Memorial Sloan Kettering Cancer Center™

COLUMBIA UNIVERSITY | MAILMAN SCHOOL of PUBLIC HEALTH
BIOSTATISTICS

Application of a method for identifying disease subtypes that are etiologically heterogeneous

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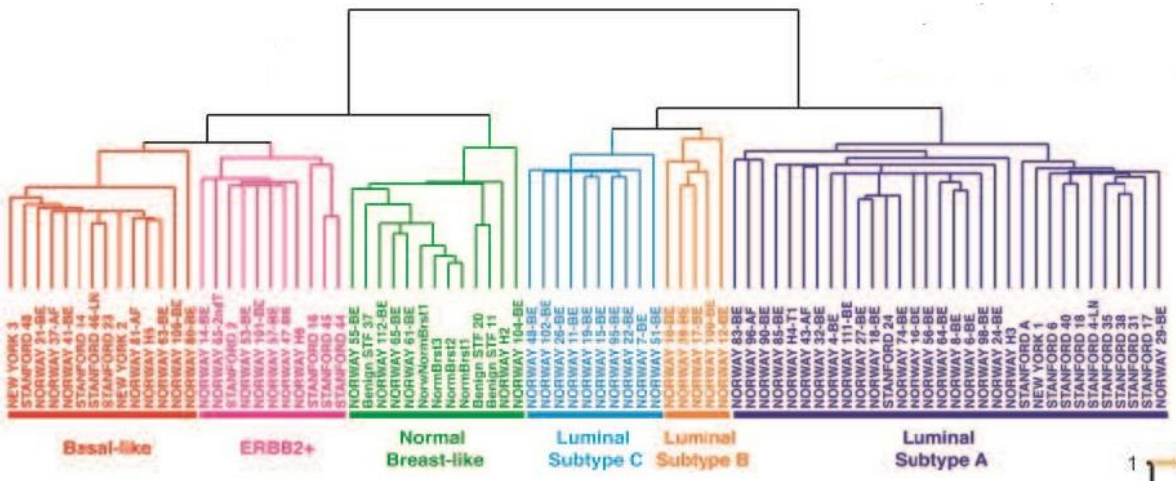
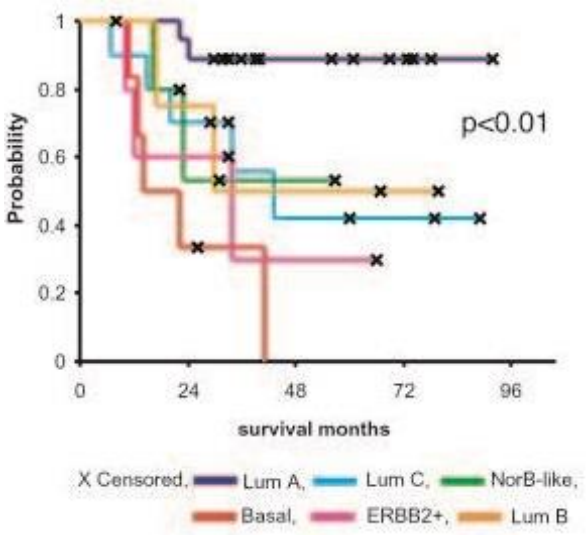
Breast cancer is biologically diverse and subtypes of disease risk and prognosis are recognized



