

Breast Cancer Heterogeneity: Providing the Need and the Rationale for Molecular Profiling

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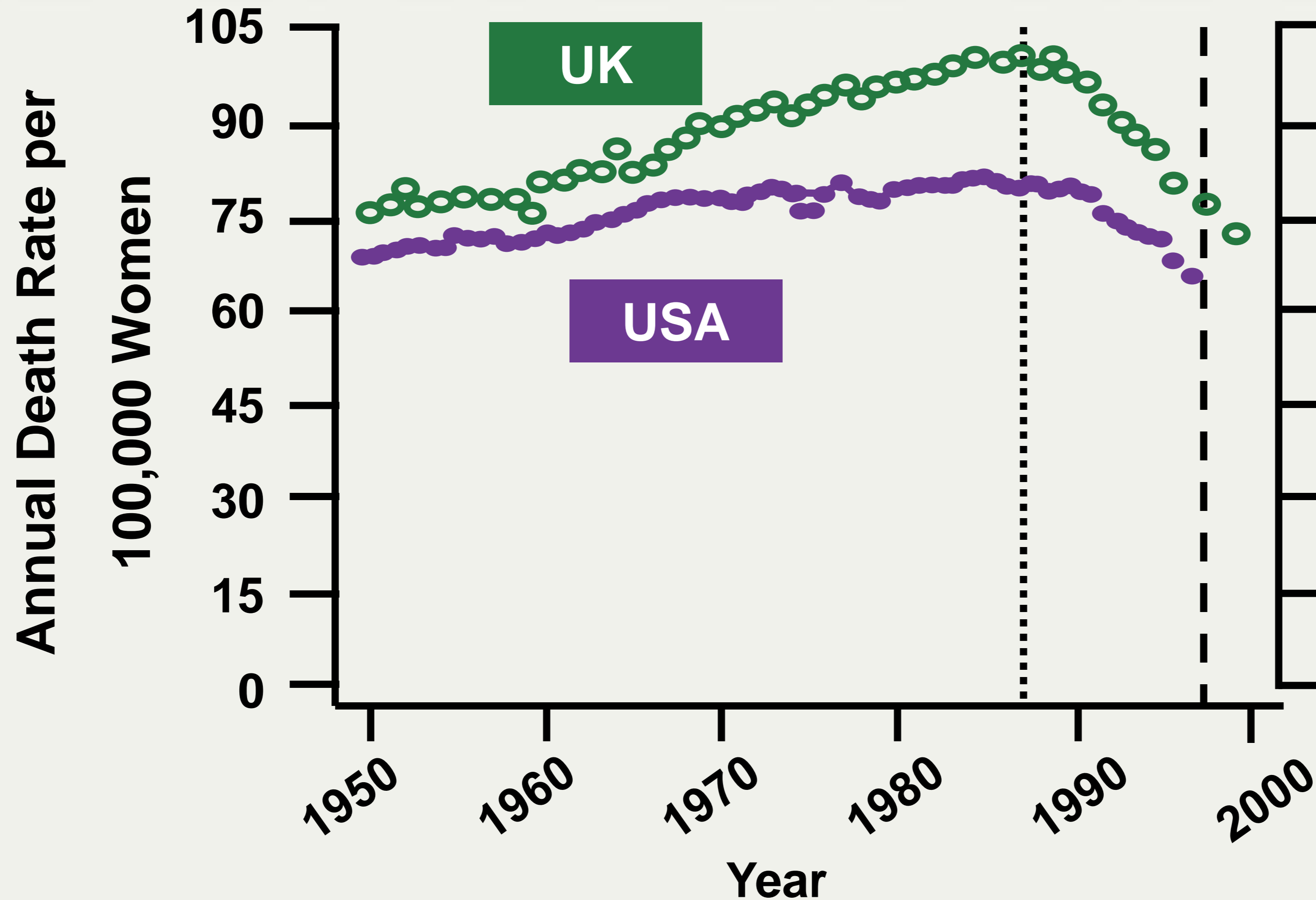
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**Can we distinguish the good apples from
the bad apples?**

Recent Decrease in UK and USA Breast Cancer Mortality at Ages 50-69 Years



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History of Adjuvant Systemic Therapy

- Should All Patients Receive All Therapy?
 - Depends on:
 - Prognostic and Predictive Factors
 - Patient's, Doctor's, and Society's Perspectives Regarding Risks, Benefits, and Costs of Therapy
 - No patient with invasive breast cancer has a **zero** chance of recurrence and death
 - No patient has a **zero** chance of benefit from any therapy
- If pt is willing to accept ANY toxicity for ANY benefit: *then treat her with everything*
- If pt is willing to forego SOME benefit to avoid SOME toxicity: *then select therapy carefully*

NIH Consensus Conference 2000

“All women with tumor > 1cm should be considered candidates for adjuvant chemotherapy irrespective of nodal status, biologic features, exact size.”

Personalized Medicine for the Patient with Breast Cancer

Assess Risk of
Recurrence and
Death from
Breast Cancer

Characterize the
Risks and Toxicities
of Treatment

Quantify the
Benefits of Treatment
For the Individual



Prognostic Factor Significance

- Used to make decisions about who to treat
- Limitations of current factors
 - 70% node-negative patients are long-term disease free in absence of systemic therapy
 - Guidelines recommend treat up to 90% node-negative patients
- Aim of newer prognostic factors
 - To better individualize treatment recommendations

Prognostic Factor Definition

- Predicts outcome in absence of systemic therapy
- Thus, tells us when (not how) to treat a patient
- Reflects biological characteristics of the tumor, such as ability to proliferate, invade, and induce angiogenesis

