Cancer Risk Prediction Models: A Workshop on Development, Evaluation, and Application

Application of Cancer Risk Prediction Models: Intervention Trials

May 20, 2004

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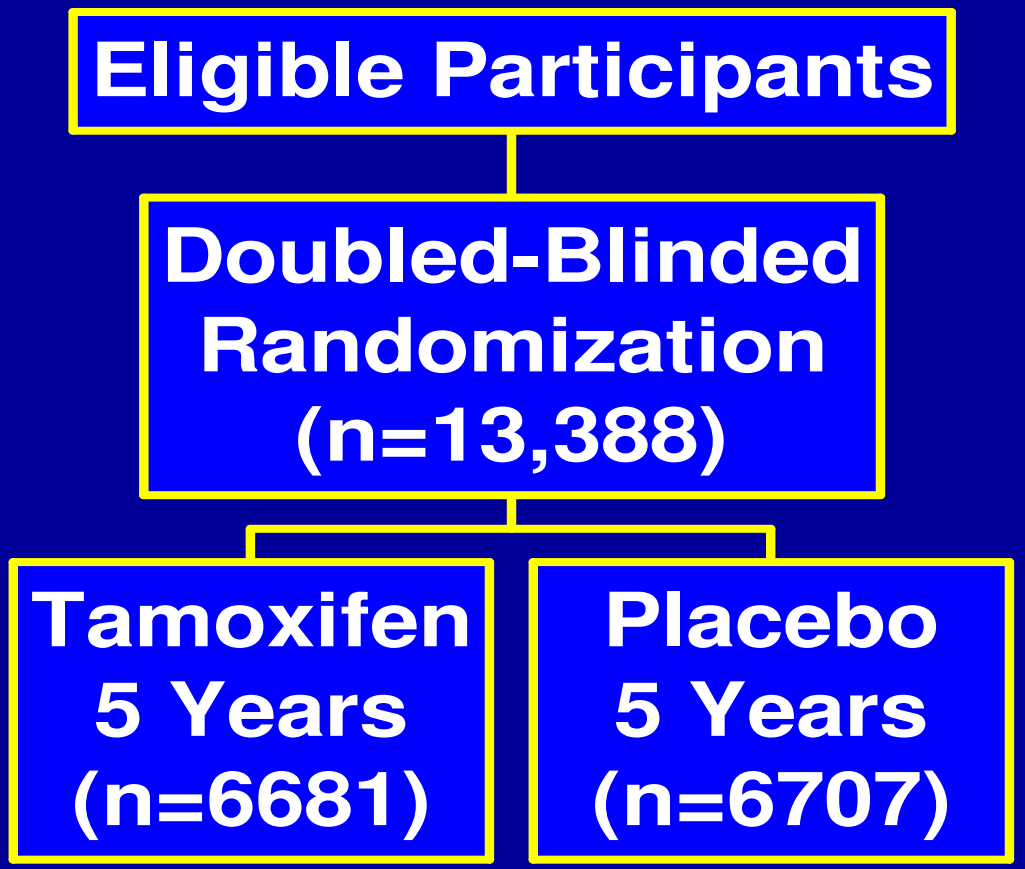
Applications in Intervention Trials - Overview

- Describe application of risk prediction models
  - focus is on the applications, not details of statistical methodology (see references)
  - use breast cancer prevention trials to illustrate applications as an example
- Identify limitations of the applications
- Define needs to improve applicability

The Intervention Trials

Breast Cancer Prevention Trial



Eligible Participants

Doubled-Blinded Randomization (n=19,000)

Tamoxifen 5 Years

Raloxifene 5 Years

Events Affected by SERM Therapy

Beneficial Events

- Invasive Breast Ca
- In Situ Breast Ca
- Hip Fracture
- Spine fracture
- Colles' Fracture

Detrimental Effects

- Endometrial Ca
- PE
- DVT
- Stroke
- Cataracts

Applications in these Intervention Trials

Applications of Predicted Risk

- Four primary applications:
  - trial design and analysis
  - screening to determine trial eligibility
  - informed consent process (benefit/risk assessment)
  - identifying target populations for study/therapy

Applications in these Intervention Trials

1. Trial Design and Analysis

Trial Design and Analysis – Sample Size

- Use the average value of the predicted risk assumed among the anticipated study population to determine study sample size
- Use average value of the predicted risk observed in the accruing population to:
  - assess the accuracy of the assumed value
  - make modification to the sample size before ending accrual to ensure that the study has the statistical power originally desired.

