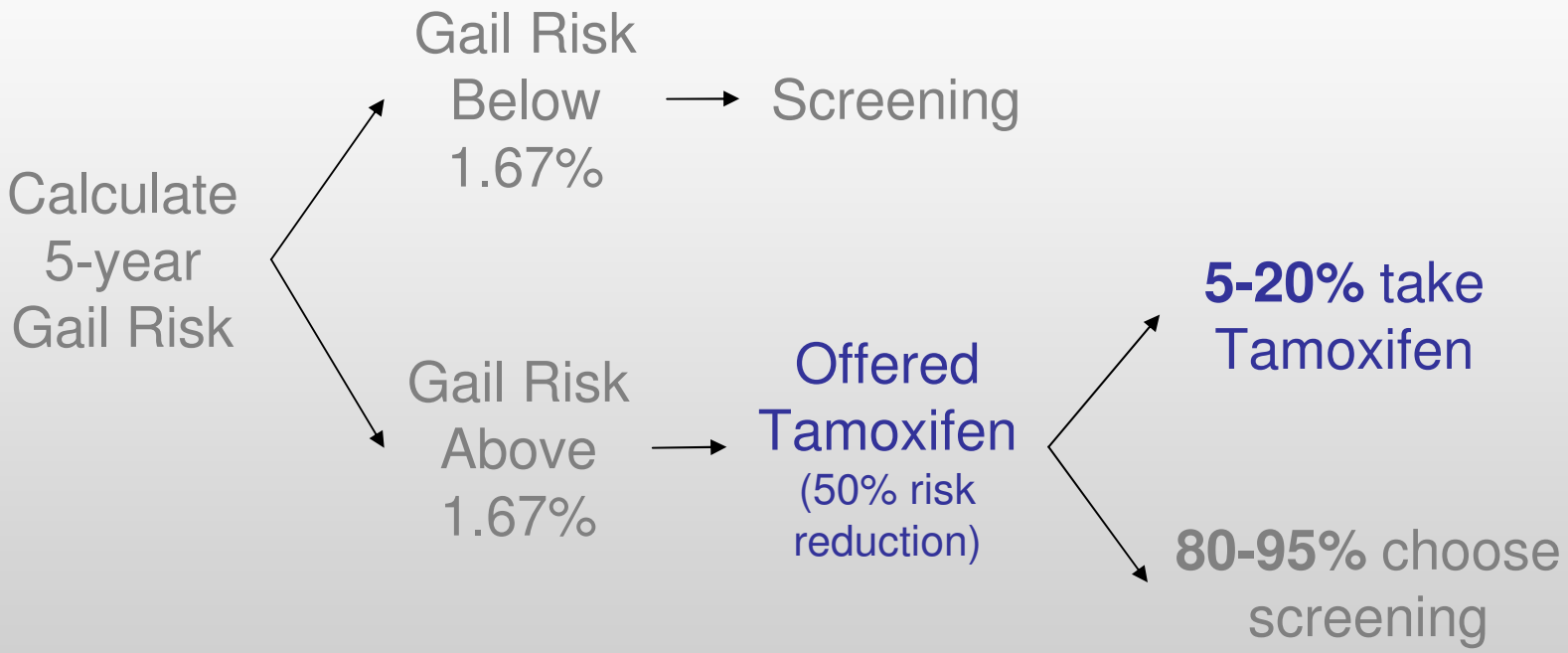
Clinical Applications of Risk Prediction Models

Laura Esserman, M.D., M.B.A.
Professor of Surgery and Radiology
Director, UCSF Carol Franc Buck Breast Care Center

Agenda

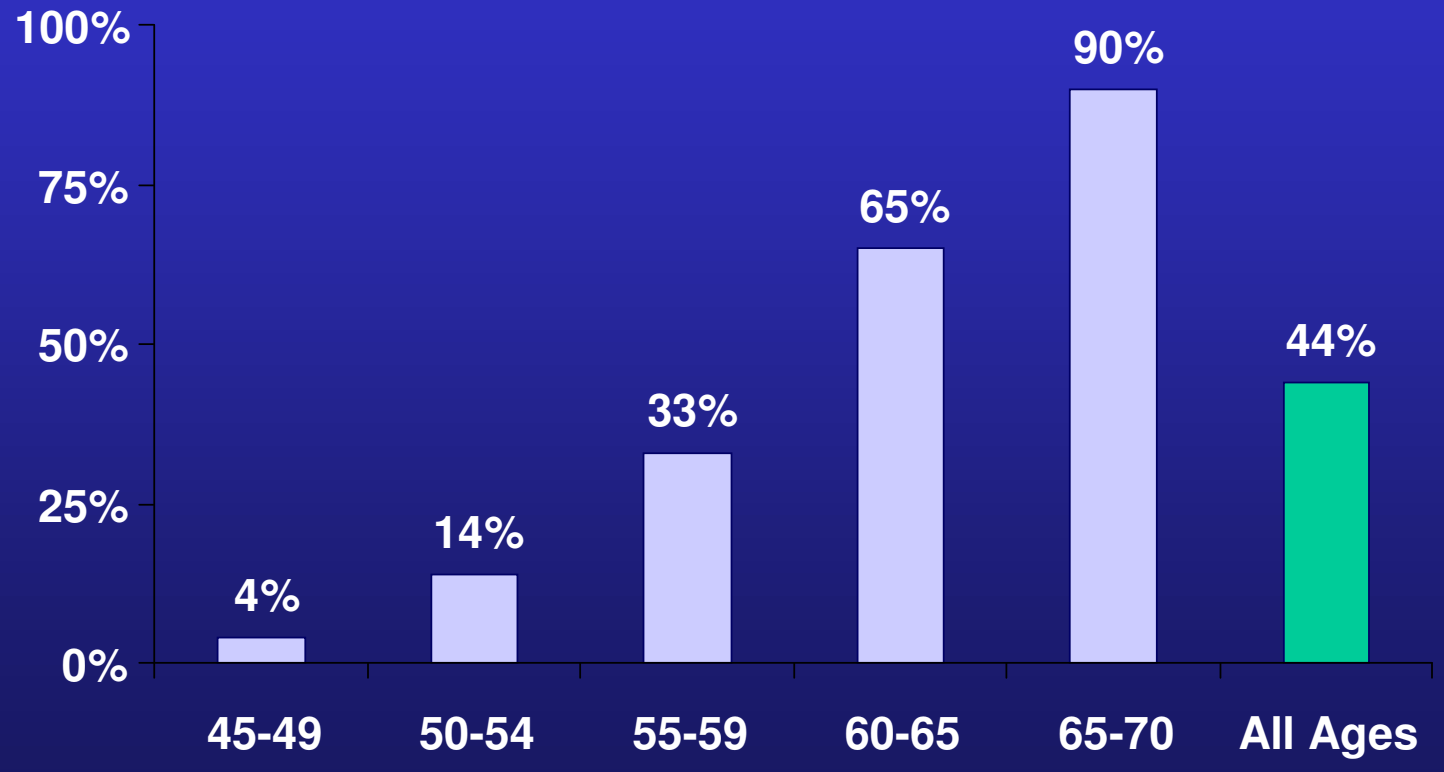
- Current Clinical Climate for Prevention
- Potential for Risk Tools to Refine Risk, motivate interventions
- Framework for Decision Aids: the need for tools that provide information in a decision ready context
- How risk models can be integrated into clinical consultations
- Insights from using decision aids, models

Current Clinical Decision Making



Rush-Port, Vogel et al.

The Gail Model Does Not Identify a Truly High Risk Group of Women

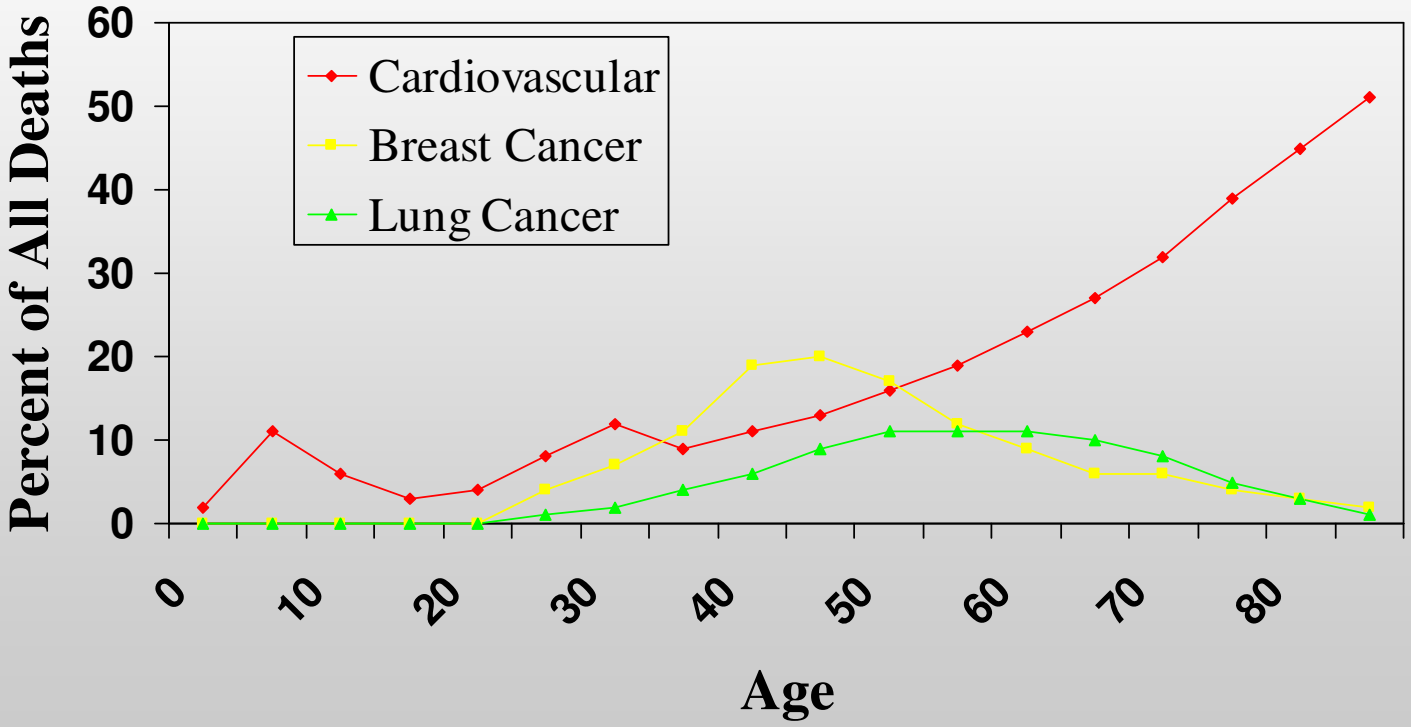


Percent of Nurses Health Study Above the High-Risk Cutoff Point
(5 yr Gail Score of 1.67%)

Rockhill et al.