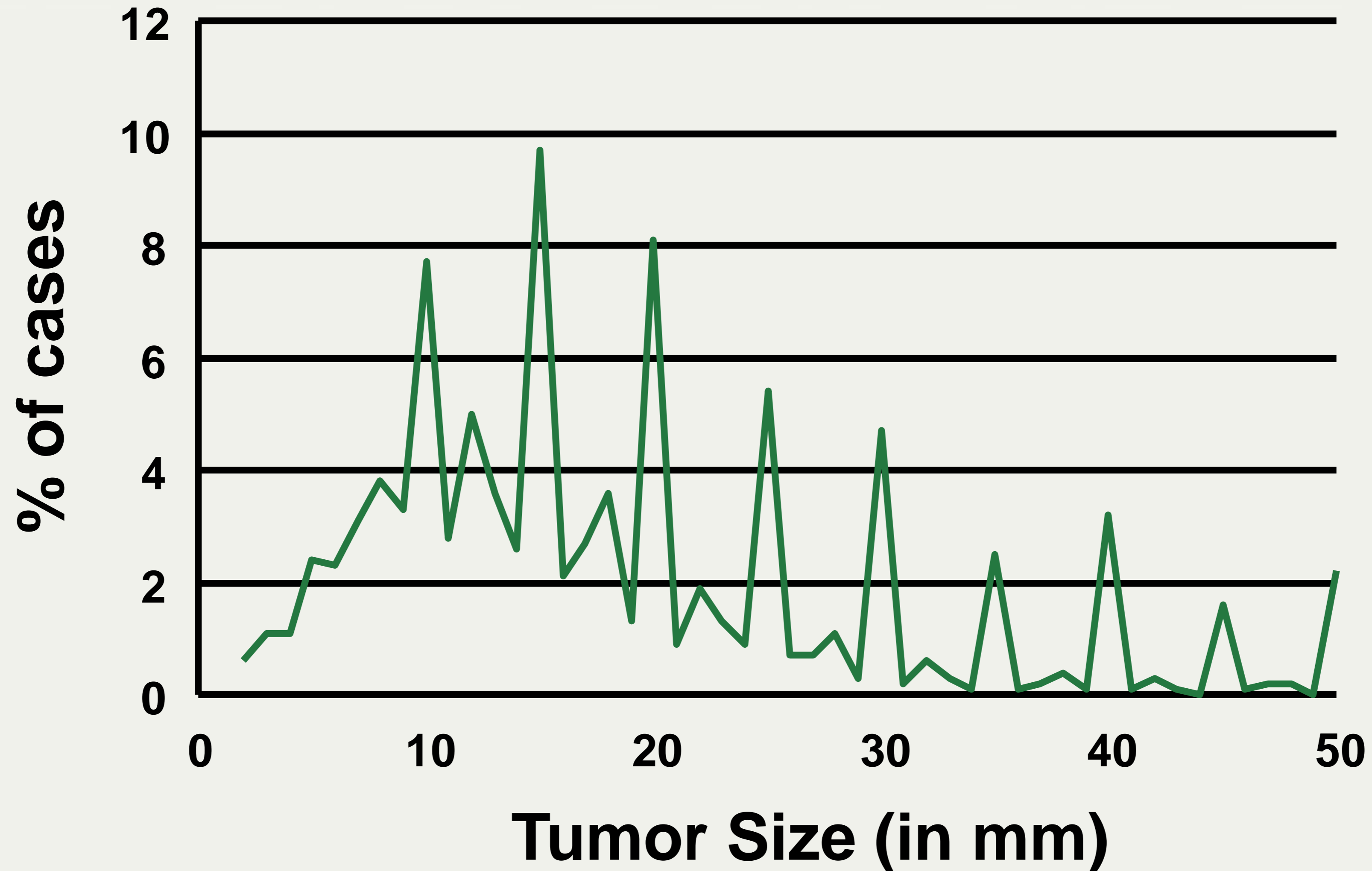
Ideal New Prognostic Factor

- Biologically plausible
- Provides prognostic data independent of accepted prognostic factors
- Ideally, evaluated in systemically untreated patients (difficult!)
- Detectable by validated, reproducible, feasible, standardized method
- Validated in prospective trial

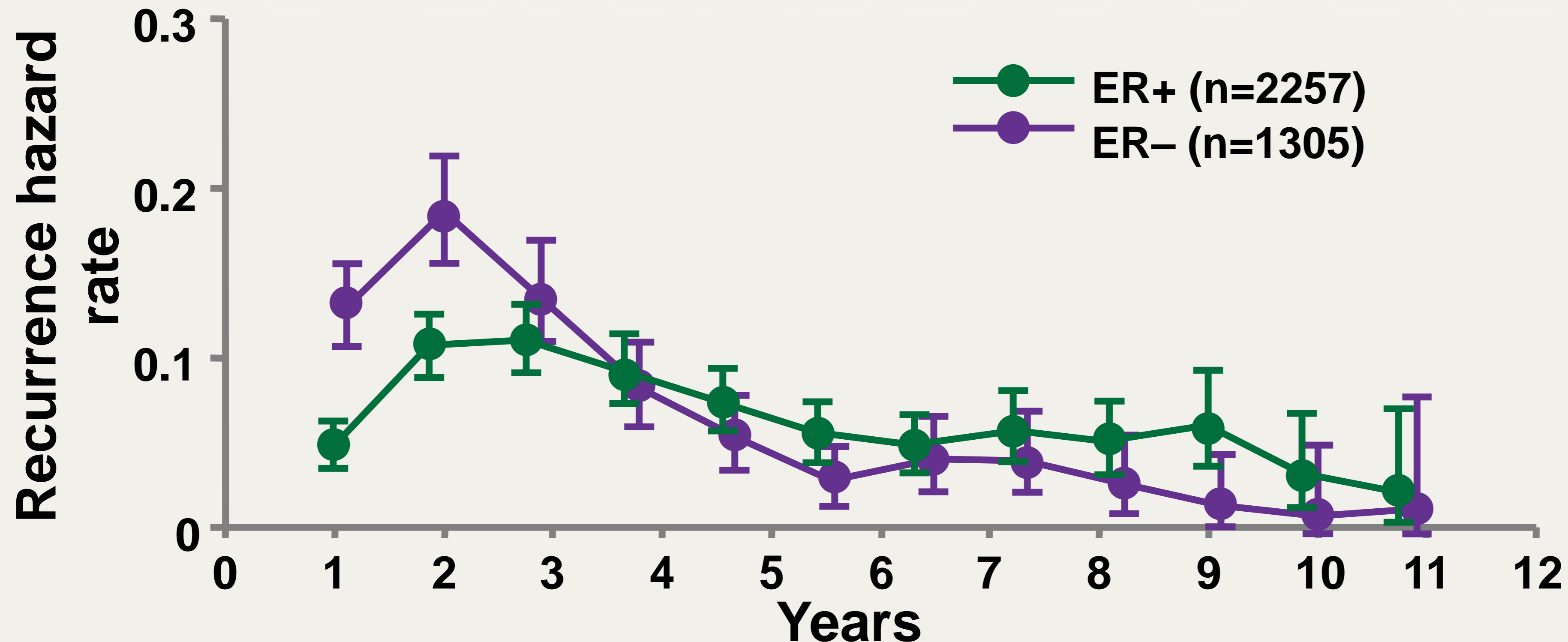
Prognostic Factors

- Standard Factors
 - Nodal Status
 - Tumour size
 - Histologic type
 - ER
 - HER2
- Frequently utilized factors
 - Tumour grade
 - Lymphovascular invasion
 - Proliferative index

Node-Negative Breast Cancer Grows in 5mm Increments! (SEER 1995, 1996)