Trial Design and Analysis – Risk Adjustment

- When performing modeling to assess the independent contribution of a factor to breast cancer risk, the predicted risk for each individual is used to adjust for breast cancer risk
- More parsimonious model (one parameter, instead of seven parameters)
- As one example: evaluation of the independent contribution HRT history to breast cancer risk

Applications in these Intervention Trials

2. Predicting Risk for Eligibility

Predicting Risk for Trial Eligibility

- Risk must be at least 1.66% in next 5-years
- Could use age as a cut-off as a basis (60+ years), but many younger women have risk factors other than age that give them a higher risk than older women
- Needed a validated risk prediction model that accounts for multiple risk factors
- Used modified Gail model with 7 key risk factors[1,2]

Breast Cancer Risk Projection Equation

- The probability that a woman who is age *a* and who has an age and risk profile-dependent relative risk *r(t)* will develop breast cancer by age a + ☺ is:

$$\int_a^{a+\tau} h_1(t) r(t) \exp\{-\int_a^t h_1(u) r(u) du\} \{S_2(t) / S_2(a)\} dt$$

- Where $h_1(t)$ is the baseline hazard of developing breast cancer derived from SEER "composite" rates $h^*_1(t)$ using $h_1(t) = h^*_1(t)F(t)$ when $F(t)$ is 1- attributable risk fraction; and

$$S_2(t) = \exp\left\{-\int_0^t h_2(u) du\right\}$$

is the probability of surviving competing risks up to age *t* based on NCHS mortality rates.

Combined Effect of Risk Factor Profile

- Profile-dependent relative risk – *r (t)*: Find the product of the relative risk for each factor.

$$y = \alpha + \beta_{Age} x_{Age} + \beta_{AgeMen} x_{AgeMen} + \beta_{AgeFLB} x_{AgeFLB} + \beta_{N\,\mathrm{Re}\,l} x_{N\,\mathrm{Re}\,l} + \beta_{NBiop} x_{NBiop} + \beta_{AH} x_{AH} + \gamma_{Age\_NBiop} x_{Age\_NBiop} + \gamma_{Age\_N\,\mathrm{Re}\,l} x_{Age\_N\,\mathrm{Re}\,l}$$

Then, $\ln r(t) = \sum_{i=1}^{8} \beta_i x_i \longrightarrow r(t) = \exp \sum_{i=1}^{8} \beta_i x_i$

