Definition of Clinically Distinct Subtypes Within Estrogen Receptor Positive Luminal Breast Carcinomas

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Applying Genomic Grade to Molecular Subtypes
Sotiriou et al. PNAS 2003

GGI
High
Low
Genomic grade genes

Background
Several microarray studies have shown that breast tumours can be grouped in at least 4 to 5 individual subtypes namely basal-like, erbB2-like and luminal-like A, B, C or 1, 2, 3.

However, although the basal and the erbB2 subtypes are repeatedly recognized as distinct entities, the definition of luminal subtypes has been far from consistent between published series.

Refinement of their molecular definition is therefore needed.

Material and Methods
Van de Vijver et al. NEJM, 2002
Sorlie et al. PNAS, 2001
Sotiriou et al. PNAS, 2003
Wang Y et al. The Lancet, 2005

Published datasets
Affymetrix U133A 22,283 probe sets

Original Datasets
ER+
Untreated
Oxford
Karolinska
N=86
Tamoxifen-
Treated
Oxford
Karolinska
Guys
N=249
Total Number ER+/luminal subtypes = 787 samples

Defining Genomic Grade in Breast Carcinoma

Clinical Outcome

Total Number ER+/luminal subtypes = 787 samples

GGI = scale xj ! xj ! cutoff

GGI = scale xj ! xj ! cutoff

Grade 1
Grade 3

Systenmically Untreated N = 417

TAMOXIFEN-TREATED N = 249

Expected rate of Developing Distant Metastases at 10 Years
ER+ UNTREATED POPULATION N = 86
Low
High
ER+ Van de Vijver et al. NEJM N = 122
ER+ Wang Y et al. The Lancet N = 209
ER+ TAMOXIFEN-TREATED N = 249

Systemically Untreated N = 417

TAMOXIFEN-TREATED N = 249

Conclusions
The use of Genomic Grade can distinguish two luminal subtypes in a highly reproducible manner across multiple datasets and microarray platforms.

Genomic Grade-defined subtypes show statistically distinct clinical outcome in both untreated and tamoxifen-treated populations.

These subtypes may provide important stratification for future breast cancer trials investigating the effect of treatment on ER+ breast cancers and hence potential to improve breast cancer management.

Further biological investigations into these phenotypes may result in identifying important therapeutic targets.