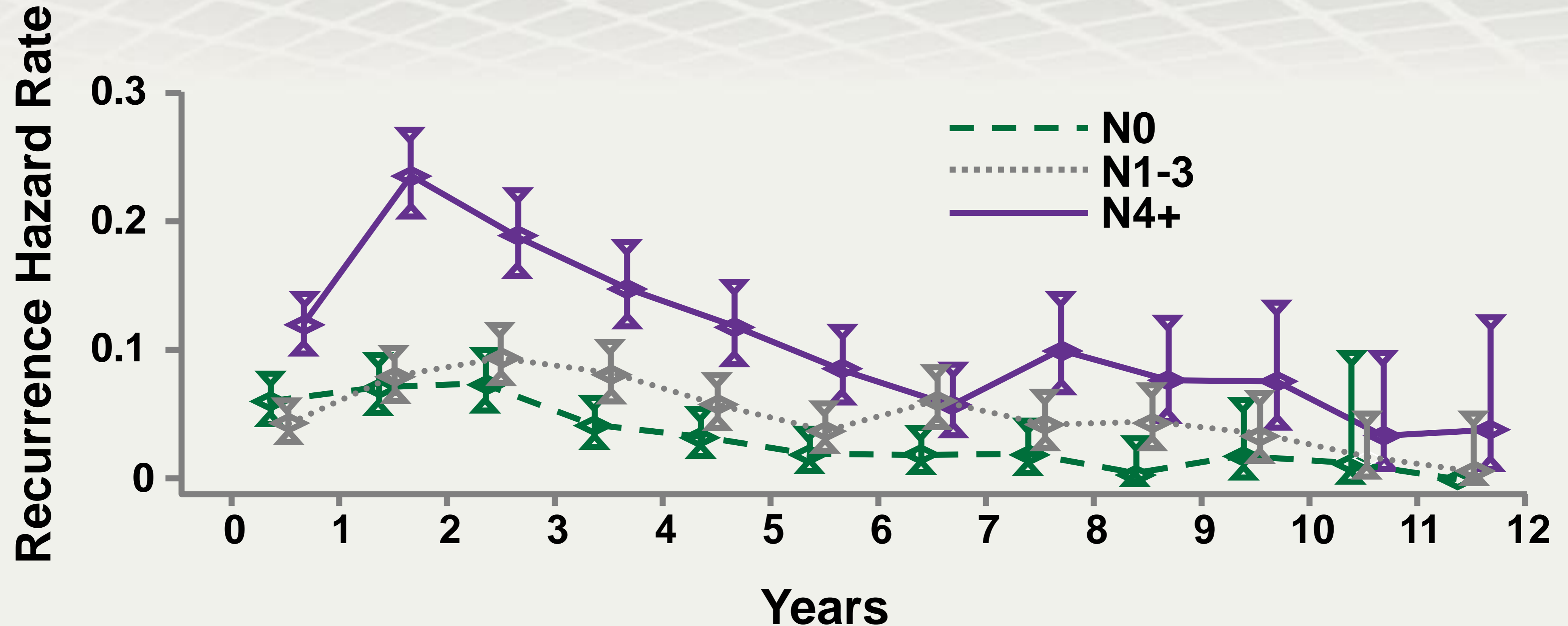


Annual Risk of Recurrence by Hormone Receptor Status



- A substantial proportion of breast cancer recurrences occur >5 years postsurgery
- The annual risk of late recurrence is higher in ER+ tumors

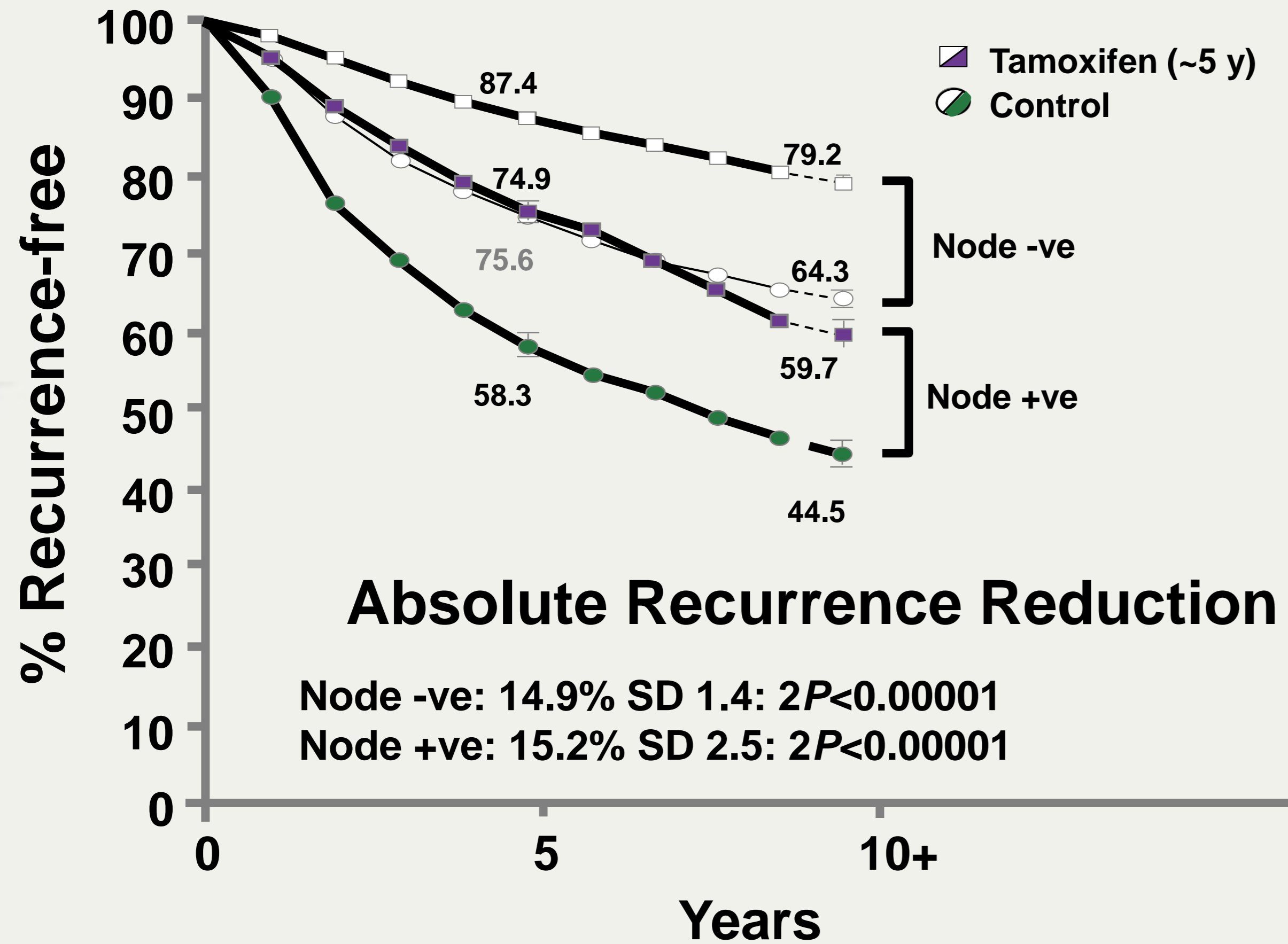
Annual Risk of Recurrence by Nodal Status