What should compel Providers to be concerned with prevention

Age and Competing Causes of Death



Phillips, *et al,* NEJM, Vol. 340, No. 2, 1999

High Risk Patients Don’t Choose Tamoxifen

2/43 high risk patients chose to take Tamoxifen for breast cancer prevention

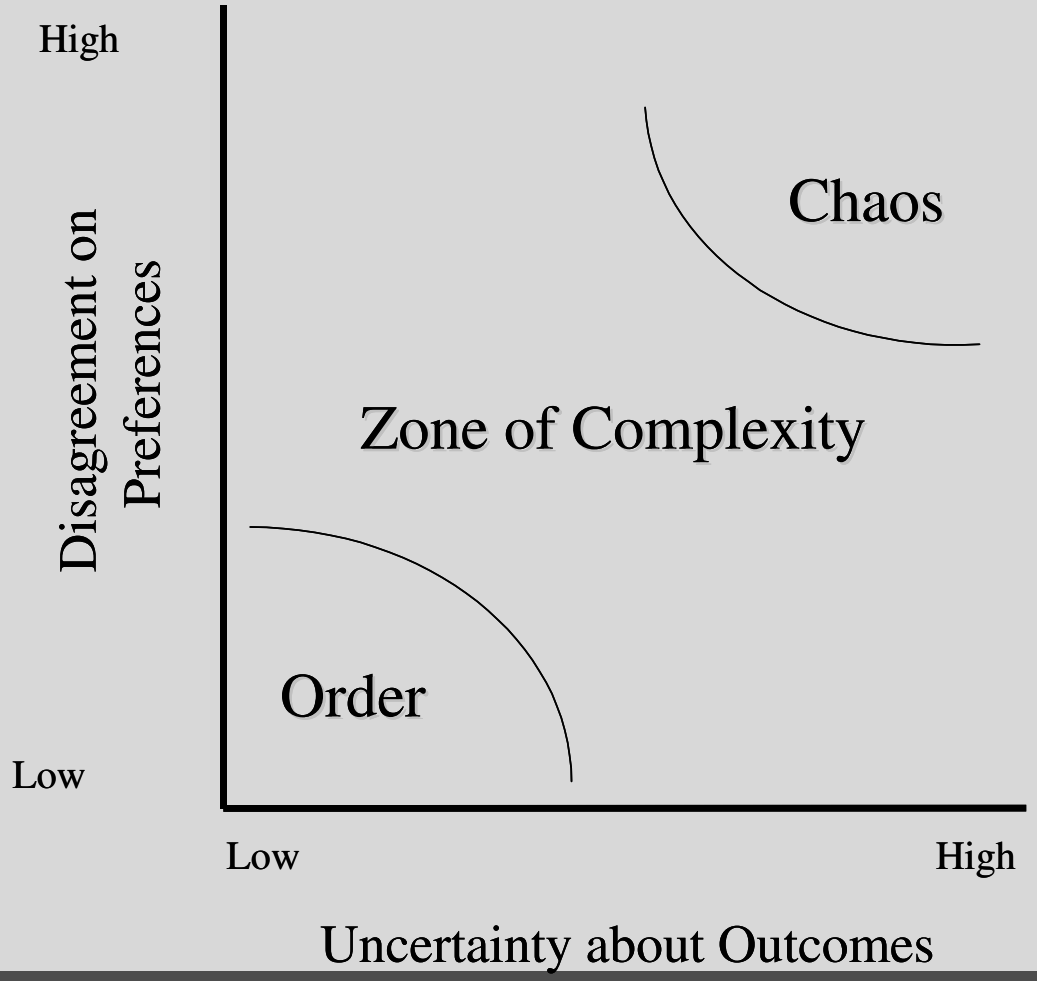
Educational sessions had no influence

Fear of side effects

**Rush Port E, et al Ann Surg Oncol, Vol.8, No. 7, 2001*

Decision Making in the Clinical Setting

Breast Cancer Prevention Decisions are complex



What compels women at high risk to consider an intervention?

1. Evidence that their risk is significant compared to others
2. Evidence that there is an intervention that will help THEM specifically
3. Evidence that the intervention will not have significant side effects
4. Evidence that the intervention is working

Improving the signal-to-noise ratio

Decision Analysis

- Decision aid strives to provide the basic elements of a decision: frame, alternatives, information, preferences and logic

Adult Learning

- Decision aids should let women choose what they want to learn
  - What are people ready to receive?
  - Layers of complexity (start simple, detail is optional)

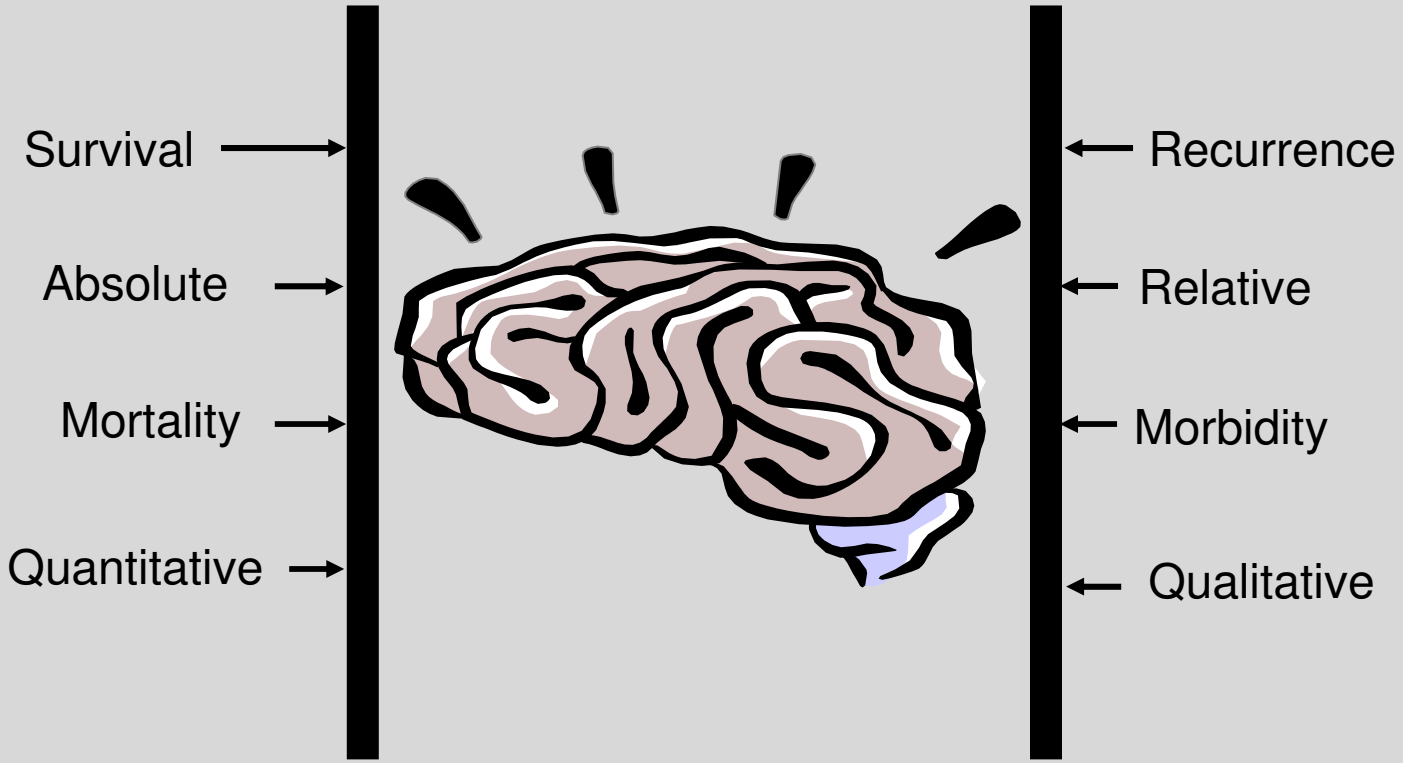
Cognitive Science (Tufte)

- Decision aid should use graphical formats that require the least amount of cognitive processing
  - Train people on small number of formats, stick to them

Risk Communication

- Relative risk presentations are confusing, misleading, and bias patients toward intervention

Potential for patient overload



Clinically Accessible Biomarkers

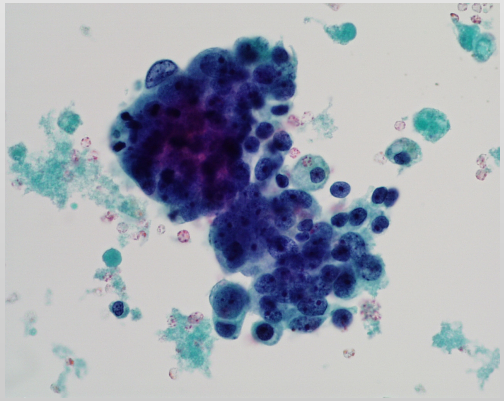
Biomarkers	Risk Discrimination	Detection Tool	Cost	Targeted intervention
Atypia	++	rFNA Ductal Lavage Open Bx	++ ++ +++	+Tamoxifen, ?AIs
Breast Density	++/+++	Mammo MRI	++ +++	?Soy, Tam?
Serum Estradiol	+	Blood Test	++	Tamoxifen, Raloxifen
Serum Testosterone	+	Blood Test	++	Tamoxifen, Raloxifen
LCIS	++	Bx MRI	++ +++	+Tam
DCIS	+++	Mammo MRI, Bx	++ +++	? Tam ?AI ?Statins ?IGFR1 ?
BRCA 1,2 mutations	++++	Blood Test	+++	Propylactic surgery, Tam (BRCA2), oophorectomy

Sources of atypical cells

Surgical biopsies
- incidental, not a method to detect biomarkers

Random Fine Needles Aspiration
- tolerable, associated with increased risk of Ca
- validated with 3-5 year outcomes

Nipple Aspirate Fluid
- cell yield poor (100's of cells)
- easy to obtain
- validated with 20 year outcome



Ductal Lavage
- clinical tools available
- feasible, but still expensive
- not validated, though similar to NAF and rFNA
- ? Sensitivity: DL on cancer patients + 20-30% of cases

Prevention Decision Model

Carol Franc Buck Breast Care Center | UCSF Medical Center

Elissa Ozanne, Laura Esserman

Learning About Your Risk

What is my risk of breast cancer?

Getting Perspective

How does my risk compare to other women?

Prevention Options

What can I do to lower my risk?

Risks and Benefits

Tests to learn more about breast cancer risks and benefits of therapies

Prevention Decision Model :

Learning About Your Risk:

What is my risk of breast cancer?

My Breast Cancer Risk Over Time

Anna Bella Smith	
Age	51
Number of years of HRT usage	none
Menopausal Status	Post

Gail Risk	
5 year	2.1%
Lifetime	17.3%

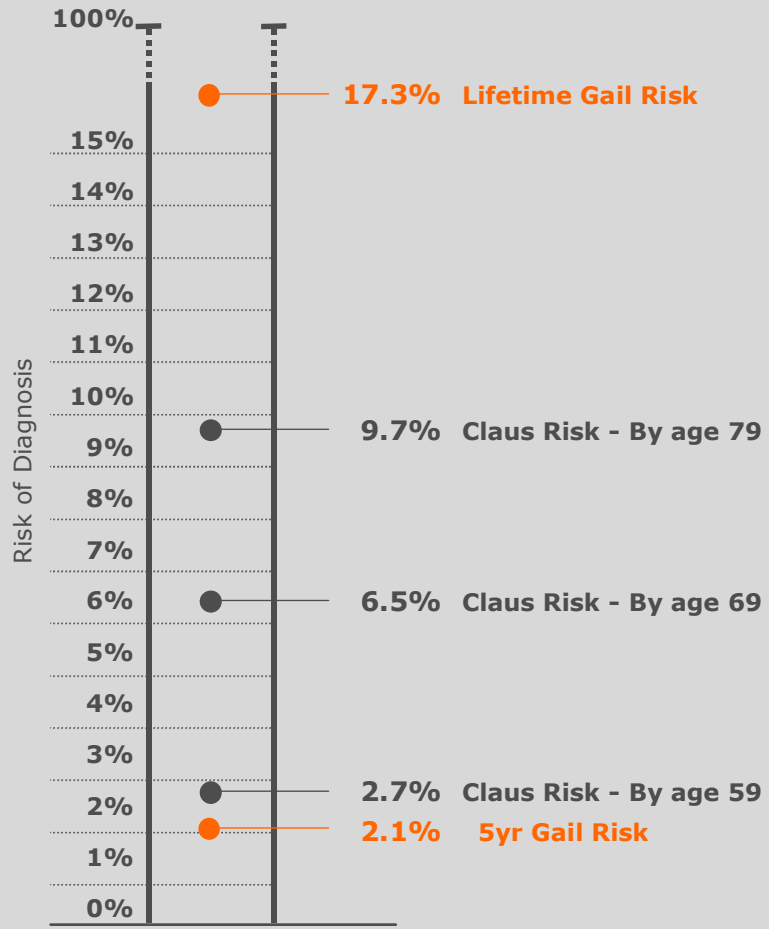
Claus Risk	
By age 39	NA
By age 49	NA
By age 59	2.7%
By age 69	6.5%
By age 79	9.7%

GAIL MODEL:
The Gail Risk Assessment Model is a statistical model for estimating the risk of developing breast cancer in women undergoing annual screening.This tool was developed to assist in providing women with a realistic and individualized risk estimate of short and long term breast cancer risk.