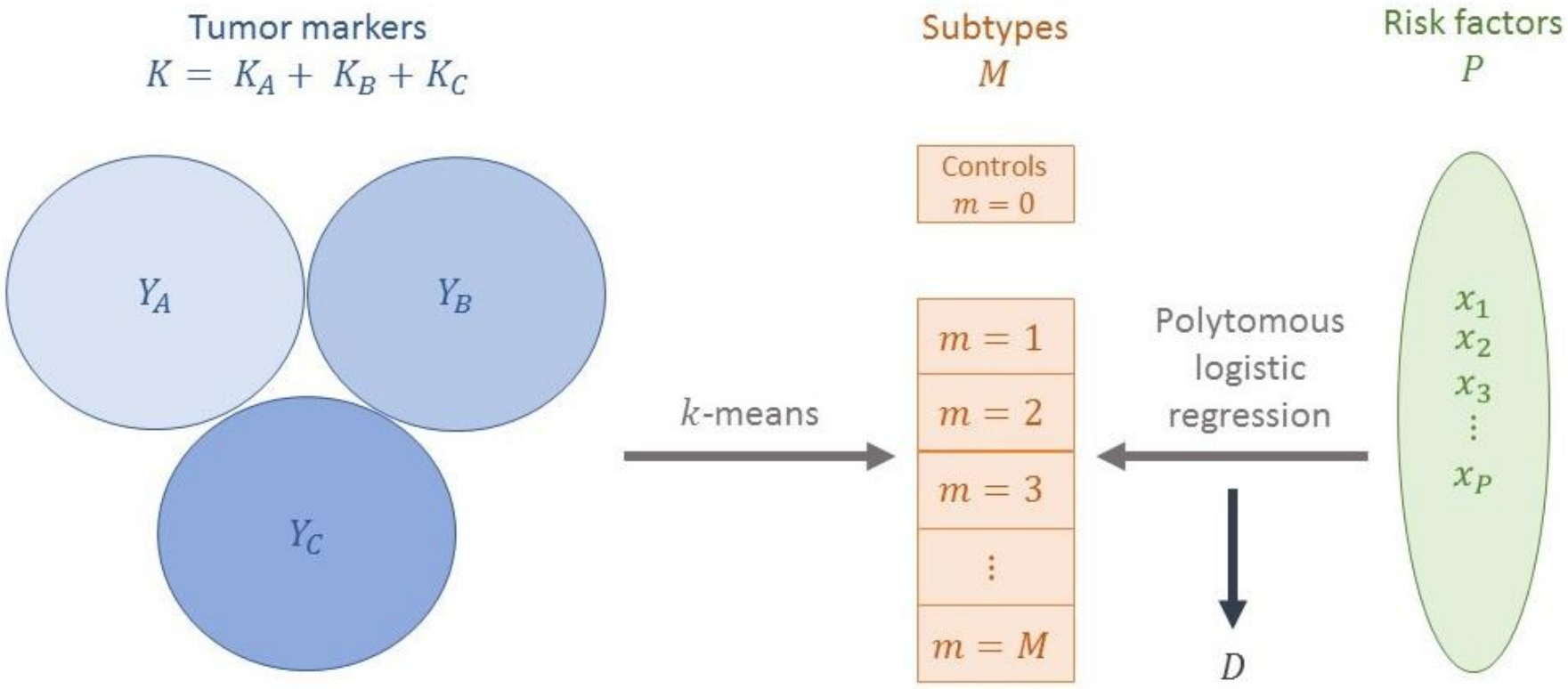
Primary molecular subtypes of breast cancer can be approximated with 4 classes based on 3 IHC markers:

- Estrogen receptor (ER)
- Progesterone receptor (PR)
- Human epidermal growth receptor (Her2)



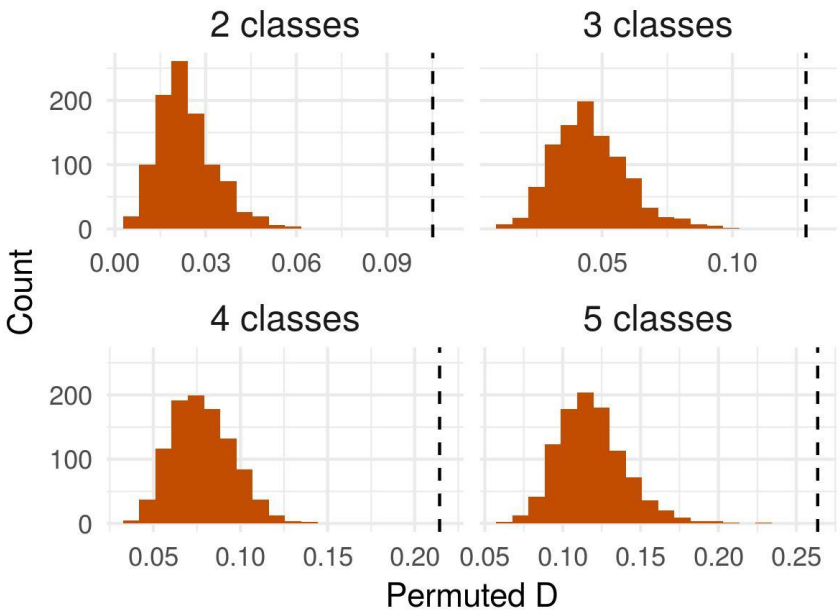
Sorlie et al (2001). Gene Expression Patterns of Breast Carcinomas Distinguish Tumor Subclasses with Clinical Implications. PNAS (19): 10869-74.

