a 50-Year Old Woman with No Risk Factors

- Non-Hispanic White Women
  11.6 million (74%)
- Non-Hispanic Black Women
  0.85 million (31%)

Wu, Graubard, Gail AIM 2012

## 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 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) |

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

| | NO TAMOXIFEN | 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**

## Benefit/risk indices for tamoxifen and raloxifene for white non-Hispanic women with a uterus

| | Tamoxifen | | | Raloxifene | | |
|---|---|---|---|---|---|---|
| 5-year risk | 50-59 | 60-69 | 70-79 | 50-59 | 60-69 | 70-79 |
| 1.5 | -133 | -310 | -325 | 21 | -11 | -15 |
| 2.0 | -105 | -283 | -298 | 43 | 11 | 7 |
| 2.5 | -78 | -255 | -271 | 65 | 33 | 29 |
| 3.0 | -51 | -228 | -244 | 86 | 55 | 51 |
| 3.5 | -25 | -202 | -217 | 108 | 76 | 71 |
| 4.0 | 3 | -175 | -190 | 128 | 97 | 93 |
| 4.5 | 29 | -148 | -164 | 150 | 119 | 115 |
| 5.0 | 56 | -121 | -137 | 172 | 140 | 136 |
| 5.5 | 83 | -95 | -111 | 193 | 161 | 157 |
| 6.0 | 109 | -69 | -84 | 214 | 183 | 179 |
| 6.5 | 135 | -42 | -58 | 236 | 204 | 199 |
| 7.0 | 162 | -15 | -32 | 256 | 225 | 221 |

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates

Combining RR from BCPT and STAR using WHI baseline rates

- Strong evidence of benefits outweighing risks
- Moderate evidence of benefits outweighing risks
- Benefits do not outweigh risks

Freedman A N et al. JCO 2011;29:2327-2333



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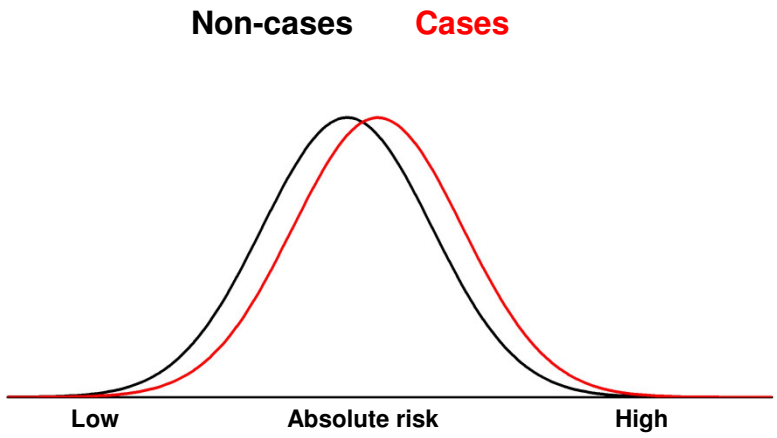
## Risk Models in Population Cancer Prevention

- Designing prevention trials
- Assessing population absolute risk reduction from prevention strategies
- “High risk” strategy for interventions with adverse side-effects
- Allocation of preventive resources under cost constraints




AUC=0.6, like BCRAT

# Some SNPs Associated with Breast Cancer

| Location | Disease Allele Frequency | Odds Ratio per Allele | Reference |
|---|---|---|---|
| FGFR2 | 0.38 | 1.26 | 1 |
| TNRC9 (or TOX3) | 0.25 | 1.20 | 1 |
| MAP3K1 | 0.28 | 1.13 | 1 |
| LSP1 | 0.30 | 1.07 | 1 |
| CASP8 | 0.87 | 1.136 | 2 |
| 8q | 0.40 | 1.08 | 1 |
| 2q35 | 0.497 | 1.20 | 3 |
| | | Geometric mean 1.15 | |


1. Easton et al., Nature 2007;447:1087-1095
2. Cox et al., Nature Genetics 2007;39:352-358
3. Stacey et al., Nature Genetics 2007;39:865-869


# Comparisons of Discriminatory Accuracy

| Model | Age-specific AUC |
|---|---|
| 7-SNPs | 0.574 |
| 11-SNPs | 0.585 |
| 18-SNPs | 0.587 |
| "Foreseeable SNPs" (70) | 0.635 |
| BCRAT | 0.607 |
| BCRAT+ 7-SNPs | 0.632 |
| BCRAT+11-SNPs | 0.637 |
| BCRAT+ "Foreseeable SNPs" | 0.670 |
| BCRAT + Mam. Density | 0.654 |

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## Decision to Take Tamoxifen in 100,000 Women with Uteri, Aged 50-59

| Health Outcome | Relative Risk | # Cases If No Tamoxifen | # Cases If All Tamoxifen |
|---|---|---|---|
| Invasive Br. Ca. | 0.51 | 246.6 | 125.8 |
| Hip Fracture | 0.55 | 101.6 | 55.9 |
| Endometrial Ca. | 4.01 | 81.4 | 326.4 |
| Stroke | 1.59 | 110 | 174.9 |
| Pulmonary Emb. | 3.01 | 50 | 150.5 |
| Total | | 589.6 | 833.5 |

## Threshold Risk *r** for Optimal Decision

- Only women with risk r*> 774.3 /$10^5$ have a positive net expected benefit from tamoxifen
- Only about 1% of this population has a risk this high
- Very small “high risk group” means limited potential for prevention, unless practically all the cancers arise from this small group

## Life-Threatening Events per Year in $10^5$ 50-59 Year Old Women with Uteri with Various Prevention Strategies

| Strategy | Expected Life-Threatening Events (Improvement) |
|---|---|
| None get tamoxifen | 589.6 |
| BCRAT > r*=744/$10^5$ | 588.2 (-1.4) |
| BCRAT+7 SNPs > r* | 587.8 (-1.8) |
| Perfect Breast Cancer Model | 469.7 (-119.9) |