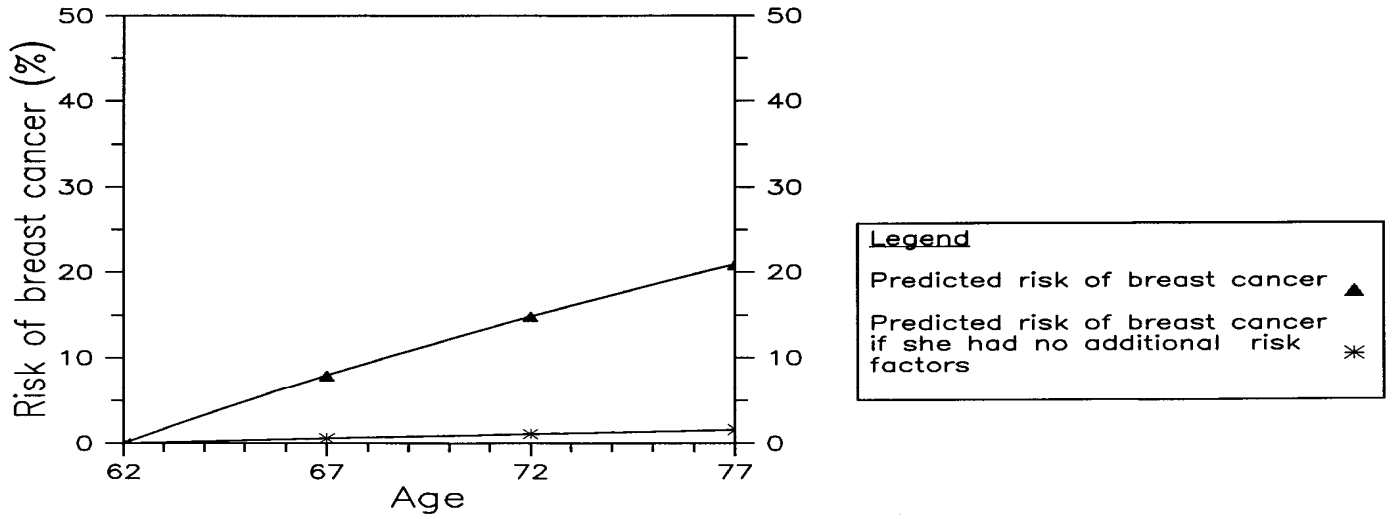
NATIONAL SURGICAL ADJUVANT BREAST PROJECT (NSABP)
BREAST CANCER RISK PROFILE

Name : JANE DOE
Address : 1234 MAIN ST.
City : PITTSBURGH State/Province: PA Zip/Postal Code: 12345
NSABP Center: NSABP Adjuvant Therapy Ctr., Pittsburgh

RISK FACTORS

Current age	: 62	Age at first live birth	: 20
Number of first degree relatives with breast cancer	: 2	Number of breast biopsies	: 1
Age at first menstruation	: 12	Atypical hyperplasia	: Y
Race	: African Am./Black		

The following graph depicts the probability of developing breast cancer for Ms. DOE based on the risk factors listed above. Her estimated probability of developing breast cancer within the next 5 years is 7.93% and to age 80 is 24%.



Based on this risk profile, Ms. DOE is considered **eligible** for participation in the NSABP STAR Breast Cancer Prevention Trial if all other entry criteria are met.

CONTROL # 000016

Example of a Breast Cancer Risk Profile

RISK FACTORS

Age: 35 yrs.