CLAUS MODEL:
The Claus model estimates the probability that a woman will develop breast cancer based on her family history of cancer. This includes the number of first and second-degree relatives with breast cancer and the age of cancer onset.

Source: Fisher B, et al, JNCI, vol 90, No. 18, 1998

My Breast Cancer Risk Over Time



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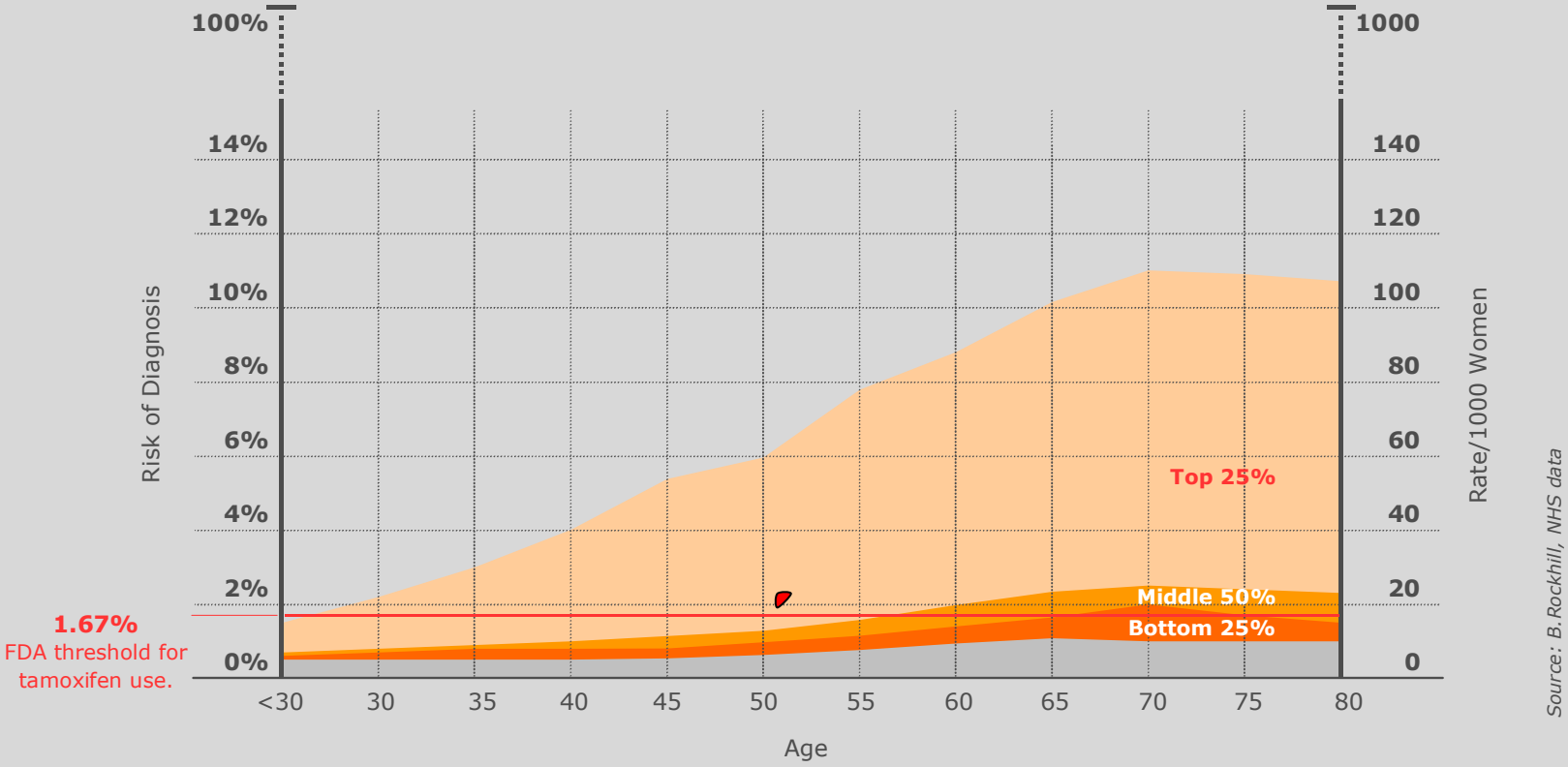
Prevention Decision Model :

Getting Perspective:

How does my risk compare to other women?

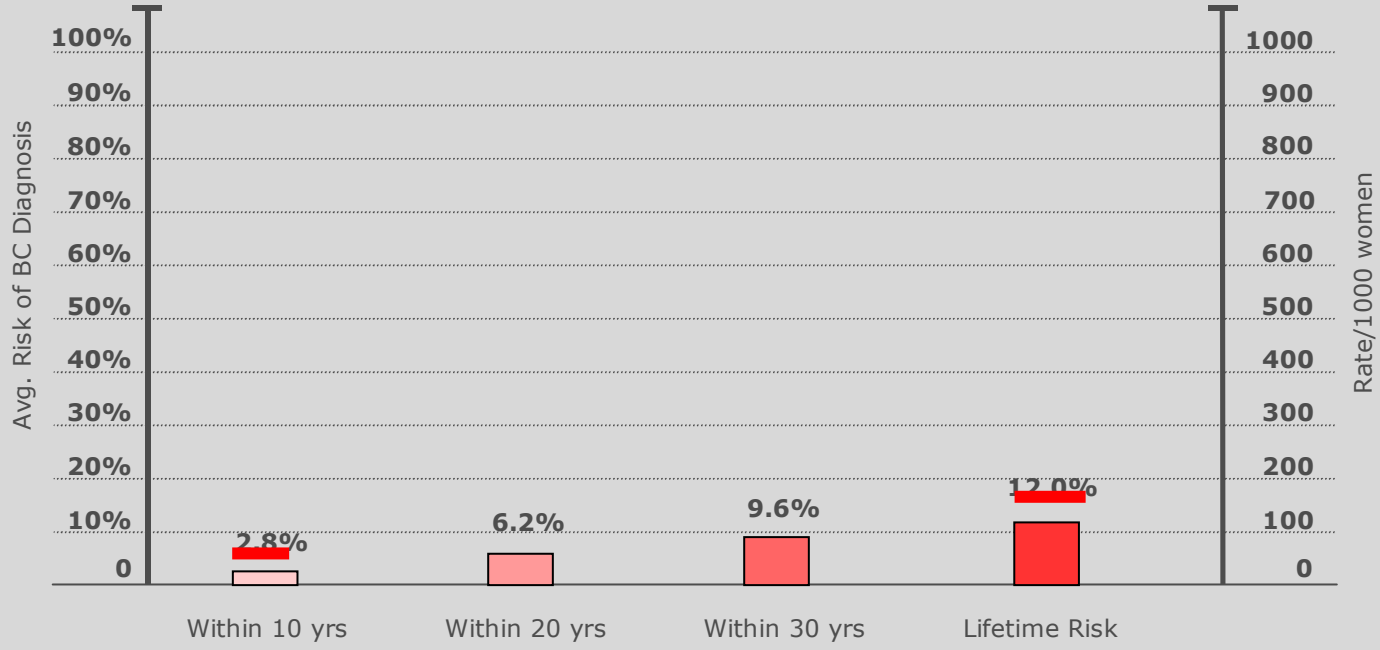
Prevention Decision Model : **Getting Perspective**

What Does My Gail Score Mean? What is My Risk Compared to Others?



EXAMPLE:
A 65 year old women with a five year Gail Score of 3% would fall somewhere in the top 25% of this distribution.

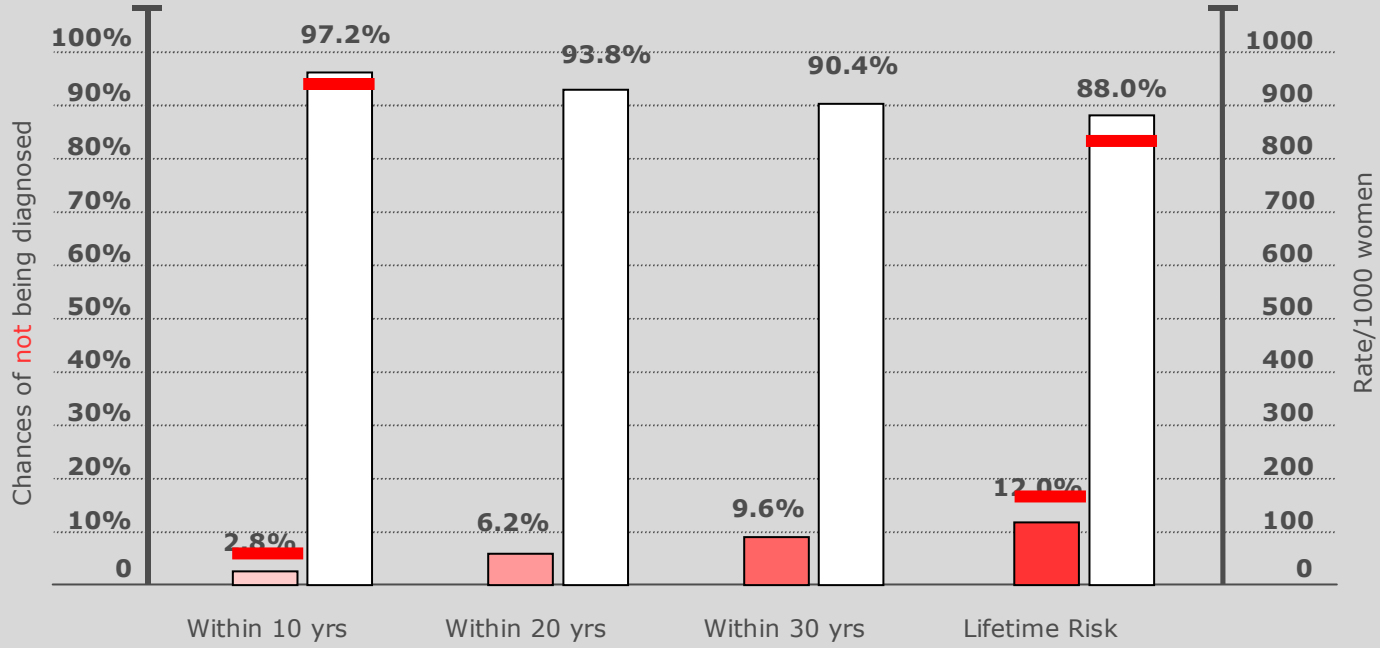
Average Risk of Breast Cancer Diagnosis for Women (Age 50~60)



Source: Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1973 - 1998.

Prevention Decision Model : **Getting Perspective**

Average Chances of NOT Being Diagnosed with Breast Cancer (Age 50~60)



Source: Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1973 - 1998.