## Approaches to Improve the High-Risk Strategy

- Improve the interventions
  - Less toxic
  - More effective in preventing breast cancer
- Improve discriminatory accuracy of the breast cancer risk model
- Model the risks of the other health outcomes affected by the intervention, such as stroke (Gail, SIM 2012)

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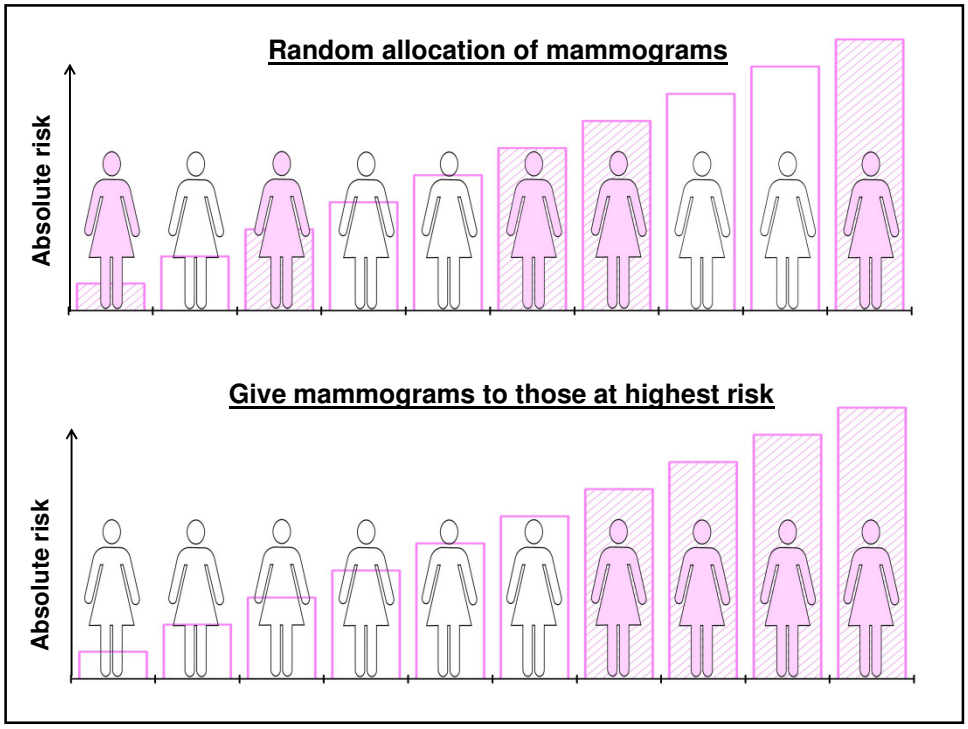
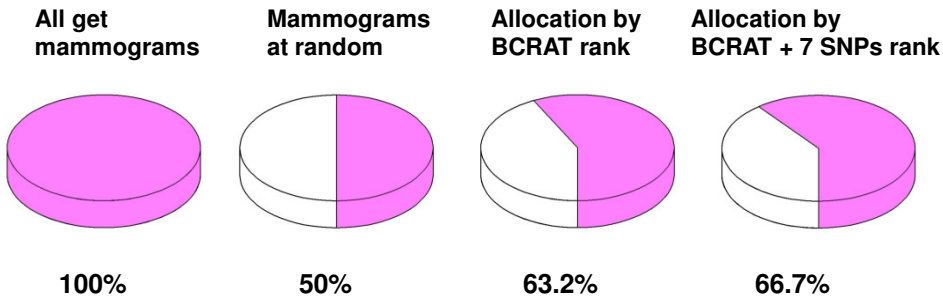



**Mammography strategies based on risk if only enough money to give mammograms to half the population**




**Percent of maximum potential lives saved**

Gail, Statistics and Its Interface, 2009

## Absolute Risk Models in Prevention - Summary

- Counseling patients
  - General perspective
  - Weighing favorable and unfavorable effects of preventive interventions
- Public health applications
  - Designing prevention trials
  - Assessing potential absolute risk reduction from preventive interventions
  - Implementing “high risk” prevention strategy
  - Allocating scarce resources
- Need stronger risk factors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# Selected References


- Gail et al, JNCI 1999; 91: 1829-1846 (tamoxifen risk/benefit)
- Gail, M.H. and Pfeiffer, R.M. Biostatistics 2005; 6: 227-239 (risk distribution and expected loss)
- Gail, M.H. JNCI 2008;100:1037-41 (SNP AUC)
- Gail, M.H. JNCI 2009;101:959-963 (SNP value in applications)
- Gail, M.H., Stat. & Its Interface, 2009;2:117-121(resource allocation)
- Park et al, JCO 2012; 30: 2157-62 (“foreseeable SNPs”)
- Petracci, E. et al, JNCI 2011;103:1–12
- Rose, G. The strategy of preventive medicine, Oxford University Press, 1992
- Wu et al, AIM 2012; 157: 597


## Additional References on SNPs for Breast Cancer Risk Models


- Pharoah et al Nature Genetics 2002;31:33-36
- Pharoah et al NEJM 2008;358:2796-2803
- Wacholder et al NEJM 2010;362:986-93
- Park et al Nature Genetics 2010;42:570575

## 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.

## Strong Breast Cancer Risk Factors

| Factor | Comparison | Relative Risk |
|---|---|---|
| **Age** 70-74 | 25-29 | 56 |
| **BRCA1** | No mutation | 2.3-24 |
| **BRCA2** | No Mutation | 4; 12-18 |
| **Chest radiation (>40 Gy)** | No chest radiation | 6 |
| **Contralateral breast cancer** | None | 5 |
| **Western Country** | Rural China | 5 |
| **% Mammographic density** >45% | <5% | 4 |