Race: Caucasian

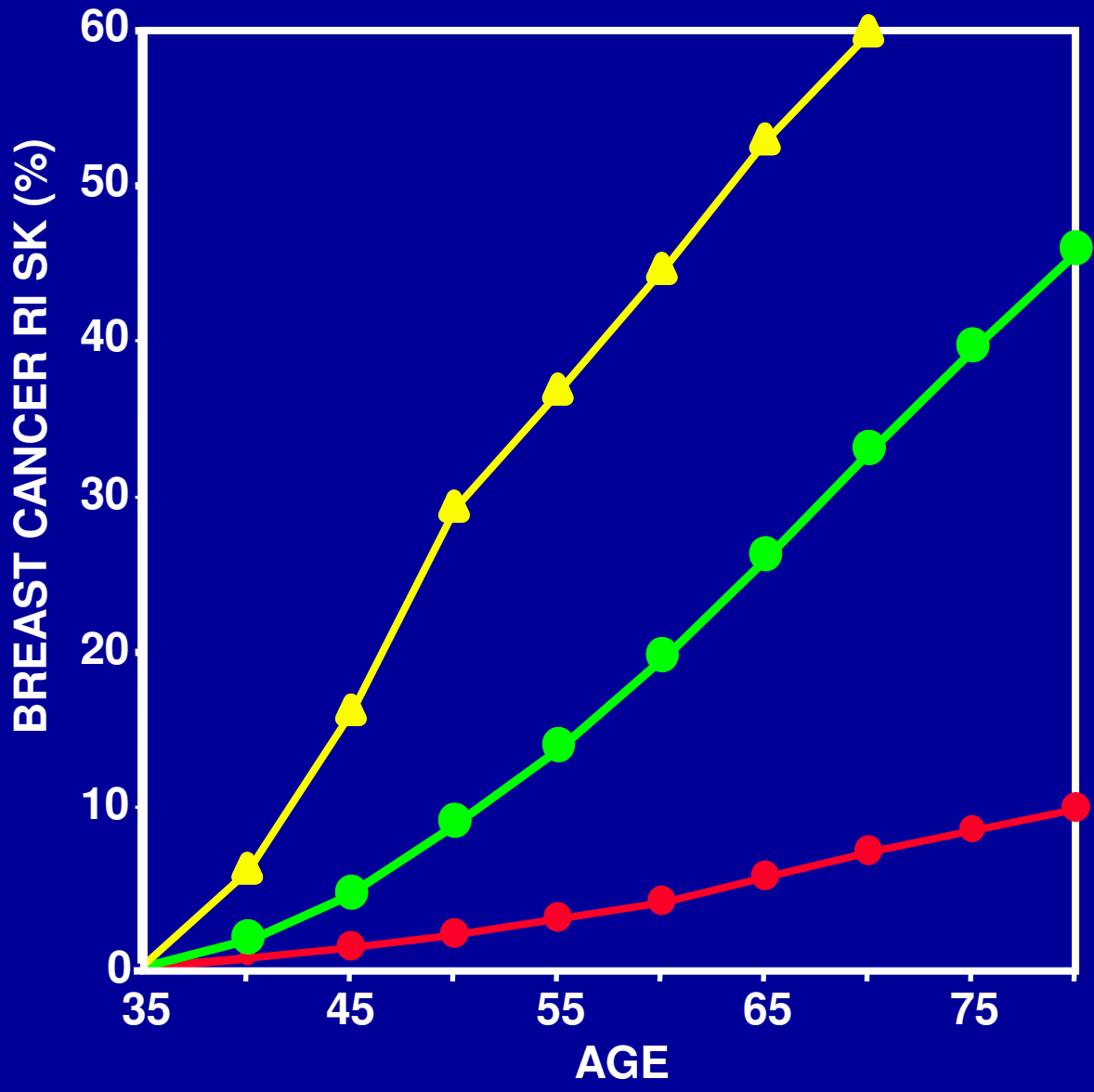
Age at Menarche: 12 yrs.

Age at 1st Live Birth: 22 yrs.

Biopsies: 2

#1st Degree Relatives: 2

Atypical Hyperplasia Hx: Yes



Breast Cancer Risk Prediction - Limitations

- Modified Gail model is based on an original model that was developed from a population that was mostly Caucasian[1]
- Modified model predicts well in the general population[2], but needs validation in non-Caucasian populations

Breast Cancer Risk Prediction - Needs

- Primary concern is the need for race-specific estimates of attributable risk for non-Caucasian populations
- Also need data from studies that included breast cancer screening of large populations of non-Caucasian women to validate predictions in these groups
- Data from WHI and other studies would be useful to accomplish both of the above items

Applications in these Intervention Trials

3. Informed Consent: Risk/benefit Evaluation

Risk/Benefit (R/B) of Trial Therapies

- Trial therapies could affect 10 outcomes - five beneficial, five detrimental
- Need a method to determine benefits and risks and to communicate this to participants
- Desired to provide a fully informed, informed consent
- Based on recommendations obtained from an expert panel of an NCI sponsored risk assessment and communication workshop [3]

Expert Panel Recommendations

- R/B assessment method should have several desirable properties. The method should be one that:
  - avoids the use of probabilities or relative risks
  - provides a comparison to expected if not treated
  - includes consideration of the relative severity of the events, and focuses on the more severe
  - includes a tool that facilitates communication
  - limits the tool to a one-page summary