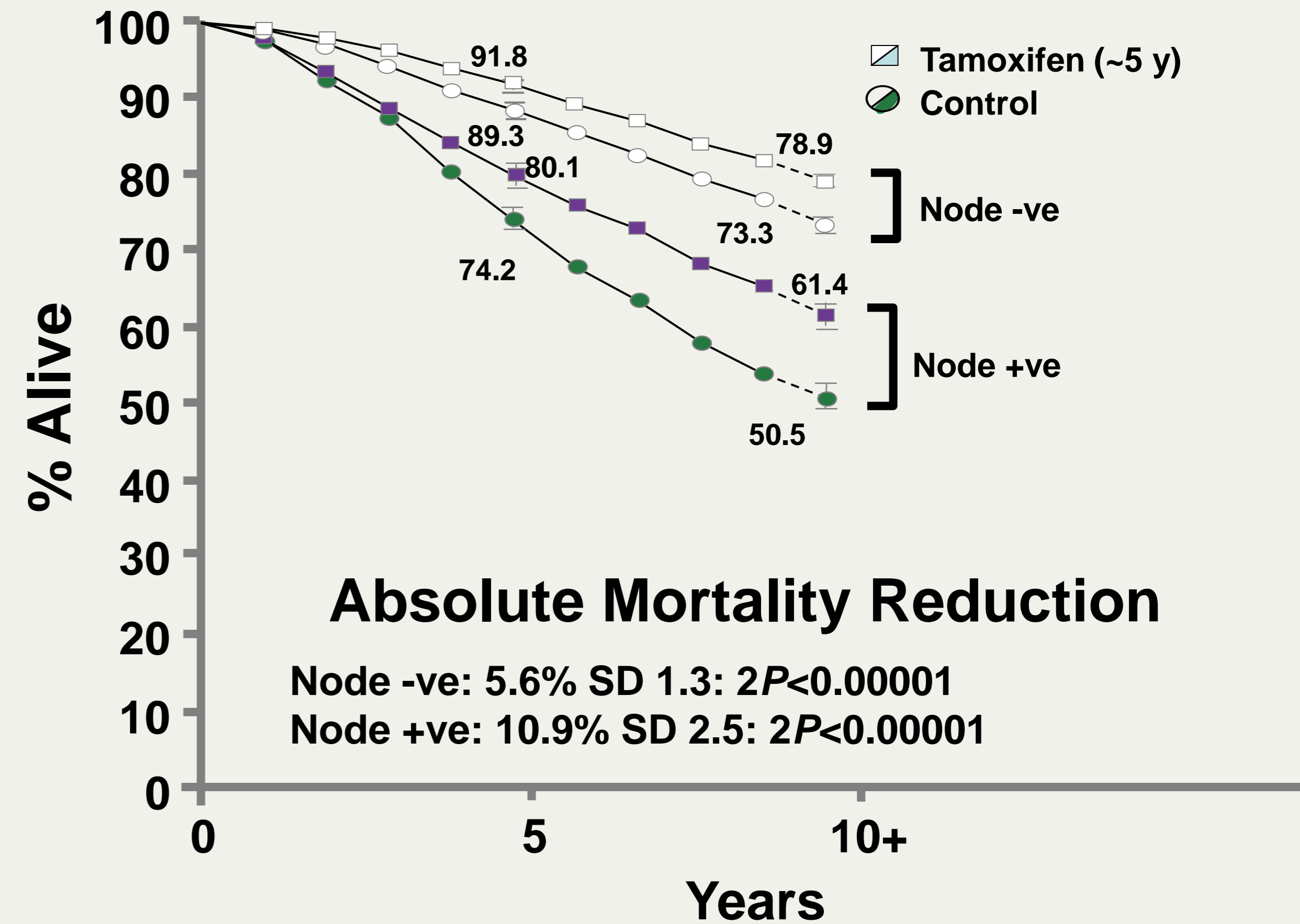
- The risk of late recurrence remains substantial even in patients with node-negative tumors

Meta-Analysis: A Substantial Part of Recurrences Occur After Tamoxifen Therapy

Recurrence as First Event



Mortality From Any Cause



Reproducibility of Tumor Histological Grade

		Pathologist B		
		Well	Moderate	Poor
Pathologist A	Well	105	114	5
	Moderate	24	241	31
	Poor	3	82	63

Concordance = 61%

		Pathologist A		
		Well	Moderate	Poor
Pathologist C	Well	76	31	0
	Moderate	140	221	52
	Poor	8	44	96

Concordance = 59%

		Pathologist B		
		Well	Moderate	Poor
Pathologist C	Well	56	50	1
	Moderate	74	309	30
	Poor	2	78	68

Concordance = 65%

Overall Concordance = 43%

Prognostic Factors

- Newer Factors
 - Adjuvant! Online
 - Gene expression profile
 - Recurrence score

Adjuvant!

Adjuvant! for Breast Cancer

Adjuvant!

System Notices

Breast Cancer

Colon Cancer

Online Resources

Downloads

Personal Info.

Log Out

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:

Chemo:

Hormonal Therapy:

Chemotherapy:

Combined Therapy:

No additional therapy:



53.9 alive and without cancer in 10 years.

44.7 relapse.

1.4 die of other causes.