## Moderately Strong Risk Factors

| Factor | Comparison | Relative Risk |
|---|---|---|
| **Affected 1st degree relatives** | | |
| 1 | None | 1.4 - 3 |
| 2 or more | None | 2.2 - 5 |
| 1 at age <40 | 1 at age ≥ 60 | 1.3 - 2.8 |
| **Biopsies** | | |
| Non-proliferative | None | 1.5 |
| Proliferative | None | 2 |
| Atypical hyperplasia | None | 2-4 |
| **HRT** for 5 y | None | 1.3-2 |
| **Age at first birth** ≥ 30 y | <20y | 1.8 |

## Weak Risk Factors

| Factor | Comparison | Relative Risk |
|---|---|---|
| **Age at menarche** <12y | ≥ 14y | 1.2 |
| **Age at menopause** 55y | 50y | 1.15 |
| **BMI (kg/m$^2$)** | | |
| >30, post-menopausal | <21 | 1.3 |
| >30, pre-menopausal | <21 | 0.6 |
| **Ethanol, 1-2 drinks/d** | None | 1.13 |
| **Adverse SNP in FGFR2** | Favorable SNP | 1.26 |

## Some Choices in Risk Modeling

- Genetic model versus empirical model
- Choice of risk factors
  - Detailed family history
  - Reproductive history (e.g. age at first live birth)
  - Medical history (e.g. biopsies, mammographic density)
- Data sources and “piecing together” the model
- Target population: e.g. general population in UK or in US; or high risk clinic

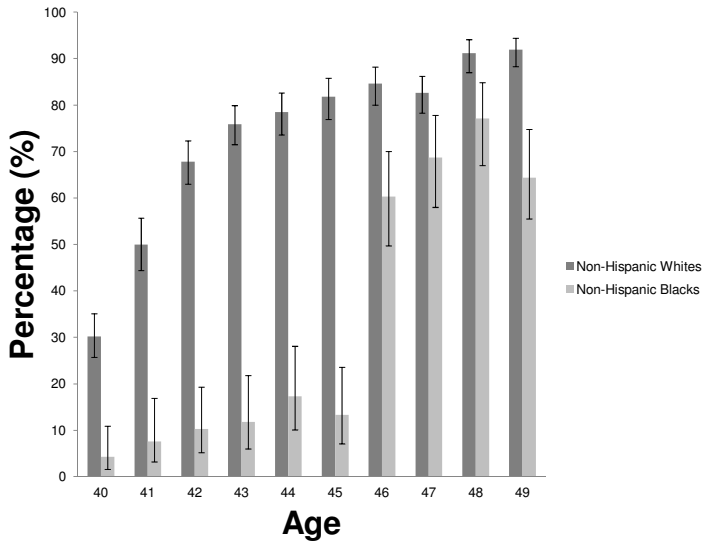
## Genetically-based Models

- Autosomal dominant
  - Use extensive family history and BRCA1/2 data
  - BRCAPRO (Berry et al, JNCI 1997)
  - Claus Model (Claus et al, Cancer,1994)
- Autosomal dominant & residual familial effects
  - BOADICEA, Antoniou et al, BJC 2008
  - IBIS, Tyrer, Duffy and Cuzick, Stat Med 2005 This model includes other factors such as LCIS, age at first live birth.

## NCI's Breast Cancer Risk Assessment Tool, BCRAT ("Gail Model")

- Relative risks from Breast Cancer Detection Demonstration Project (BCDDP)
- Incorporates ethnicity-specific SEER data
- Risk factors
  - Age
  - Age at menarche
  - Age at first live birth
  - Number of biopsies (and whether atypical hyperplasia is present)
  - Number affected mother or sisters

## Percentage of 40-49 year old women with breast cancer risk greater than a 50-year old woman without risk factors




Unpublished data related to Wu, Graubard, Gail, AIM 2012

# Summary for Tamoxifen

- Young women at high risk stand to benefit most
- Women without uterus have more favorable risk benefit ratio
- There is no single risk level (e.g. 1.67%) that applies to all women. Decision depends on age and risks of other outcomes.

## Benefit/risk indices for tamoxifen and raloxifene for white non-Hispanic women without a uterus

| | Tamoxifen | | | Raloxifene | | |
|---|---|---|---|---|---|---|
| 5-year risk | 50-59 | 60-69 | 70-79 | 50-59 | 60-69 | 70-79 |
| 1.5 | 3 | -53 | -93 | 27 | 2 | -4 |
| 2.0 | 31 | -26 | -66 | 49 | 23 | 18 |
| 2.5 | 57 | 2 | -39 | 71 | 45 | 40 |
| 3.0 | 84 | 29 | -12 | 92 | 67 | 62 |
| 3.5 | 111 | 56 | 15 | 114 | 88 | 82 |
| 4.0 | 138 | 83 | 42 | 134 | 109 | 104 |
| 4.5 | 164 | 109 | 69 | 156 | 131 | 126 |
| 5.0 | 191 | 136 | 96 | 178 | 152 | 147 |
| 5.5 | 218 | 163 | 121 | 199 | 173 | 168 |
| 6.0 | 244 | 189 | 148 | 220 | 195 | 190 |
| 6.5 | 270 | 215 | 175 | 242 | 216 | 210 |
| 7.0 | 297 | 242 | 201 | 262 | 237 | 232 |

- Strong evidence of benefits outweighing risks
- Moderate evidence of benefits outweighing risks
- Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates

Combining RR from BCPT and STAR using WHI baseline rates

Freedman A N et al. JCO 2011;29:2327-2333

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## Calibration of BCRAT in the Breast Cancer Prevention Trial (Costantino et al, JNCI 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 |

## Model Validation

- Use independent cohort data to validate
- Calibration
  - Does the model correctly predict the number of cancers that develop?
- Discriminatory accuracy
  - AUC= the probability that a randomly selected case will have a larger predicted risk than a randomly selected control