Seek to cluster tumor marker data and optimize a scalar measure of etiologic heterogeneity, D



For three subtypes A, B, and C: $D = (\pi_A V_A^2 + \pi_B V_B^2 + \pi_C V_C^2) - V^2$,
where π_j is the relative frequency and V_j^2 is the coefficient of variation for subtype j.

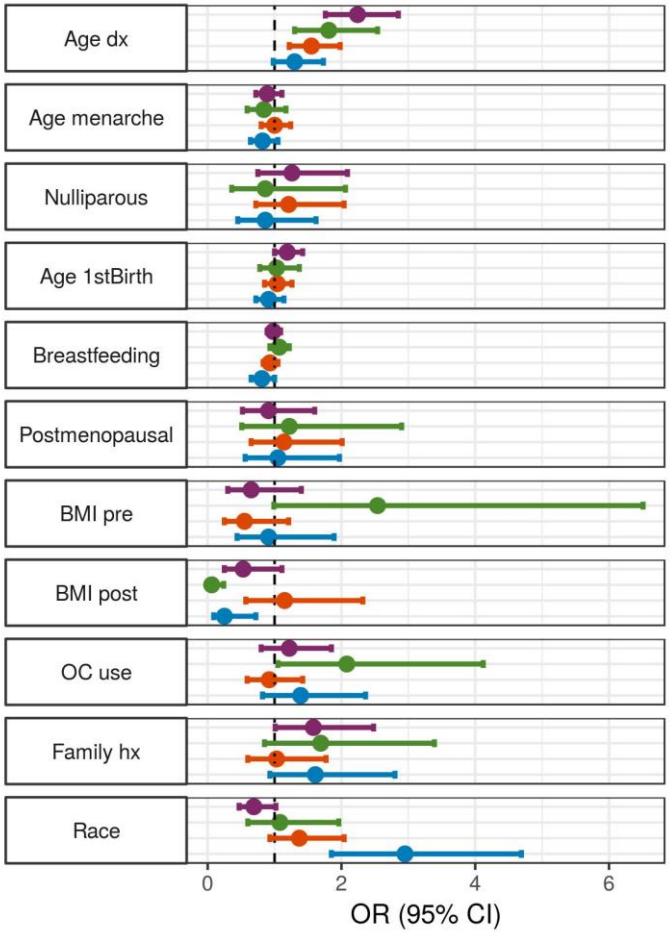
Discovery analysis selects 112 genes and identifies 4 classes



Class size	D difference	P-value
3 vs 2	0.023	0.454
4 vs 2	0.109	0.002
5 vs 2	0.159	0.012
4 vs 3	0.086	0.007
5 vs 3	0.135	0.015
5 vs 4	0.049	0.358

- 532 breast cancer cases from Carolina Breast Cancer Study used for discovery
- Top-ranked genes selected for inclusion in clustering based on individual gene D

Age at diagnosis, menopausal status, and race are driving the heterogeneity across subtypes



Class size	D
Discovery	0.214
Validation	0.245
Traditional IHC 4-class	0.148

- Validation produces reasonably similar gene rankings
- Optimal 4-class D exceeds that in traditional IHC 4-class
- ER is a key gene in distinguishing subtypes