With hormonal therapy: Benefit = 16.5 without



With chemotherapy: Benefit = 11.9 without relapse

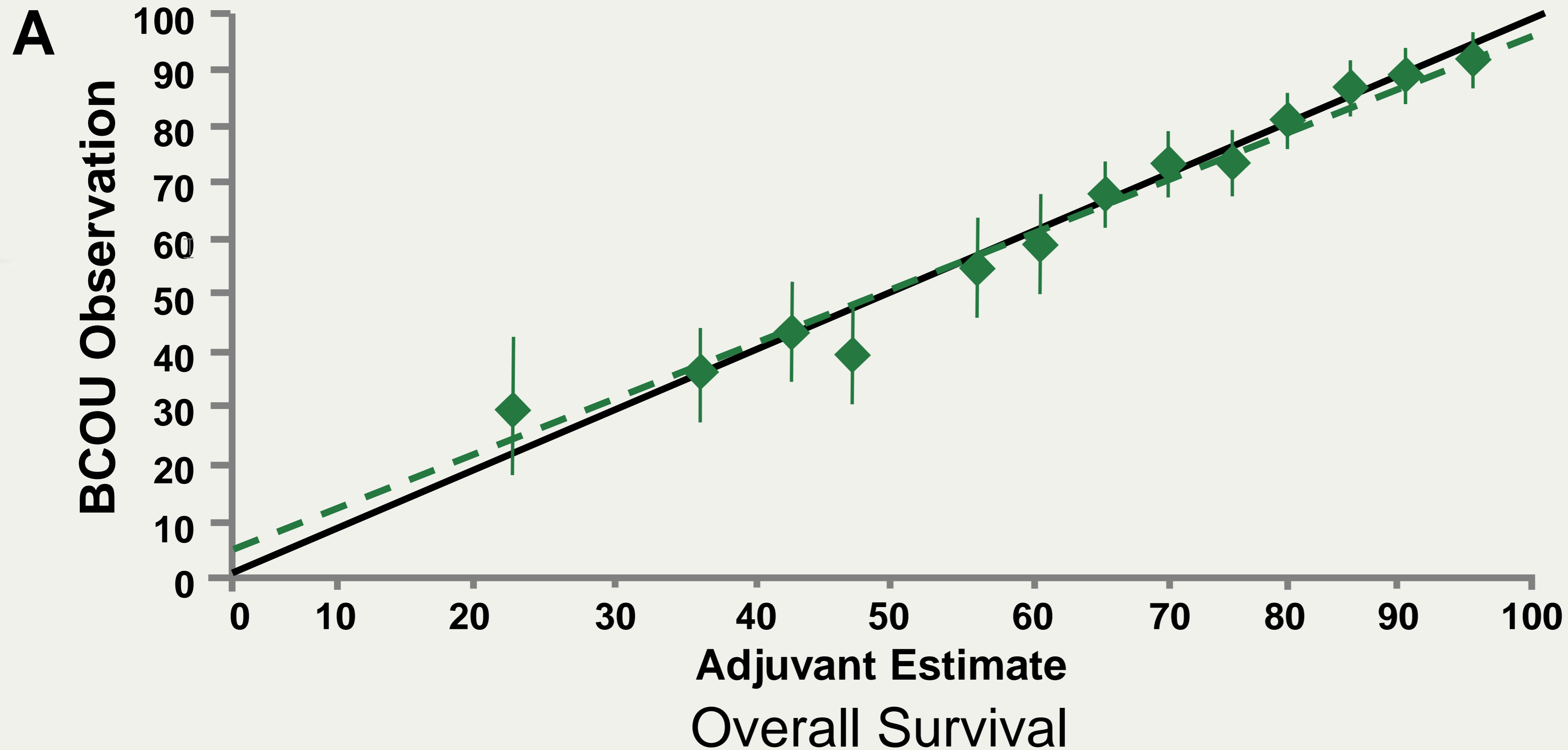


With combined therapy: Benefit = 24.4 without relapse



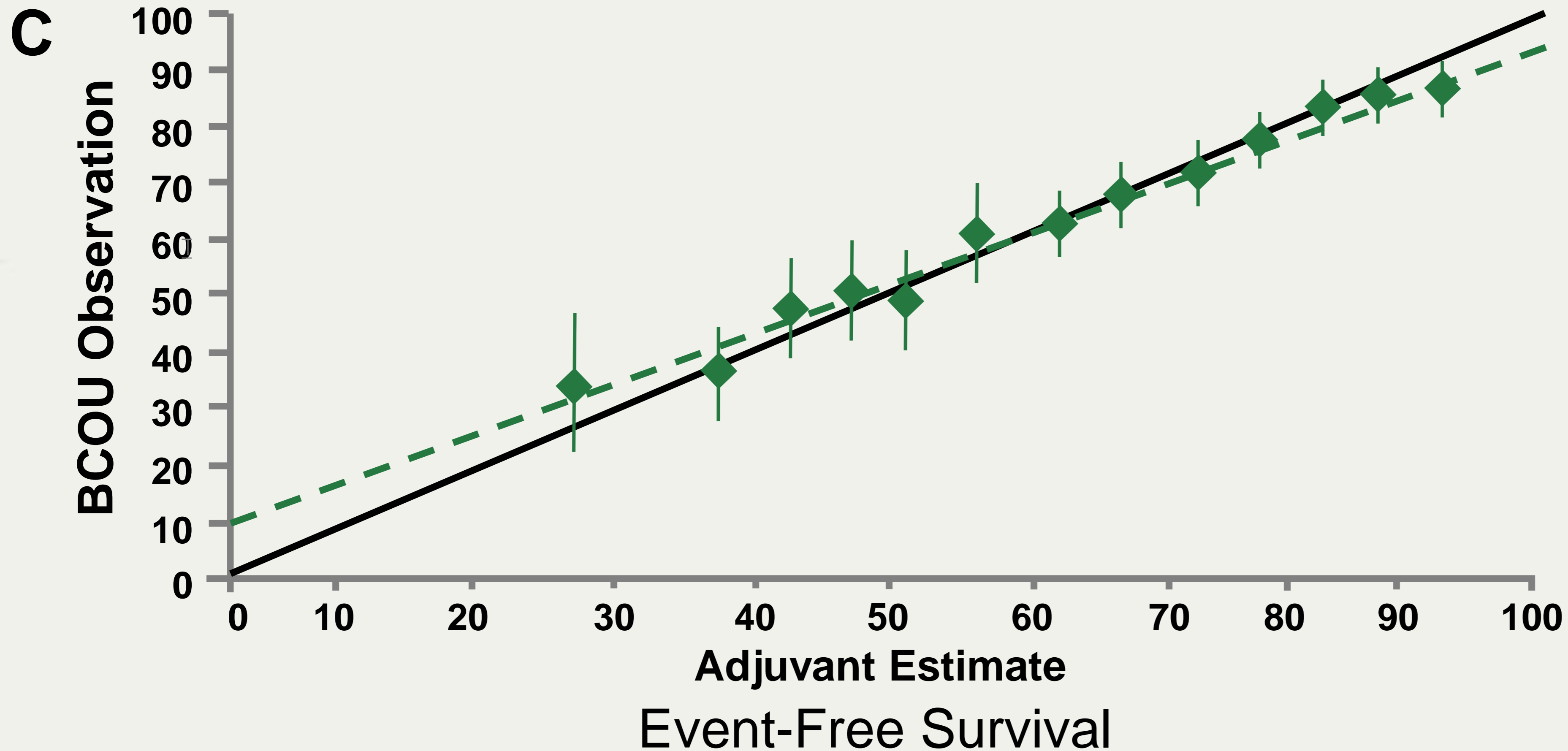
Adjuvant! Validation

4083 women with T1-2, N0-1, M0 breast cancer Compared predicted vs. observed 10 yr outcomes