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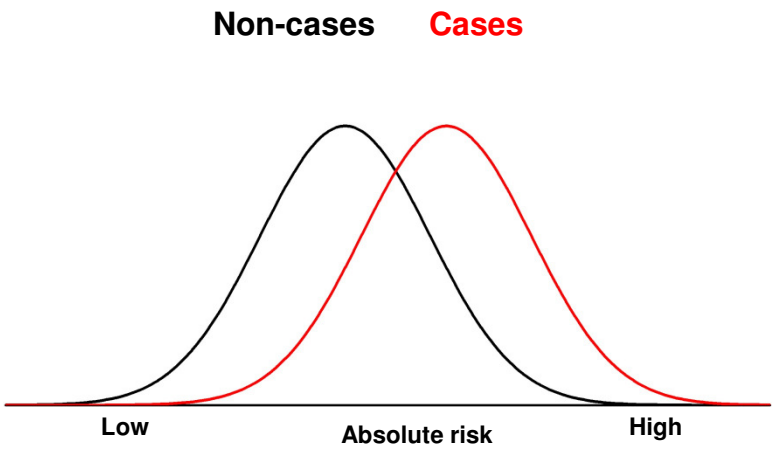
## Designing Prevention Trials

- **Statistical power**
  - Depends on the number of events
  - Number of events is proportional to average absolute risk of trial participants
- **Eligibility criteria**
  - Select subjects who stand to benefit from intervention
  - Increase efficiency of trial by including high risk subjects
- **Examples:** BCPT (P-1) Trial, STAR Trial




Good discriminatory accuracy, AUC=0.8

# Usefulness of SNPs for Breast Cancer Risk Models

- Increase discriminatory accuracy (AUC)?
- In public health applications?

- Selected references
  - Gail and Pfeiffer, Biostatistics, 2005
  - Gail, JNCI 2008, 2009
  - Wacholder et al, NEJM 2010
  - Park et al, JCO, 2012

# The Strategy of Preventive Medicine[1]

- The population strategy of prevention
- The "high-risk" strategy

[1]Geoffrey Rose, Oxford University Press,1992

## 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

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

$h_1(t)$ 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)

## Factors Affecting Absolute Breast Cancer Risk

- Factors that increase absolute risk
  - Increasing the risk projection interval
  - Increased age at the beginning of the projection interval (usually)
  - Having multiple or strong risk factors for breast cancer
- Factors that decreases absolute risk
  - Mortality from non-breast cancer causes

## BCRAT for Ethnic/Racial Groups

- Special models have been developed for African-American (JNCI, 2007) and Asian-American (JNCI, 2011) women
- Work needed for Hispanic women and other subgroups
- BCRAT calibrates to SEER data for subgroups

## Individual Breast Cancer Risk Projections

**Current age (20-80): 40**

**Upper age limit (20-80): 50**

**Age at menarche: 12**
**Age at first live birth (0 if no live birth): 0**
**Number of previous breast biopsies: 1**
**At least one biopsy with hyperplasia (y:yes, n:no, u:unknown): u**

**Number of first degree relatives (mother or sister(s)) with breast cancer: 0**

**Absolute risk = 3.6% with 95% CI = (3.0%, 4.3%)**

## Model with Perfect Discriminatory Accuracy

- Treat only the 246.6 women destined to get breast cancer
  - Breast cancers 246.6 x .51 = 125.8
  - Net adverse effects

  (55.9+326.4+174.9+150.5)x246.6/$10^5$= 1.7
- Events among those not destined to get breast cancer and therefore not treated

  (589.6-246.6)x{(100,000- 246.6)/$10^5$}= 342.2
- Grand total 469.7

## Threshold Risk *r** for Optimal Decision

**Expected net benefit from tamoxifen for woman with BC risk *r***

$$r(1-0.51)+101.6(1-0.55)+81.4(1-4.01)+110.0(1-1.59)+50.0(1-3.01)$$
$$=0.49r-364.7.$$

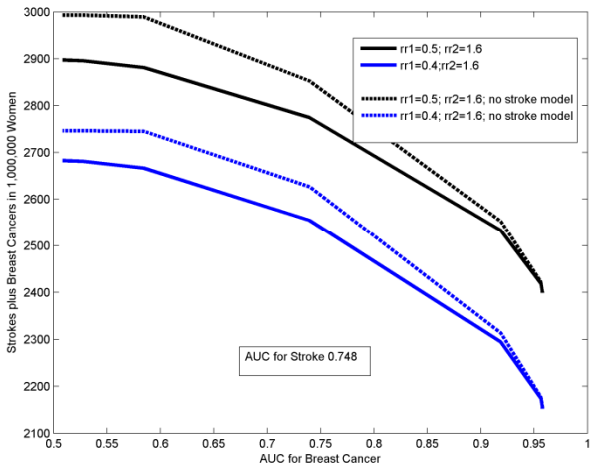
**Expected net benefit positive if *r* > 364.7/0.49=774.3 ≡ *r****

**Only give tamoxifen if *r* > 774.3 /$10^5$ · This is a "high-risk" strategy, because only 1% of women aged 50-59 have risks this high.**

## Summary (Continued)

- Public health applications
  - Designing Prevention Trials
  - Assessing absolute risk reduction from prevention
  - To implement "high risk" prevention strategy
    - Find safer interventions that can be used broadly
    - Increase discriminatory accuracy
    - Model risks of the several health outcomes
  - Allocating scarce resources
    - Cost of risk assessment should be small
- Improvements from SNPs small in these applications. Allocating scarce resources
- .