Risk/Benefit Methodology Utilized

- Methodology is based on a comparison of the:
  - number of expected cases, if untreated
  - number of prevented or caused cases, if treated
- Projections made for a hypothetical population of 10,000 women of the same age, race and breast cancer risk profile as the individual considering participation in the trial

NATIONAL SURGICAL ADJUVANT BREAST PROJECT (NSABP)
BREAST CANCER RISK PROFILE (continued)

Name: JANE DOE Control Number: 000016

Possible Benefits and Risks Associated with Treatment in the STAR Trial

The information in the table below is provided to help you understand the potential benefits and risks to your health as a participant in the STAR. The table shows the number of selected events that might be expected in five years among 10,000 women like you who are not participating in the STAR. Also shown is the number of potential cases that may be prevented or caused among the 10,000 women if they all participated in the STAR.

- The expected numbers of cases of breast cancer are individualized for you based on your current age, race and breast cancer risk factors.
- The expected number of cases of uterine cancer and hip fracure are based on the "average" for women of your race and age group. Because studies of stroke and blood clots have not been performed in large populations of non-Caucasian women, accurate baseline rates of stroke and blood clots for non-Caucasian women in the general population are not available. The number of cases of stroke and blood clots shown in the table are based on the "average" for Caucasian women of your age group. Your risk for these conditions may differ from this "average" because of your general health status, personal and family medical history, and lifestyle. For example, risks of stroke and blood clots for women who exercise regularly and are nonsmokers will likely be less than that shown; for women who are obese, smokers, and do not exercise regularly the risks will likely be higher than that shown.

Severity of Event	Type of Event	Expected Number of Cases in Five Years Among 10,000 Women Not Participating in STAR	Potential Effect Among 10,000 Women If They All Participate in STAR and Are Treated for Five Years
Life Threatening Events			Potential Benefits
	Invasive Breast Cancer	793 cases expected	380 of these cases may be prevented
	Hip Fracture	44 cases expected	20 of these cases may be prevented
			Potential Risks
	Uterine Cancer	42 cases expected	126 more cases may be caused
	Stroke	78 cases expected	46 more cases may be caused
	Blood Clot in Lung	21 cases expected	43 more cases may be caused
Other Severe Events			Potential Benefit
	In Situ Breast Cancer	246 cases expected	122 of these cases may be prevented
			Potential Risk
	Blood Clot in Large Vein	47 cases expected	28 more cases may be caused
Other Events	Potential Benefits:	Treatment may reduce the yearly rate of wrist fractures and fractures of the spine. For your age and race group the reduction in the rate would be about 1 case for every 1,000 women treated.	
	Potential Risk:	Treatment may increase the yearly rate of cataract development. For your age and race group the increase in the rate would be about 7 cases for every 1,000 women treated.	

Example of Risk/Benefit Summary
- Projecting Among 10,000 Women -

Severity Of Event	Type of Event	Expected Cases in Untreated	Potential Effect if Treated
Life Threatening Events			**Potential Benefits**
	Inv. Br. Ca.	793	380 of these may be prevented
	Hip Frac.	44	20 of these may be prevented
			Potential Risks
	Endo. Ca.	42	126 more cases may be caused
	Stroke	78	46 more cases may be caused
	P.E.	21	43 more cases may be caused
Other Severe Events			**Potential Benefits**
	In Situ Br.Ca.	246	122 of these may be prevented
			Potential Risks
	D.V.T.	47	28 more cases may be caused

Risk/Benefit Method - Limitations

- Predictions of the number of events for non-breast cancer outcomes in the risk/benefit assessment are limited by the availability of:
  - age and race-specific baseline rates of disease among the general population of untreated women
  - multi-factorial models accounting for all known risk factors for non-breast cancer events

R/B Limitations - Baseline Rates

- Baseline rates for cancers are solid - SEER data
- Baseline rates for non-cancer events are not available from broadly representative populations
  - particularly true for women and non-Caucasians
  - as a result, for some non-cancer events the baseline rates are “best guesstimates”