In the next ten years, an average 50 year old woman has...

Risk of **Diagnosis** from:	
Breast Cancer	4.2
Risk of **Death** from:	
Breast Cancer	0.75-1.0%
Heart Attack	0.4 ~ 1.4%
Lung Cancer (smoker)	2.1 ~ 6.5%
Lung Cancer (non-smoker)	0.2 ~ 0.5%
Pneumonia (smoker)	0.1 ~ 0.2%
Accidents	0.2%

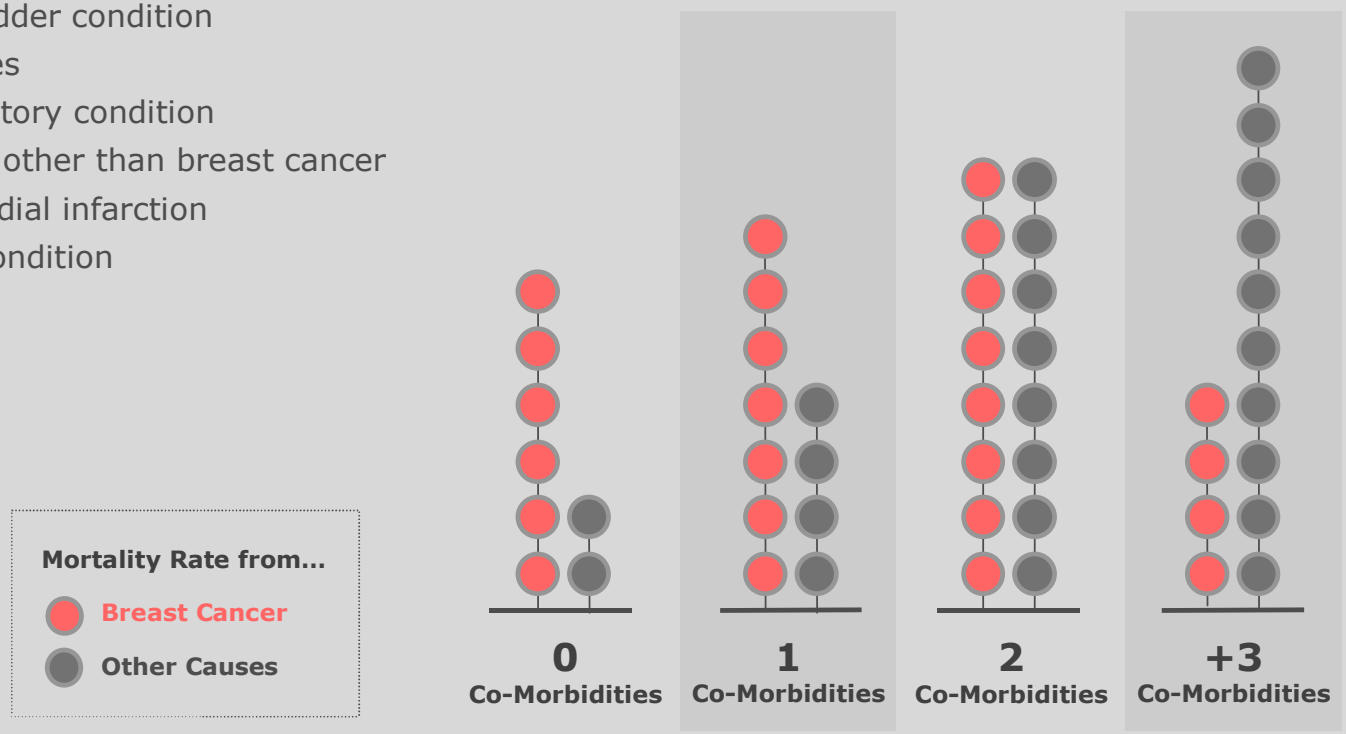
Other Risks **this year alone:**	
Increase in breast cancer for each year of HRT use	1 ~ 2%
Injured in an automobile accident	8%
Visit the doctor about the flu	38%

Source: Journal of the National Cancer Institute, Vol. 94, No. 11, June 5, 2002.

Comparison of Cause of Death by Number of Co-Morbidities for Women Diagnosed With Breast Cancer

If you develop breast cancer, your general health plays a big role.
Am I likely to die of breast cancer or other causes?

- Heart disease
- Gallbladder condition
- Diabetes
- Respiratory condition
- Cancer other than breast cancer
- Myocardial infarction
- Liver condition



Source: Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1973 - 1998.

Prevention Decision Model :

Prevention Options: What can I do to lower my risk?

Lifestyle Changes

These moderate modifications are recommended for all women as potential risk reduction strategies, in addition to vigilant surveillance.

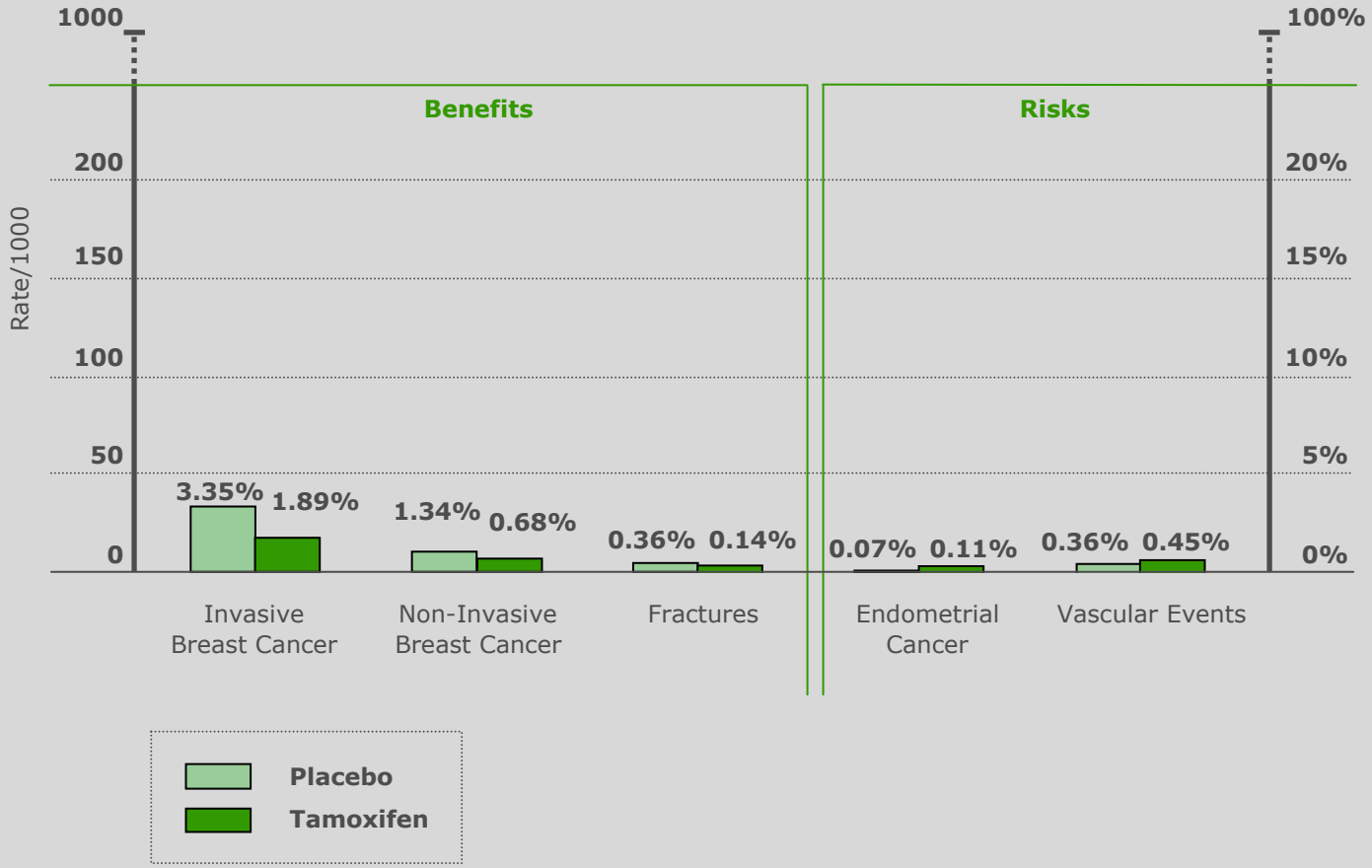
-Weight control
-No cigarette smoking
-Decreased alcohol consumption
-**Exercise**

Click **here** to learn about Hormone Replacement Therapy and Breast Cancer Risk.

Source: Ross D, 23rd annual San Antonio Breast Cancer Symposium, 2000: Summary by Pritchard, KI Vogel VG, Cancer Journal for Clinicians, Vol. 50, No. 3, 2000