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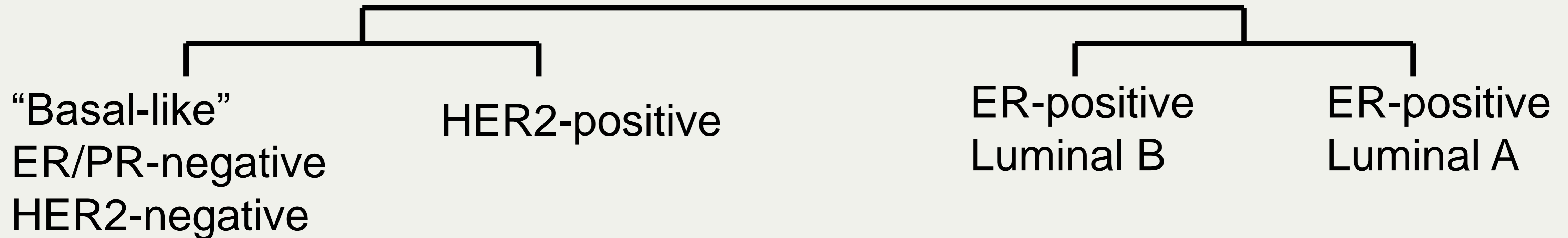
Gene Expression Profiles

Gene Expression Analysis

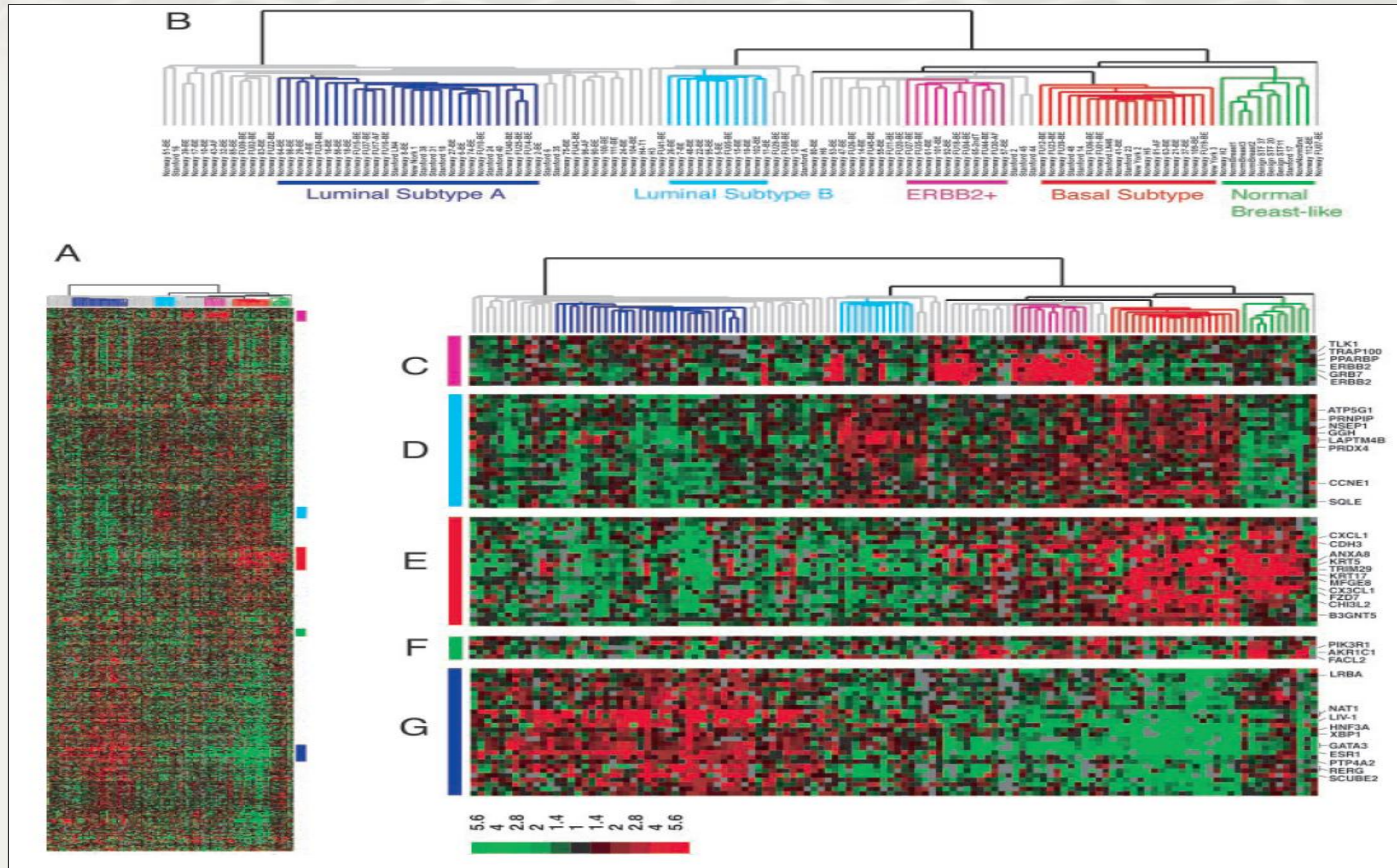
- Studies of gene expression analysis focused on two different situations
 - Defining distinct subtypes of breast cancer
 - Utilizing gene expression analysis to predict clinical outcome
- In both situations, this technology demonstrates known heterogeneity of breast cancers

Breast Cancer is a Family of Diseases

- Convergence of clinical and genomic data
- Unclear how many distinct members of this family
- At a minimum:
 - HER-2 +
 - Basal-like or triple negative
 - ER + (luminal A)
 - ER + (luminal B)