## Expected Strokes plus Breast Cancers in 1,000,000 50-59 Year Old Women in One Year: Modeling Stroke and Breast Cancer



## Women in Forties with Absolute Risk of a 50-Year Old Woman

- Consider screening mammography because these women have nearly the same prevalence of detectable cancer and intervention effect as the 50-year old woman (Gail and Rimer, JCO,1998)
- 74% of white women in 40's have at least the risk of 50-year old woman with no risk factors (Wu, Graubard, Gail, AIM, 2012)
- "Tipping the Balance" (van Ravesteyn et al, AIM 2012)

## Mammographic Screening of a Population under Cost Constraints

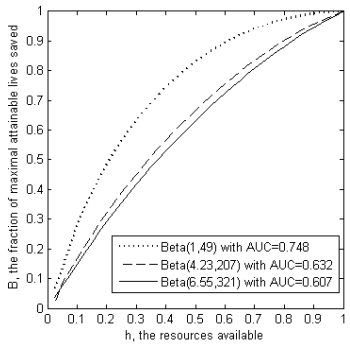
- Screening reduces the number of deaths from $N\mu$ to $N\,\mu(1-\rho)$, a reduction of $N\,\mu\rho$ deaths
- We take as the unit of cost, the total cost required to screen the entire population, $NC_S = 1$. The fraction of this total cost that is available for the screening program is $h \leq 1$.
- We perform a risk assessment on members of the population to decide who should get screening. Risk assessment costs $C_R = kC_S$ , where $k$ is the cost ratio of risk assessment to screening.

## Using Risk Models to Allocate Mammograms under Cost Constraints

- Perform a risk assessment
- Allocate mammograms to those with high risks
- Optimal strategy
  - h is the fraction of needed money available
  - k is the cost ratio for risk assessment:
  - g is proportion given risk assessment
  - p is proportion assessed who are given mammograms
  - m is proportion given mammogram at random among those without risk assessment

## Fraction of Maximal Attainable Lives Saved, B, versus Resources, h

**B**




**h**

## Lives Saved

$$N\mu - Ng\int_0^{\xi_{1-p}} rdF(r) - Ng(1-\rho)\int_{\xi_{1-p}}^{1} rdF(r)$$
$$- N(1-g)\mu m(1-\rho) - N(1-g)(1-m)\mu$$
$$= N\mu\rho[g\{1-L(1-p)\}+(1-g)m]$$

where $\xi_{1-p} = F^{-1}(1-p)$.

Fraction of the maximum possible lives saved

$$B = g\{1-L(1-p)\}+(1-g)m$$

## Goal

Maximize the proportion of lives saved,

compared to giving all women mammograms,

$g\{1-L(1-p)\}+(1-g)m$,

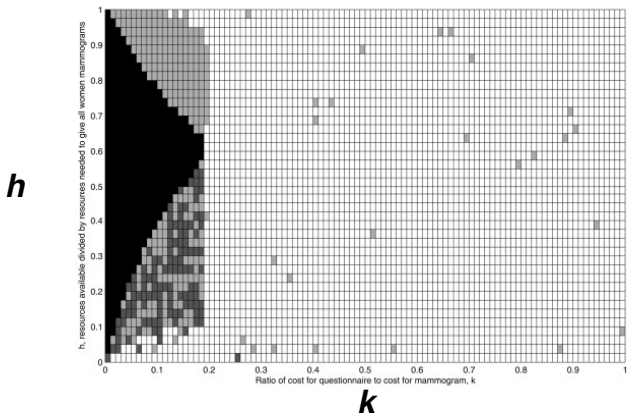
subject to cost constraints

$gk + gp + (1-g)m \le h$

## Four Basic Strategies

- Assess risk in all and screen a top proportion p of those assessed until the remaining money is used. (g=1, p>0, m=0)
- Assess risk in a fraction g<1 and use all the remaining money to screen a top proportion p of those assessed. (0<g<1, p>0, m=0)
- Assess risk in a fraction g<1, screen a top proportion p of those assessed and a random sample of a proportion m>0 of the un-assessed. (0<g<1,p>0,m>0)
- Screen as many as possible at random with no risk assessment. (g=0, m>0)

## Plot of Optimal Strategy for Various Pairs (*k*,*h*)




***h***

***k***

**Optimal Strategy is: (1) *g*=1 (Black); (2) 0<*g*<1, *m*=0 (Dark Grey); (3) 0<*g*<1, *m*>0 (Light Grey); or (4) *g*=0 (White).**

## Allocating Mammograms When Only Enough Money for Half the Population

| Risk assessment | Proportion of lives saved compared to giving mammograms to all women | % Improvement versus no risk assessment |
|---|---|---|
| **None** | **0.500** | |

## Allocating Mammograms When Only Enough Money for Half the Population

| Risk assessment | Proportion of lives saved compared to giving mammograms to all women | % Improvement versus no risk assessment |
|---|---|---|
| **None** | **0.500** | |
| **BCRAT[a]** | **0.632** | **26.4%** |
| **BCRATplus7SNPs[b]** | **0.667** | **33.4%** |

**[a]AUC=0.607; [b]AUC=0.632; k=0.02**

Gail, Statistics and Its Interface, 2009

## Key Role of Distribution of Risk, *F(r)*, in the Population

$R(x)$ is risk for person with covariates, $x$

$$F(r) = P(R \le r) = \int_{x:R(x)\le r} dF_X(x)$$

**From *F(r)*, compute**

- **Distribution of risk in cases and in non-cases**
- **Functionals of *F* like AUC**
- **Expected losses for decision-making**

**References**


- **Gail & Pfeiffer, Biostatistics 2005;6:227-239**
- **Gail, JNCI 2008;100:1037-1041**
- **Gail, JNCI 2009;101:959-963**


## Distributions of risk in cases and controls and the Lorenz curve

Distribution $G$ of risk in cases

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

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

Lorenz curve of $F$ is $L(p) = \mu^{-1}\int_0^{F^{-1}(p)} r dF(r) = G(F^{-1}(p))$

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

## Key Assumptions to Compute *F*

- **Hardy-Weinberg equilibrium**
- **Linkage equilibrium across SNPs**

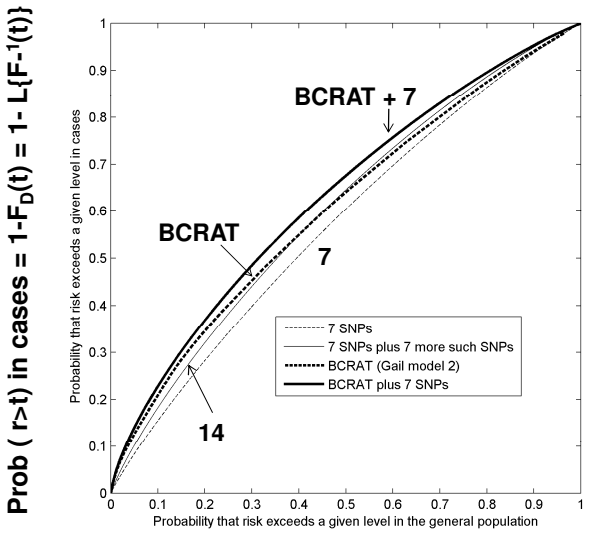
$$P(\mathbf{X}) = \prod_{i=1}^{7} p_i(X_i)$$