Chemoprevention

Benefits and Risks of Tamoxifen Usage (Ages 35~49): 5 Year Estimates



Source: Gail, et al, JNCI, vol 91, No. 3, 1999

Chemoprevention

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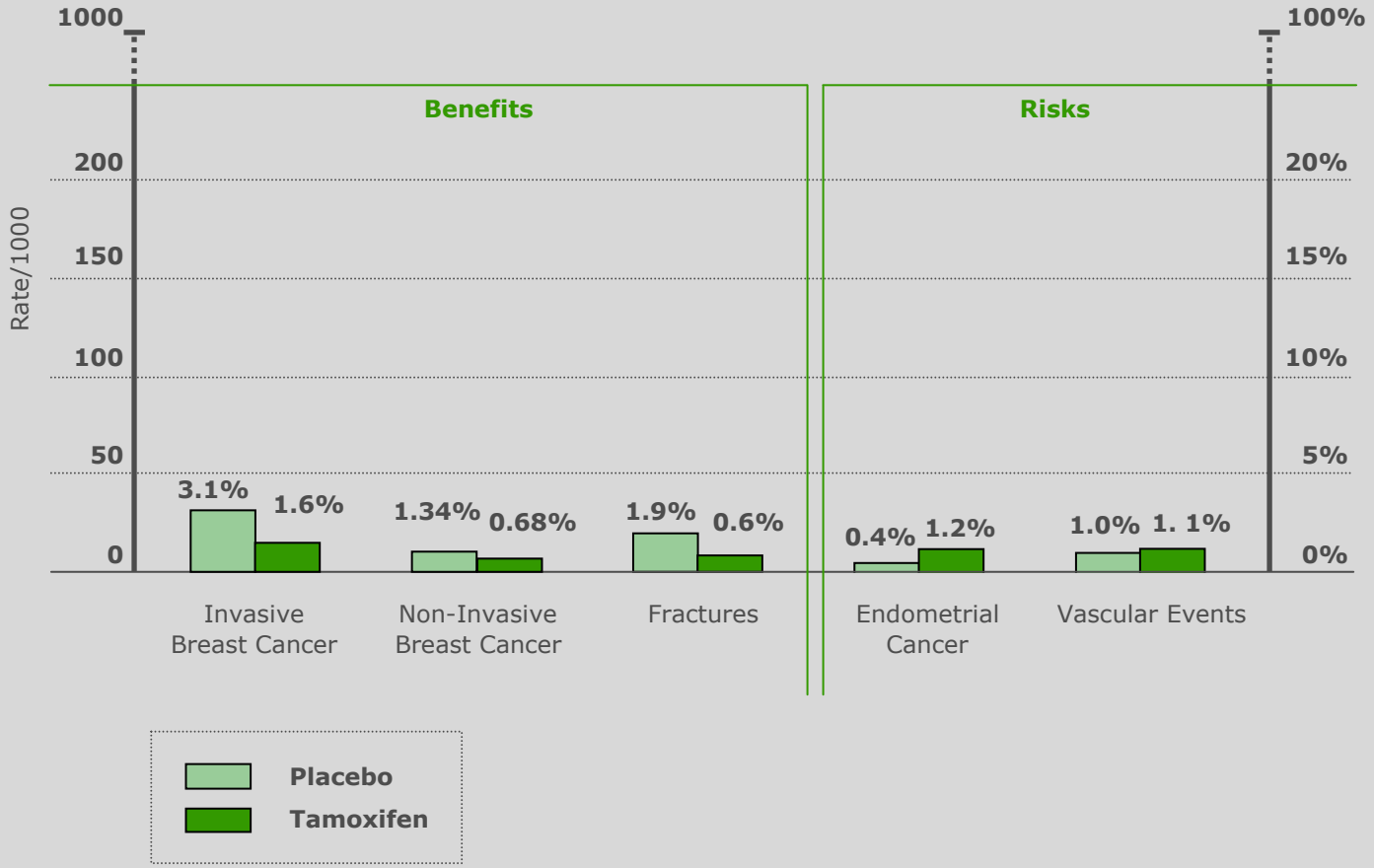
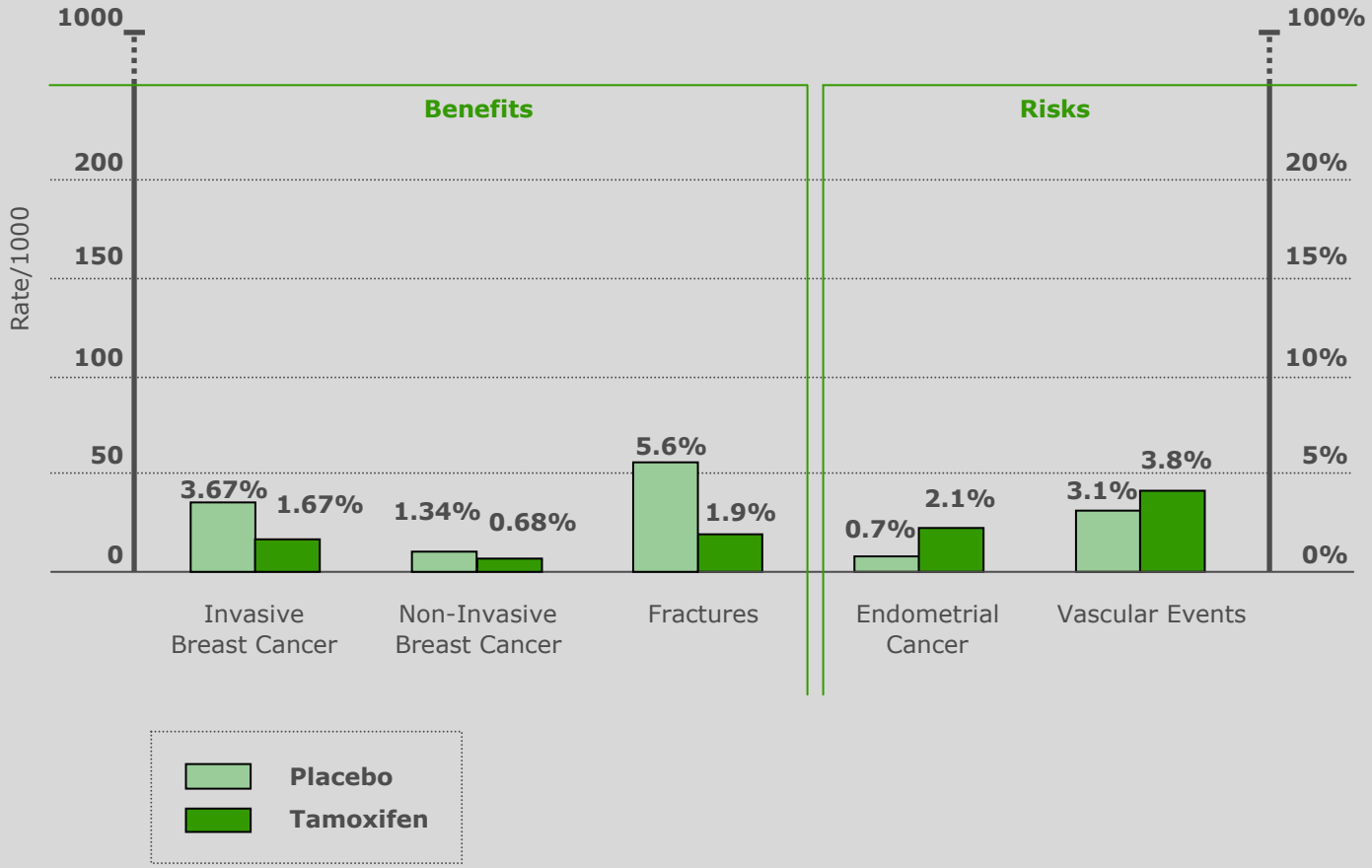


Source: Gail, et al, JNCI, vol 91, No. 3, 1999

Chemoprevention

Benefits and Risks of Tamoxifen Usage (Age 60+): 5 Year Estimates



Source: Gail, et al, JNCI, vol 91, No. 3, 1999

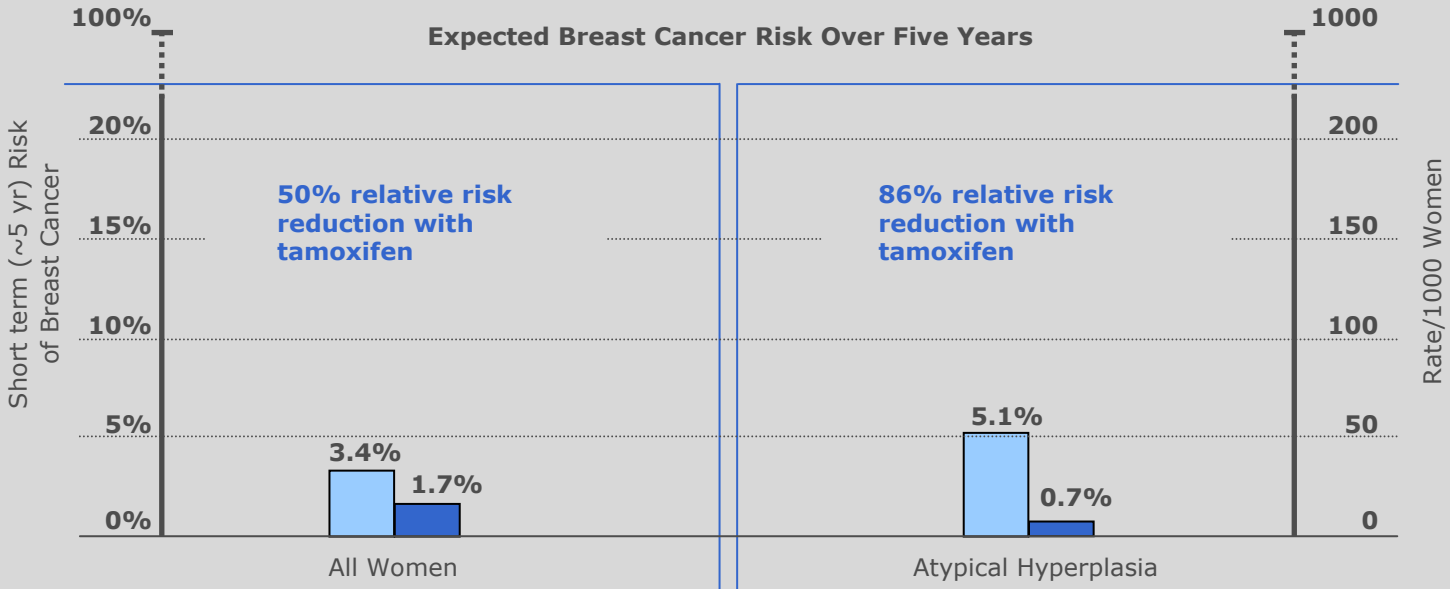
Prevention Decision Model :

Risks and Benefits:

Tests to learn more about breast cancer risks and benefits of therapies

Ductal Lavage and Fine Needle Aspiration

Atypical Hyperplasia Predicts Benefit from Tamoxifen



Women on tamoxifen had about 50% of the number of breast cancers seen in the placebo group – 50% relative risk reduction.

The absolute benefit is smaller - only 3.4% high-risk women are expected to develop breast cancer as compared to 1.7% in women using tamoxifen – 1.7% absolute risk reduction over 5 years.

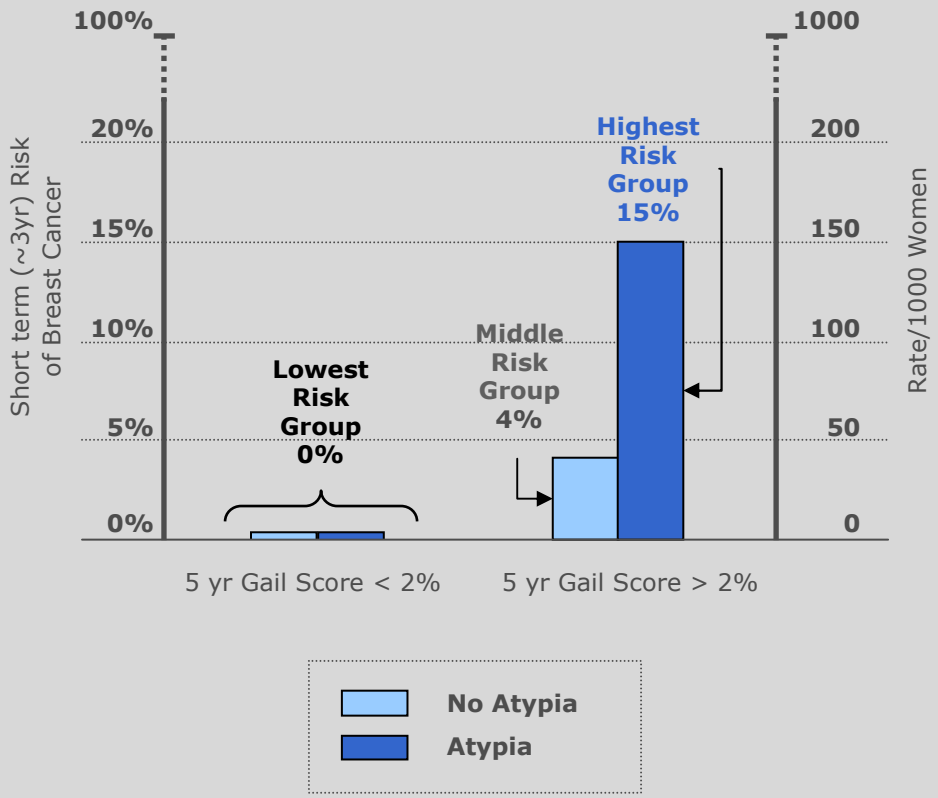
Women with atypical hyperplasia on tamoxifen had about 14% of the number of breast cancers seen in the placebo group – 86% relative risk reduction.

The absolute risk decreased from an expected 5.1% to 0.7% - a 4.4% absolute risk reduction over 5 years.

Source: Fisher B, et al, JNCI, Vol 90, No. 18, 1998

Ductal Lavage and Fine Needle Aspiration

Learning from Atypical Hyperplasia (AH)



Lowest risk group

For women with 5 yr Gail risk less than 2%, risk decreases to below 1% over 3 years for both women with AH and no AH.

Middle risk group

For women with 5 yr Gail risk greater than 2% but with no AH, risk is about 4% in 3 years.

Highest risk group

For women with 5yr Gail risk is greater than 2% with the presence of AH, risk is about 15% in 3 years.