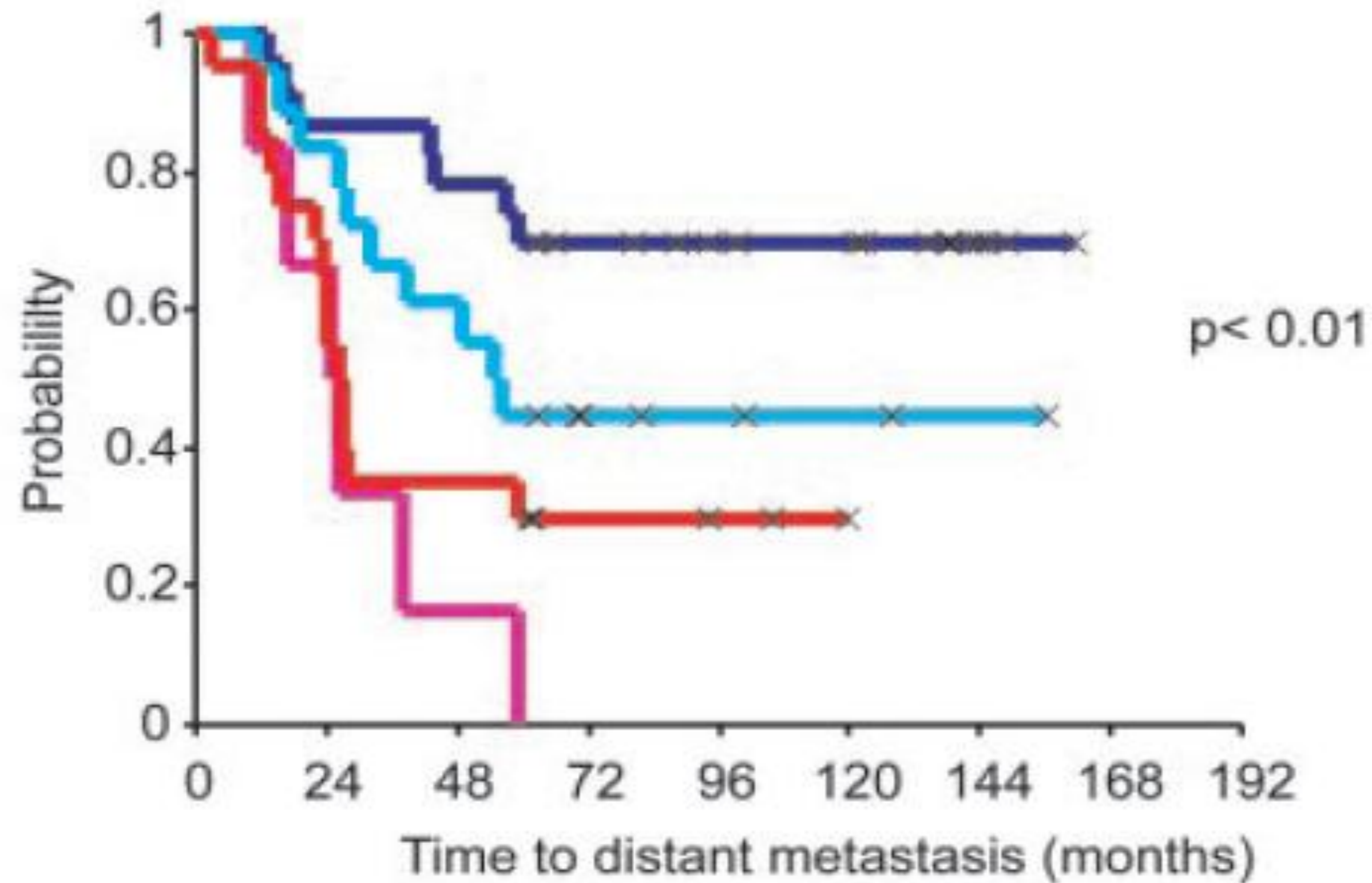
Breast Cancer Subtypes



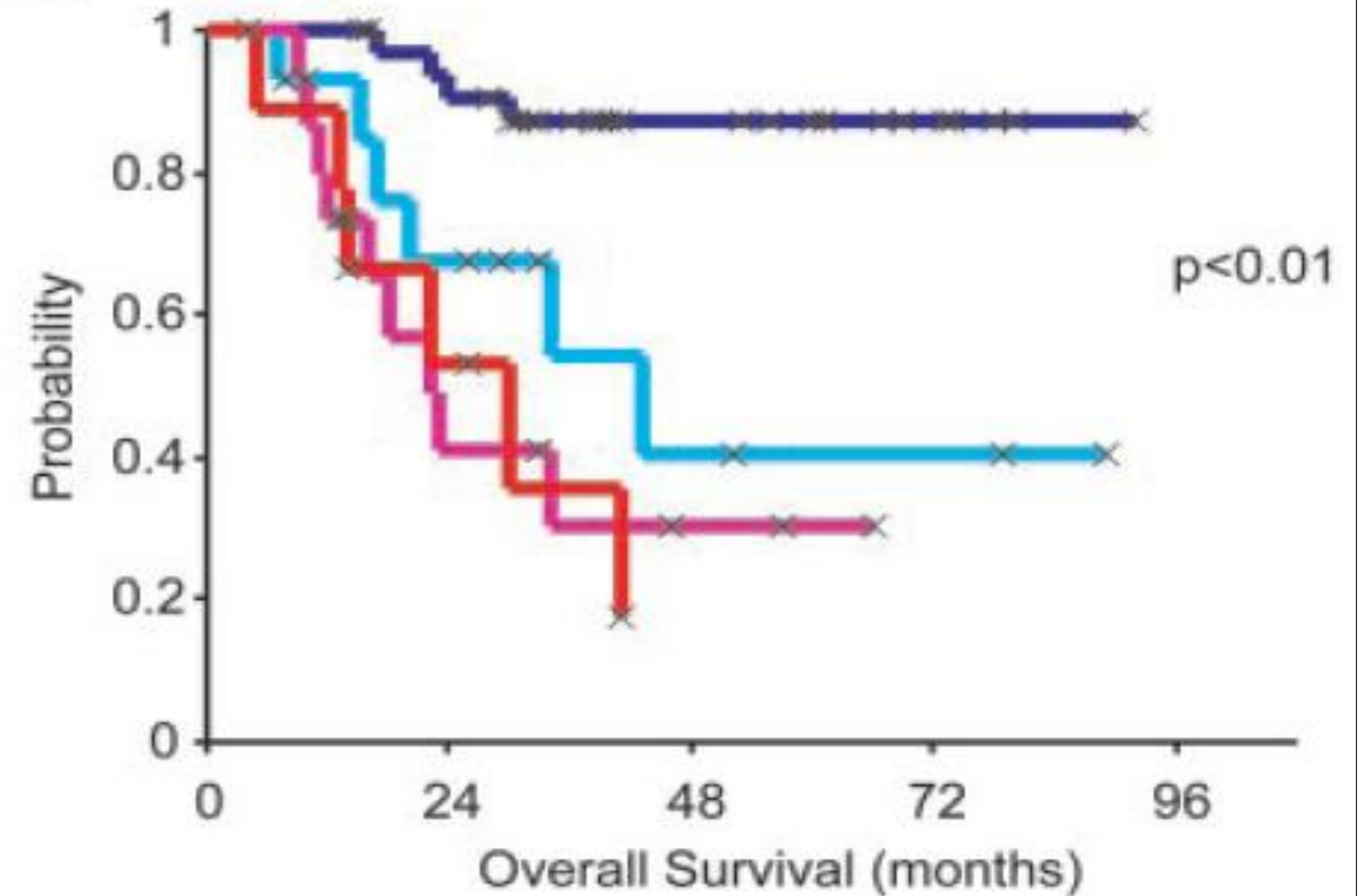
Sorlie T, Tibshirani R, Parker J, et al. *Proc Natl Acad Sci U S A*. 2003;100(14):8418-23.