- **Additive effects of disease alleles**
- **Odds ratios multiply across SNPs**

$$rr(\mathbf{X}) = \prod_{i=1}^{7} (OR_i)^{X_i}$$

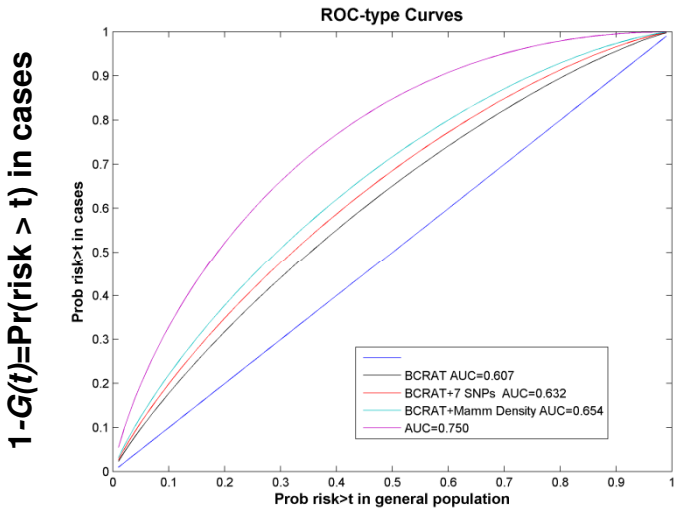
- **SNP ORs multiply BCRAT ORs**
- **SNPs independent of factors in BCRAT**

## ROC-type Plots




**Prob ( r>t) in general population =1-F(t)**

## ROC-Type Curves to Assess Discriminatory Accuracy of Risk Models




*1-F(t)*=Pr(risk > t) in general population

## Uses of Absolute Risk for the Individual Patient

- General perspective in counseling
- Making clinical decisions for preventive interventions with risks and benefits
- Clinical management after diagnosis (prognostic risk models)

## Individual Breast Cancer Risk Projections

**Current age (20-80): 40**

**Upper age limit (20-80): 50**

**Age at menarche: 12**
**Age at first live birth (0 if no live birth): 0**
**Number of previous breast biopsies: 1**
**At least one biopsy with hyperplasia (y:yes, n:no, u:unknown): u**

**Number of first degree relatives (mother or sister(s)) with breast cancer: 0**

**Absolute risk = 3.6% with 95% CI = (3.0%, 4.3%)**

## Preventive Action Applied Throughout the Population

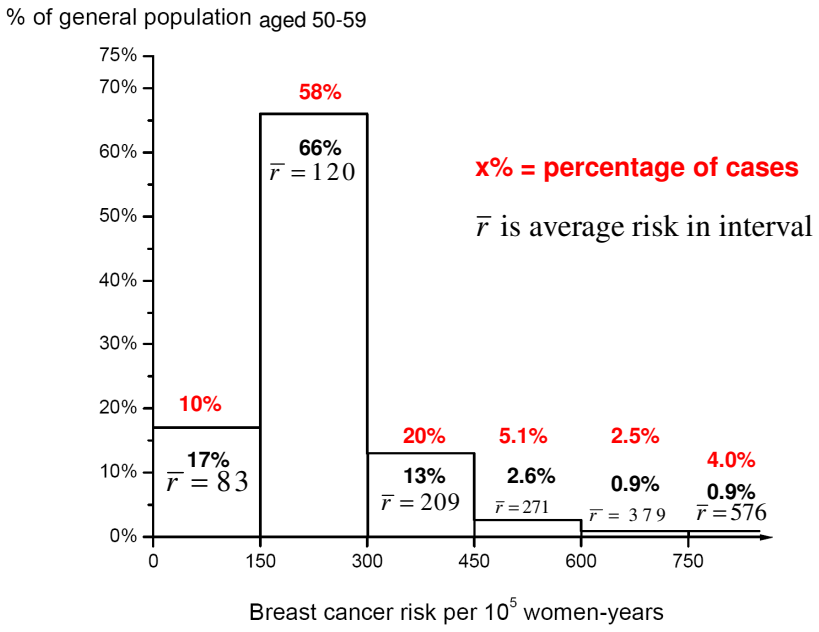
- Must be very safe
- Usually has the greatest potential for disease prevention
- Examples
  - Reduce environmental or occupational exposure
  - Behavioral change: e.g. more exercise or decreased alcohol
  - Take an hypothetical safe cancer preventive agent

## Preventive Action Applied To High Risk Subgroup

- Useful if intervention poses adverse side effects or risks
- Useful if intervention is too costly for widespread use
- Limited potential for disease prevention
- Examples
  - Tamoxifen to prevent breast cancer
  - Oophorectomy and/or prophylactic mastectomy
  - MRI screening

## Enhancing Effectiveness of High Risk Strategy

- Increase discriminatory accuracy of risk model to concentrate most of the cases in a small high risk group
- Find interventions with less toxicity that can be applied to a larger high risk subgroup (e.g. raloxifene, aromatase inhibitors?) (Cuzick, Breast Cancer 2008)




# Other Breast Cancer Risk Models

- **Based on detailed family history**
  - **Rare autosomal dominant** transmission only
    - Claus (Cancer,1994)
    - BRACAPRO (can incorporate BRCA genotype) Berry, JNCI 1997
  - **Rare autosomal dominant plus residual familial aggregation**
    - BOADICEA (polygenic, can incorporate BRCA genotype) Antoniou BMJ 2004,2008
    - Tyrer, Duff, Cuzick (common dominant and non-genetic risk factors) Stat Med 2004