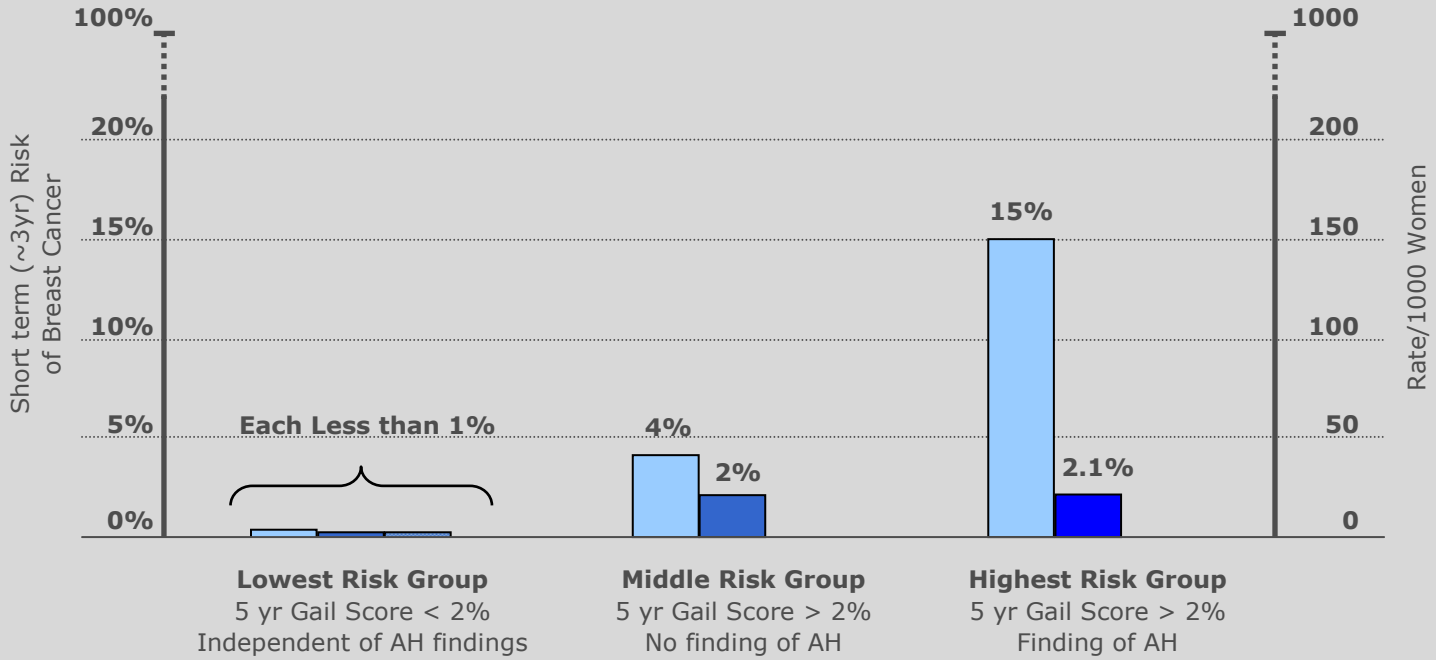
Source: Sauter, 1997; Fabian CJ, et al, JNCI Vol. 92, No. 15, 2000

Fabian JNCI 2001

Prevention Decision Model : **Risks and Benefits**

Ductal Lavage and Fine Needle Aspiration

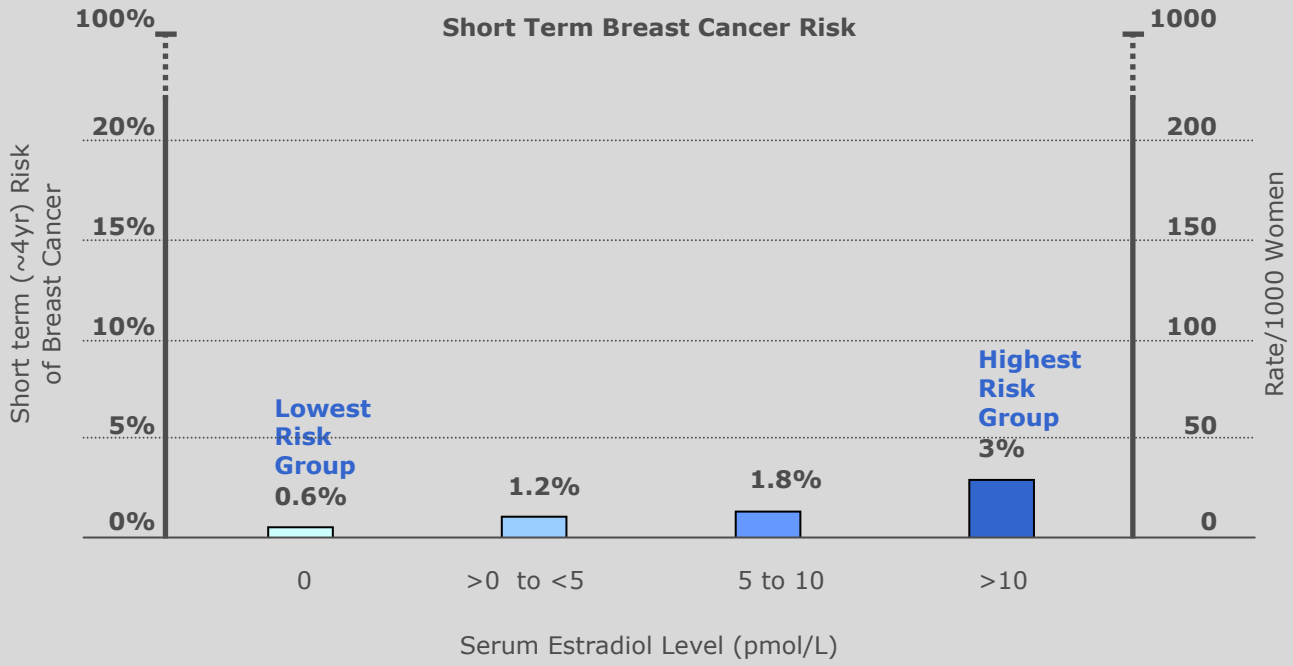
Atypical Hyperplasia and the Benefit from Tamoxifen



Source: Sauter, 1997; Fabian CJ, et al, JNCI Vol. 92, No. 15, 2000

Serum Estradiol

Learning From Serum Estradiol Level: Postmenopausal Women



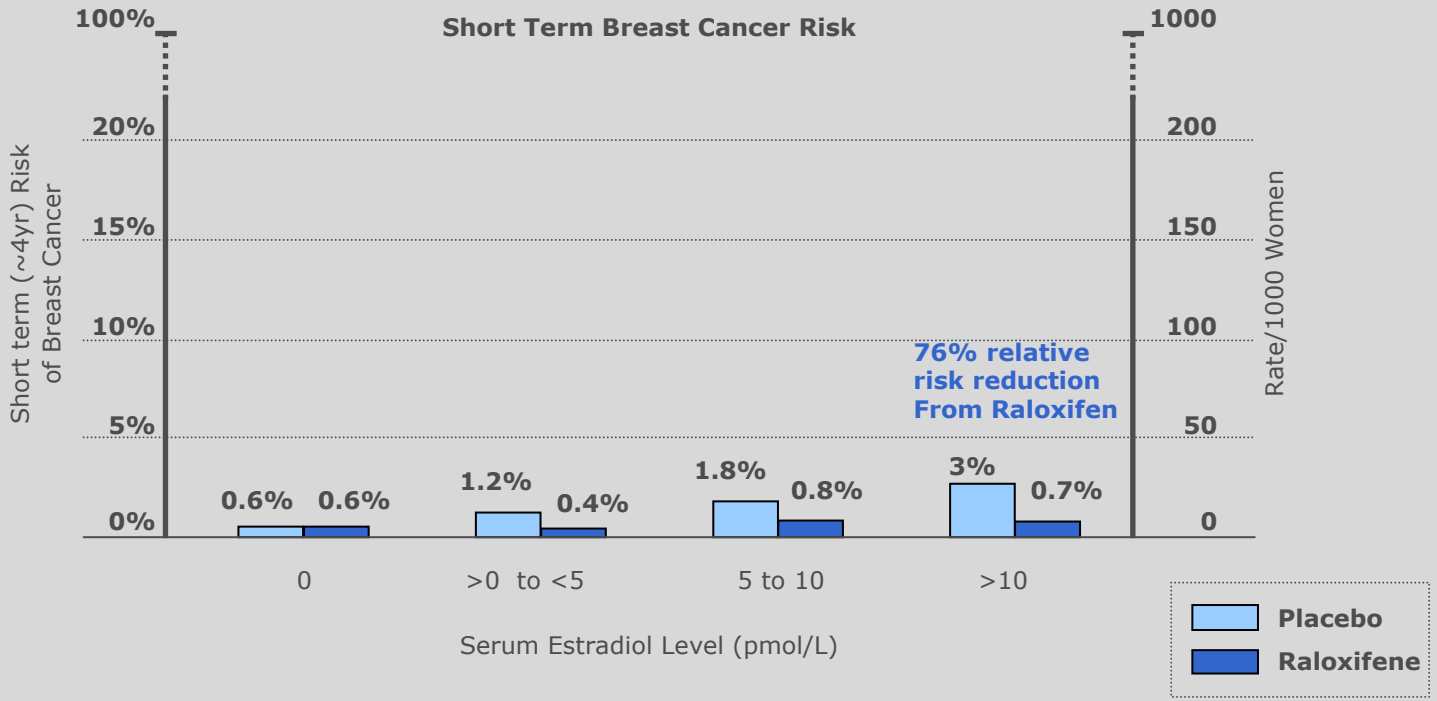
Source: Cummings S. et al, JAMA, 287: 22, 2002

Women with the highest estradiol level had about a three fold risk of breast cancer as compared to the women with the lowest estradiol level.

Higher hormone levels in the blood are associated with a higher risk of breast cancer.

Serum Estradiol

Learning From Serum Estradiol Level: Postmenopausal Women



Source: Cummings S. et al, JAMA, 287: 22, 2002

Women with the highest estradiol levels on raloxifene had about 24% the number of breast cancers seen in the placebo group. The absolute risk decreased from 3% to 0.7%. As hormone levels in the blood is higher, the benefits of raloxifene increase. Side effects of raloxifene are similar to those of tamoxifen but do not include endometrial events.