Breast Cancer Subtypes

A van't Veer data set



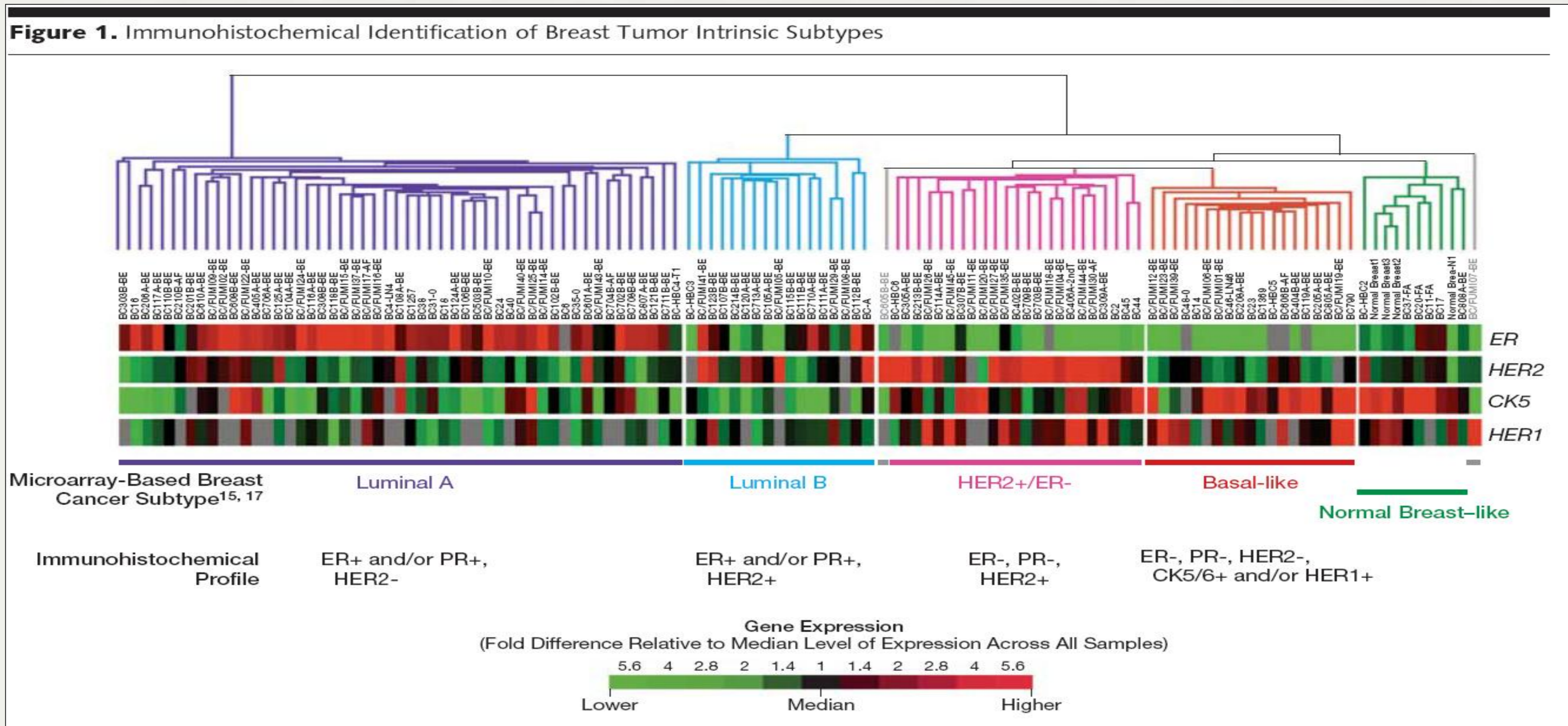
B Norway/Stanford data set



× Censored, ■ Luminal A, ■ Luminal B, ■ Basal, ■ ERBB2+

Breast Cancer Subtypes

Correspond to Clinically Recognized Subtypes



Breast Cancer Subtypes HER2 Array Group

- Many tumors that are clinically HER2 positive (by IHC/FISH) will be in this group
- However, those tumors that are HER2 positive (by IHC/FISH) and ER/PgR positive typically fall in luminal group
- In two population-based studies, using IHC correlates of subtypes, HER2 subtype found in about 6-9% of pts
- Associated with poor prognosis – this is now likely altered by use of targeted therapy

Breast Cancer Subtypes Basal Group

- Mimicked expression pattern of normal myoepithelial cells of the breast and basal epithelial cells of other parts of the body
 - Lack of expression of ER & ER-related genes
 - Low expression of HER2
 - Strong expression basal cytokeratins CD5, CD6, and CD17
 - Frequently high grade
 - Low expression of *BRCA1*

Breast Cancer Subtypes Basal Group

- In population-based study in North Carolina oversampling African American women, basal-like subtype seen in 20%
 - Premenopausal African American (39%) vs. postmenopausal African American (14%) vs. non-African American women of any age (16%) ($p < 0.001$)
- In population based study from Poland seen in 12%

Breast Cancer Subtypes Basal Group

- Associated with poor prognosis
- In pre-operative setting, see high response to chemotherapy, but poor outcome overall

Breast Cancer Subtypes Luminal Breast Cancers

- Accounts for majority of breast cancers (population-based studies ~ 67% of cases)
- Includes two separate subtypes of HR+ disease with differing characteristics and prognoses
 - Luminal A vs. Luminal B
 - Higher expression ER related genes
 - Lower expression of proliferation genes than luminal B
 - Histopathologically, lower grade
 - Luminal A associated with better prognosis
- In keeping with clinical data regarding heterogeneity of hormone receptor-positive disease

Breast Cancer Subtypes

Luminal Breast Cancers

- Incidence Luminal A varies by age and race
 - Premenopausal African American (36%) vs. postmenopausal African American (59%) vs. non-African American women of any age (54%) ($p < 0.001$)



The Role of Multi-gene Predictors in Early Breast Cancer