R/B Limitations - Multi-factorial Models

- Other than for breast cancer, there are no multi-factorial models to predict the risk of disease
- The individual's profile of risk factors for non-breast cancer events are not considered in the R/B (obesity, diabetes, activity, smoking, hypertension, etc.)
- Thus, predictions for non-breast cancer outcomes are accurate for the population as a whole or for the "average woman" within a given age and race group, but are less accurate for each individual

Applications in these Intervention Trials

4. Identifying Target Populations

Identifying Populations with Net Benefit

- The number of cases prevented and caused as determined from the R/B assessment can be summed (with or without weighting for disease severity) to form a point estimate representing an “Index of Net Effect”
- The probability that the point estimate of the “Index” is greater than 0 can be determined (net positive effect)
- This can be used to identify populations likely to benefit from therapy or those who are potential candidates for a study[4,5]

Example of Net Effect Index for White Women

5-Year risk (%)	Age groups for women with a uterus					Age groups for women without a uterus				
	35-39	40-49	50-59	60-69	70-79	35-39	40-49	50-59	60-69	70-79
1.5	81**	57**	-63	-173	-199	83**	73**	58**	34*	25
2.0	111**	87**	-35	-145	-171	113**	103**	86**	62*	53*
2.5	143**	119**	-6	-116	-142	145**	135**	115**	91**	82*
3.0	173**	149**	22*	-88	-114	175**	166**	142**	118**	109*
3.5	204**	180**	50*	-60	-86	206**	196**	170**	146**	137*
4.0	234**	210**	78*	-32	-68	236**	226**	298**	174**	165*
4.5	265**	241**	106*	-5	-31	268**	257**	226**	202**	193*
5.0	296**	272**	134**	24	-3	298**	288**	254**	230**	221**
5.5	326**	302**	162**	52*	25	328**	318**	282**	258**	248**
6.0	356**	332**	189**	79*	53	358**	348**	309**	285**	276**
6.5	387**	363**	216**	106*	80*	389**	379**	336**	312**	303**
7.0	417**	393**	244**	134*	107*	419**	409**	364**	340**	330**

Limitations of the Net Index

- Issues regarding the use of weighting when determining the “Index” to account for differences in severity of the various events being summed
- As the R/B methodology has limitations, the “Index” should not be considered an absolute criterion for decision making regarding study participation or use of preventive therapy
- Personal perspectives regarding the weighting of risks and benefits should also be considered

Summary and Conclusions

- There are several clinical trial applications involving breast cancer risk prediction models
- The methods and applications developed for breast cancer can be easily modified for application to other types of cancer
- The lack of studies in non-Caucasian populations limits the ability to develop and validate cancer risk prediction models

Summary and Conclusions - continued

- There are also deficiencies in the areas of non-cancer diseases which limit the application of cancer risk prediction models in R/B assessment
  - Solid estimates of age-specific incidence rates for common diseases other than cancers are needed, particularly for non-Caucasians and females
  - to provide accurate individualized estimates of R/B from cancer preventive therapies, multivariate models predicting the risk of common non-cancer diseases are needed

References

1. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989; 81:1879-85.

2. Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J. Validation studies for models to project the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst* 1999;91:1541-48.

3. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer and Vogel V. Weighing the risks and benefits of tamoxifen for preventing breast cancer. *J Natl Cancer Inst* 1999;91:1829-46.

4. Costantino JP. Benefit/risk assessment. In: Biostatistics in Clinical Trials Redmond K, and Colton T. Ed.Wiley, p.18-25, 2001.

5. Freedman AN, Graubard BI, Roa SR, McCaskill-Stevens W, Ballard-Barbash R, Gail MH. Estimates of the number of U.S. women who could benefit from tamoxifen for breast cancer chemoprevention. *J Natl Cancer Inst* 2003; 95:526-32.