Genetic Testing

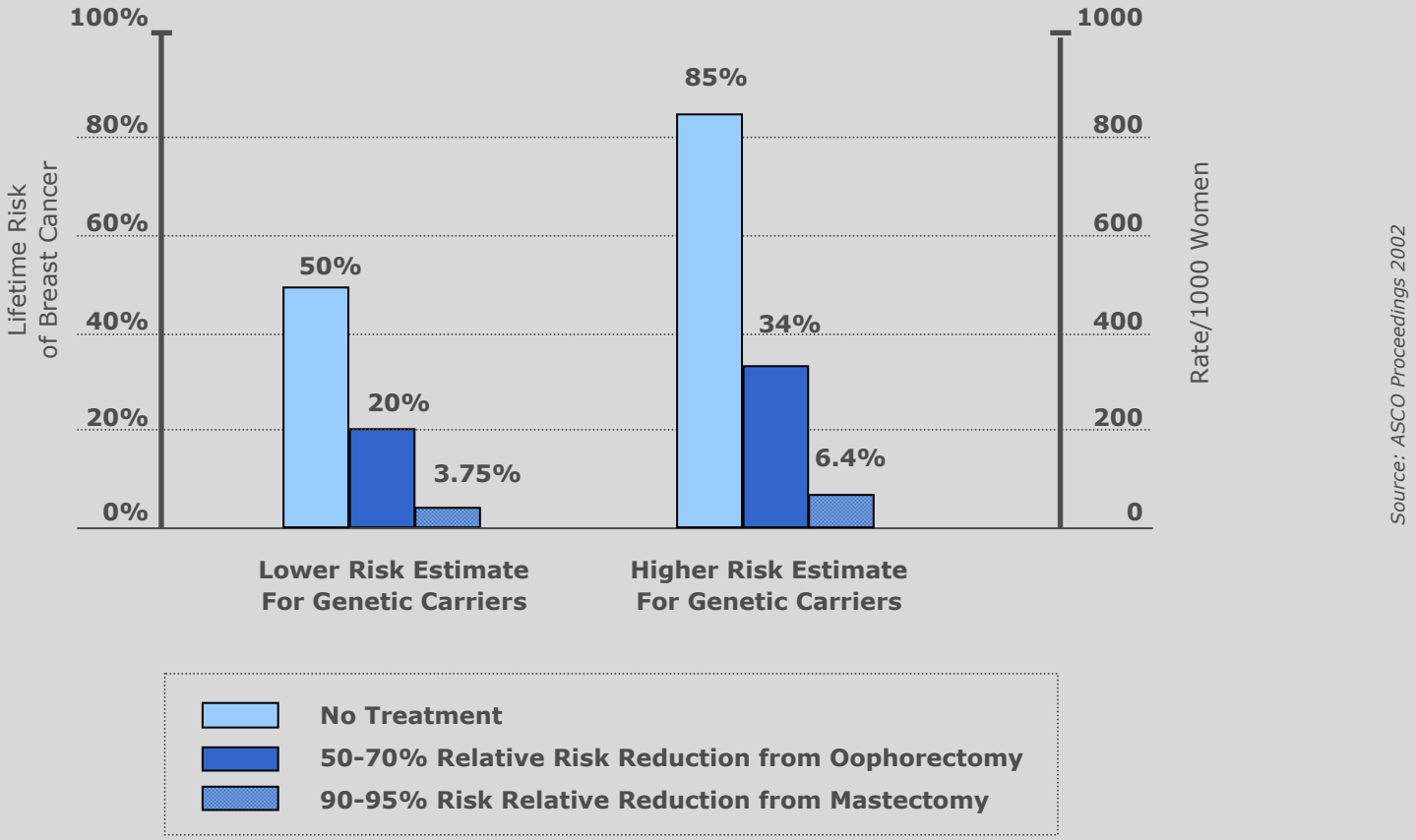
What Can My Genetics Tell Me About My Risk of Breast Cancer?

Associated Cancer	Lifetime Risk	
	BRCA1 Carriers	**BRCA2 Carriers**
Breast Cancer	50-85% (often at early onset)	50-85%
Second Primary Breast Cancer	40-60%	Unknown
Ovarian Cancer	15-45%	10-20%
Other Cancer Risks	Possibly prostate and colon	Unknown

Source: ASCO Proceedings 2002

Genetic Testing

Genetic Testing and the Benefit of Prevention Options



Source: ASCO Proceedings 2002

Insights

There is a critical need for dynamic models that enable us to assess the impact of interventions-

- that is what patients want

Biomarkers that predict effectiveness of interventions will increase willingness/motivation to accept interventions

There is a hierarchy of risk models

- e.g. BRCA trumps Gail
- Determines impact of and discussion about options,interventions

Risk that motivates patients to choose an intervention:

- 10-15% risk at 5 years
- Risk of recurrence after surgery for non-comedo DCIS
  10-12% at 5 years, 20% risk at 10 years
- Maybe DCIS is the best opportunity for prevention?

Cost Benefit Model

Elissa Ozanne PhD; Laura Esserman MD MBA

Goals

Understand value of biomarkers for breast cancer risk

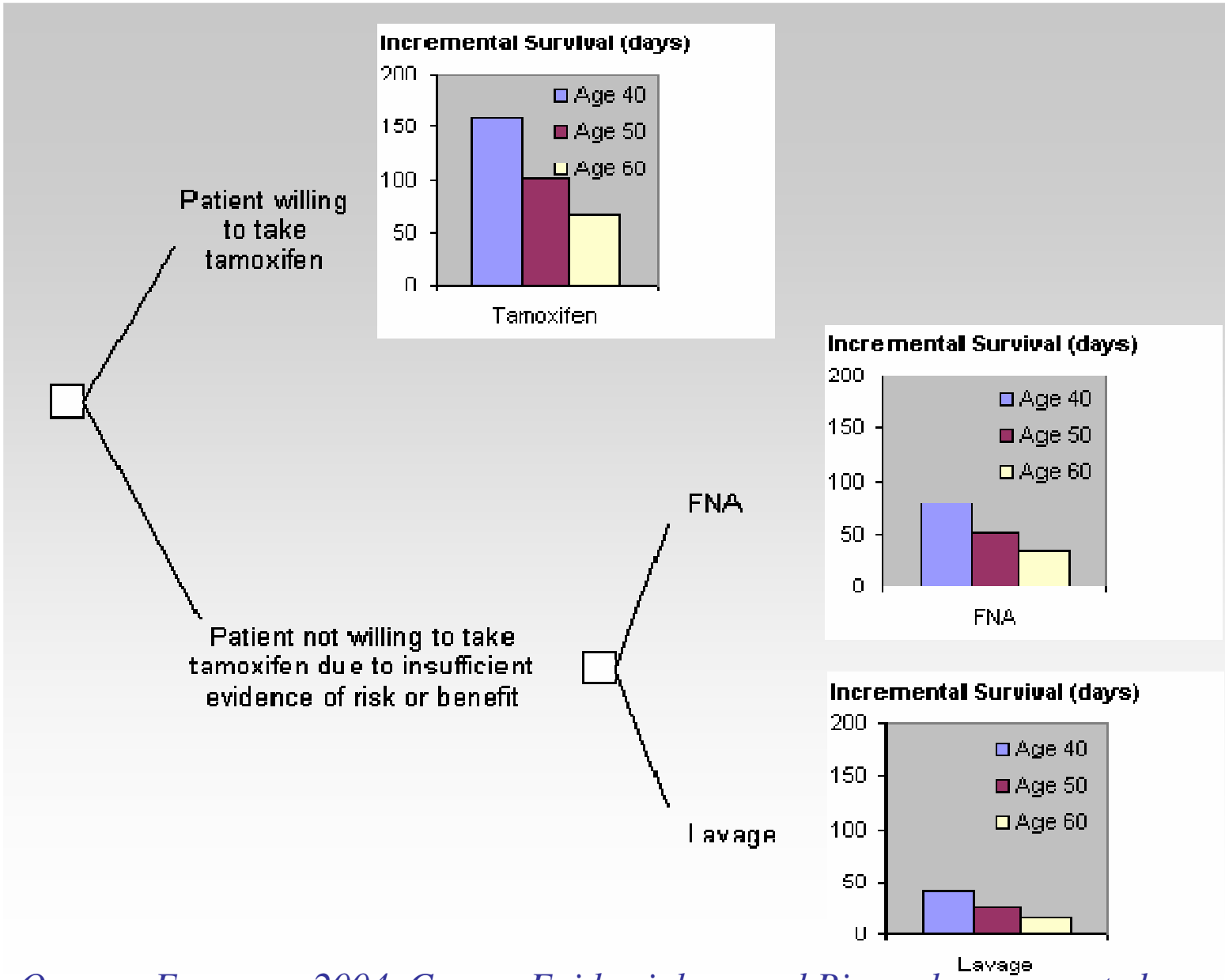
Evaluate cost effectiveness using atypia as an example

Methods

Markov model, evidence from clinical studies

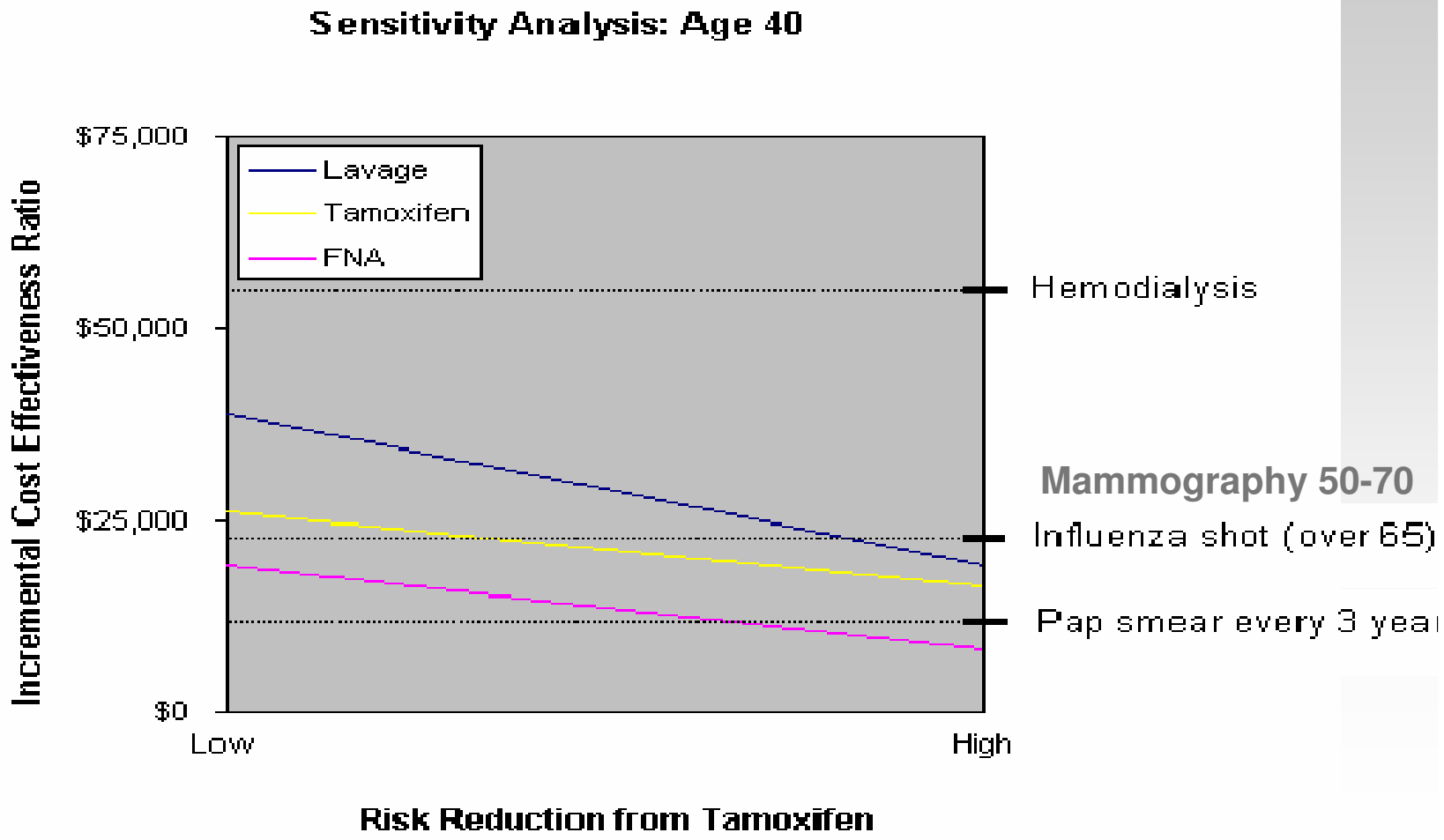
Strategies Examined:

1. 1. Screening: Routine screening (mammography) all women
2. 2. Tamoxifen: Tamoxifen therapy for all women
3. 3. Lavage: Attempt lavage, tam use if DL possible and atypia found
4. 4. FNA: 4 quadrant FNA all women, tam use only for atypia