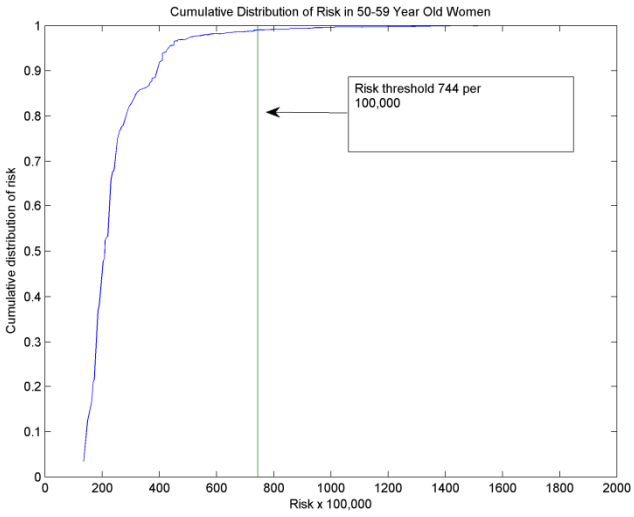
## Other models (continued)

- Family history plus other factors
  - Rosner (**detailed reproductive history**) JNCI 1996
  - **Mammographic density**
    - Chen (BCRAT risk factors) JNCI 2006
    - Barlow (BI-RADS, fam. Hx, biops) JNCI 2006
    - Tice (BI-RADS, fam. Hx, race, biops) Ann Int Med 2008
  - **SNPs** plus BCRAT

    Gail JNCI 2008,2009; Pharoah NEJM 2008
- **Biopsy Histopathology**

  Hartmann, JCO 2007

## Distribution of Risk in Women aged 50-59 years




Note that only 1.0% of women in this age group satisfy BCRAT > r*.

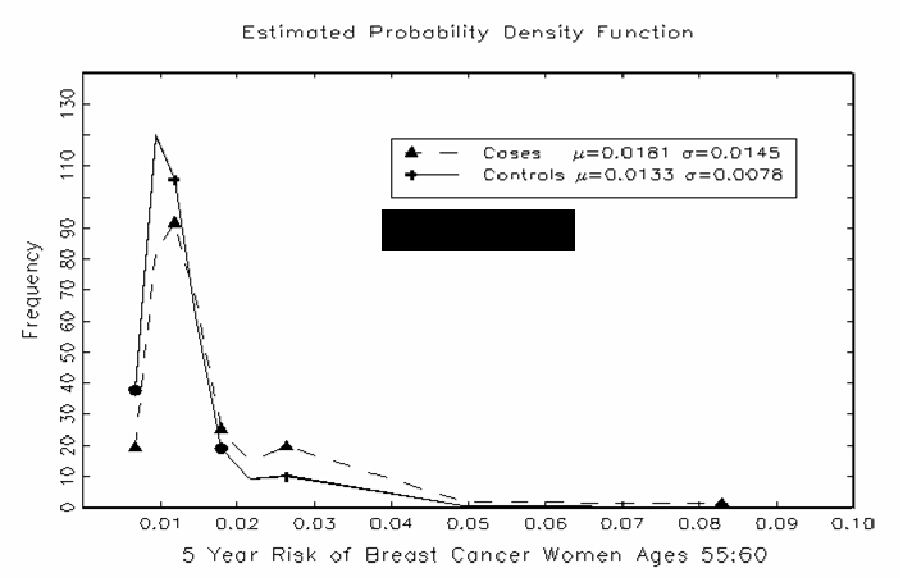
## Some standard criteria for evaluating the performance of risk models

- **Calibration:** Are risk estimates 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)?