Ozanne, Esserman 2004, Cancer Epidemiology and Biomarkers, accepted

Sensitivity

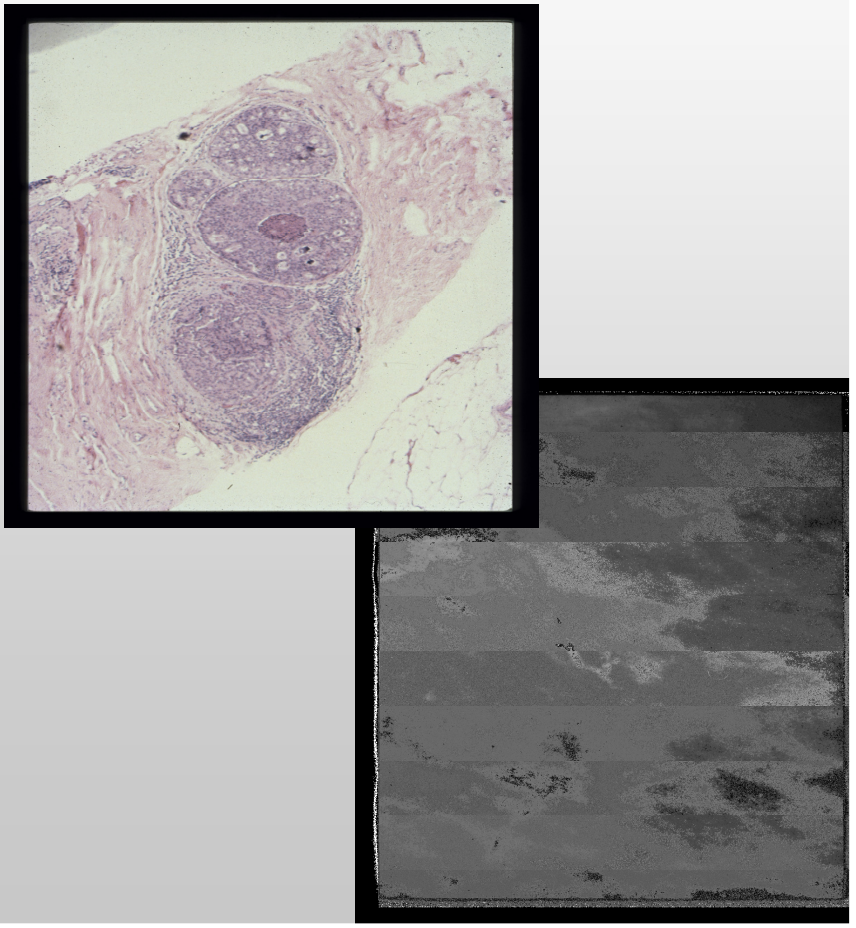


Insights on How Best to Use/Develop Biomarkers for Prevention

- Biomarker with an associated inexpensive, well tolerated way to measure and assess it
- Safe, inexpensive, health promoting intervention that can be targeted to the biomarker or some other factor to predict likelihood of benefit
- Short term assays for measuring impact

What is the yearly hazard rate for progression to cancer for . . .

	Annual Hazard
DCIS	1-3%
Atypia Gail Risk > 2 Gail Risk < 2	 4% 1%
LCIS family history none	 1-2% 0.5-1%
BRCA1/2	1-5%
5 yr Gail Risk >5	1-2%
60 yr old Gail <2	0.3-0.5%
CBC for pt with Ca	0.5%



How do the treatments vary? . . .

	Treatment
DCIS	BCS BCS + XRT BCS + XRT+Tam Mastectomy
Atypia Gail Risk > 2 Gail Risk < 2	 Screen Tam Bilat Mastectomy
LCIS family history none	 Screen Tam Bilat Mastectomy
BRCA1/2	Screen Oophorectomy Tam Bilat Mastectomy
High Risk *Gail>1.7; Inv Ca*	Screen Consider Tam

What makes DCIS treatment hard to change?

- Perspective not optimal
- ***Poor*** *understanding of Risk, timing of progression*

What is the harm in waiting?

Survival: *impact < 1%*

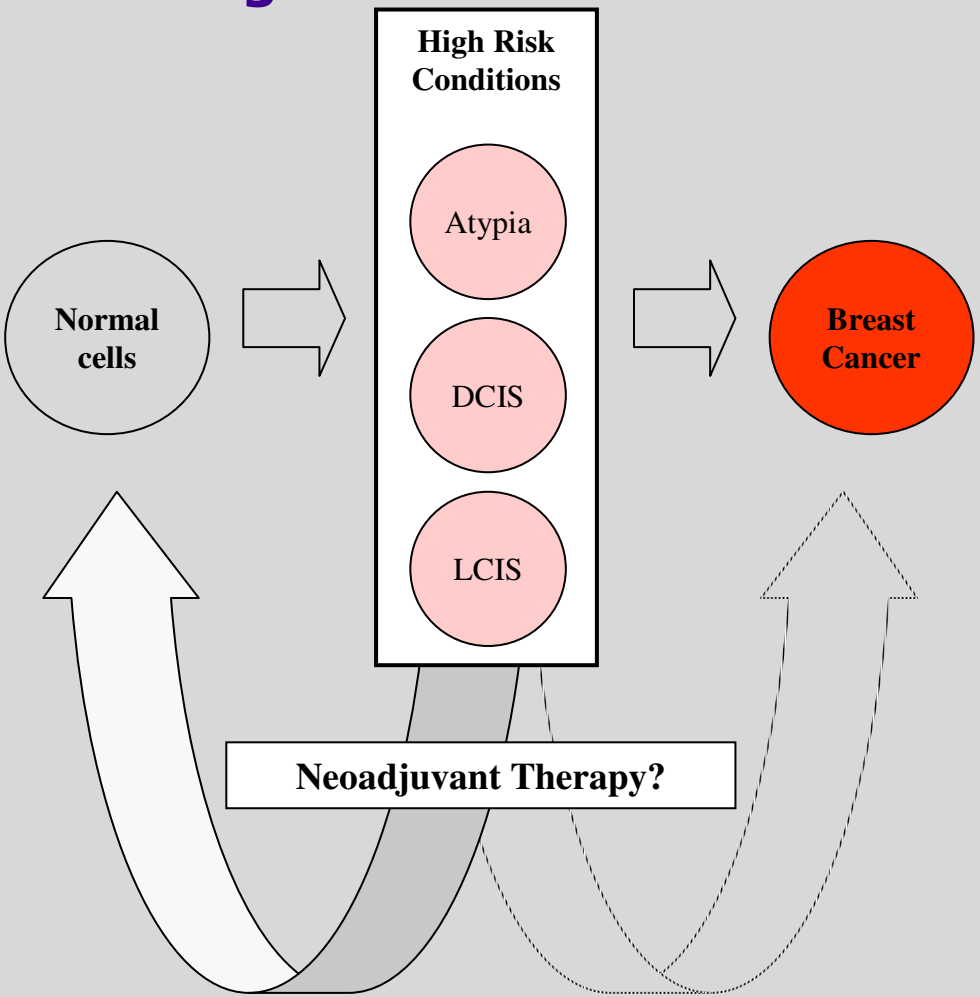
Emotional: *Women, physicians, are risk averse*

Standard of Care: *hard to choose different option*

What would change care?

- Risk models/Tools to characterize risk of DCIS progression
- Tools to track change
- Pre-operative interventions to assess change, impact of interventions

Prevention Paradigm



Improvements

The Prevention Tool we developed is a physician decision aid

- evidence is organized using common outcome: Risk at 5,10 years

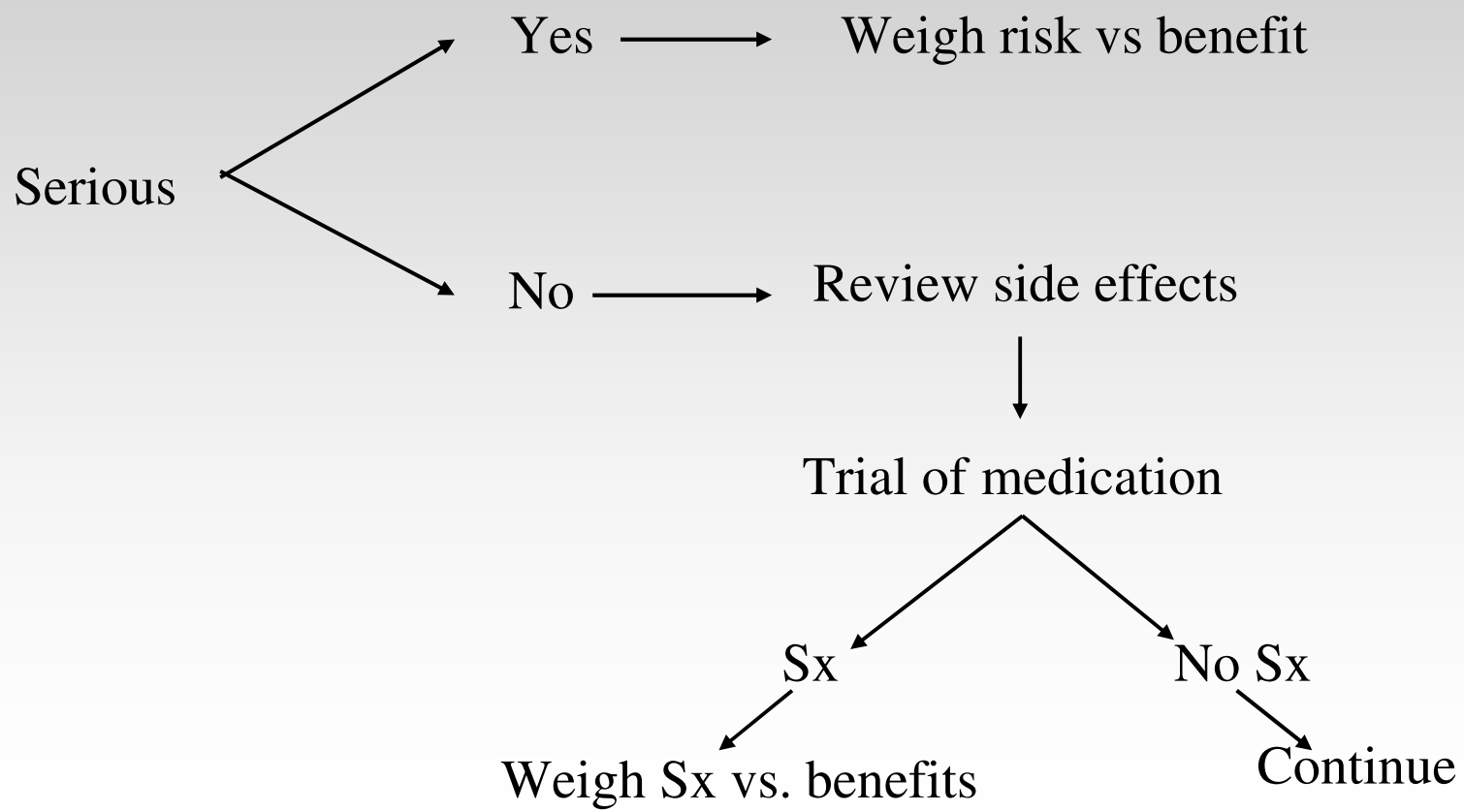
Patient Physician Aids should include more layering of information

- Decisions can be layered by side effects: serious vs. QOL

Trial of tool vs. not

- desire for risk stratification
- choice of interventions

Side Effects



A Good Decision Aid

Enables insight

Facilitates dialogue among providers, patients, families

Reduces confusion

Motivates change in approach based on personal preferences

Requires models that provide risk in perspective, and enable tailoring of risk based on interventions