## Modest Discriminatory Power

Rockhill et al., JNCI 2000

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



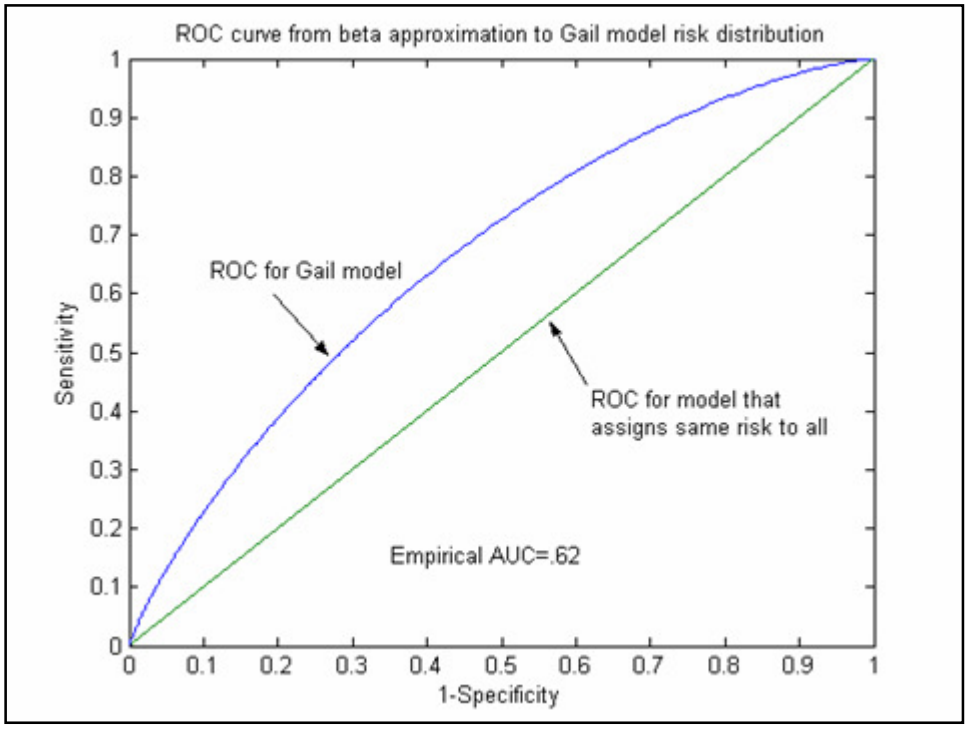

# Comments on Area Under ROC (AUC)

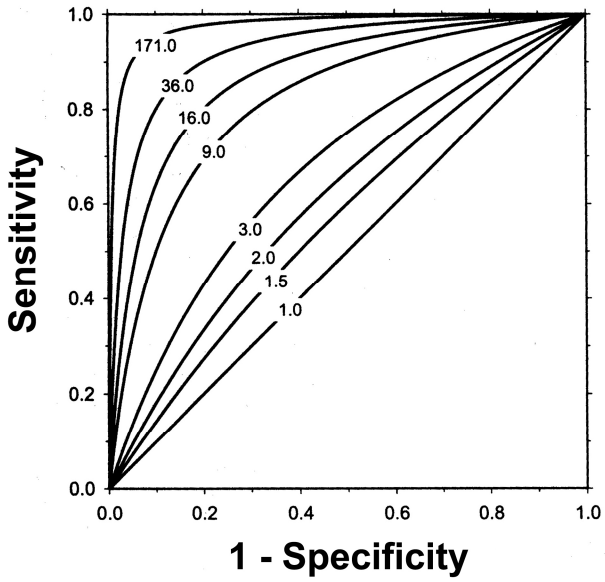
- Can be estimated from case-control data
- Hard to increase
  - Incorporation of mammographic density, a strong risk factor, only increases from e.g. 0.60 to 0.66 for 60-64 yrs women (Chen, . . . Gail, submitted)
- Comparable to AUC for age-specific AUC for cardiovascular risk models

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

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

$$\text{sens}(r^*) = P(\delta = 1 \mid Y = 1) = P(r \geq r^* \mid Y = 1)$$
$$= 1 - F_{case}(r^*-)$$
$$\text{spec}(r^*) = P(\delta = 0 \mid Y = 0) = P(r < r^* \mid Y = 0)$$
$$= F_{control}(r^*-)$$




**ROCs for various risk factor odds ratios. From Pepe et al. AJE 2004**

## 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 $P(Y_i = 1)$
- $\pi_i$ is the true $P(Y_i=1)$

Gail and Pfeiffer, Biostatistics, 2005

## 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 $E_k$**

## Specific Loss Function-Based Approach to Model Assessment

**Two applications:**

- **Screening**
- **Weighing risks and benefits of an intervention**

**Gail and Pfeiffer, Biostatistics 2005**

## Expected Loss

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

## 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**

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

## 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:**

$$r_{010}(x)=\text{Gail model estimate for breast cancer}$$
$$r_{110}(x)=0.5r_{010}(x)$$
$$r_{011}(x)=r_{111}(x)=0$$

# Assessing Model Calibration

The model r(x) is **perfectly calibrated (unbiased)** if for each x

$$r(x) = E(\pi \mid x) = \int \pi dG(\pi \mid x).$$

Then

$$\int_0^1 rdF(r) = \int_x E(\pi \mid x) dG_x(x) = E(\pi) = P(Y = 1)$$

**Unbiased (well calibrated) in the whole population**

$$\frac{1}{N}\sum_{i=1}^{N} Y_i \approx \int_0^1 rdF(r) = \mu$$

# Extend Notation to Intervention Setting

**True event probabilities for bivariate outcomes for δ=0, 1**

$$\pi_{\delta i} = \{P_\delta(Y_{\delta 1i} = 1, Y_{\delta 2i} = 1), P_\delta(Y_{\delta 1i} = 1, Y_{\delta 2i} = 0),$$
$$P\delta(Y_{\delta 1i} = 0, Y_{\delta 2i} = 1), P\delta(Y_{\delta 1i} = 0, Y_{\delta 2i} = 0)\}^T$$

**Risk models to predict quadrinomial outcomes in presence and absence of intervention (δ=0, 1)**

$$r_\delta(x) = \{r_{\delta 11}(x), r_{\delta 10}(x), r_{\delta 01}(x), r_{\delta 00}(x))\}^T$$

## Measures of Discrimination

- ROC curve (plot of sensitivity against 1-specificity)
- Area under the ROC curve (AUC)
  - Concordance statistic (Rockhill et al, 2001; Bach et al, 2003)
  - ~ (Gini index+1)/2 for rare events
- Partial area under the curve (Pepe, 2003; Dodd&Pepe, 2003)

## Assessing Model Accuracy

For clinical decision making a decision rule is needed to classify subjects

$$\delta_i = \begin{cases} 1, & \text{if } r \geq r^* \\ 0, & \text{otherwise} \end{cases}$$

for some threshold r*

## Accuracy Criteria

- Positive predictive value
- Negative predictive value
- Weighted combinations of both, eg

P(correct decision) = $P(r \geq r^*)\ P(Y=1|r \geq r^*) + P(r<r^*)P(Y=0|r<r^*)$

Depend on sensitivity, specificity, and P(Y=1)

Cannot be estimated from samples of cases and controls alone

## An Alternative Approach to Incorporate Covariates*

- Model $F_1(t;X)$=(T≤t from cause 1|X) directly via $g\{F_1(t;X)\}= v_0(t)+X\beta$
- Use counting process methods, but "risk set" at t consists of those who have not failed plus those who failed earlier but not from cause 1

*** Fine and Gray, JASA 1999**

## Fine, JP and Gray RJ, JASA 1999

- F(t|X)=absolute risk to age t given X
- $g\{F(t|X)\} = h_o(t)+X\beta$
- E.g. g(u)=log{-log(1-u)}
- λ=hazard={dF(t|X)/dt}/(1-F(t|X))
- Issues
  - No cause-specific interpretation
  - Requires cohort data
  - Complex estimation with censoring

## 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)**