Biological mechanisms that trigger breast cancer (BC) tumor progression are molecular subtype dependent

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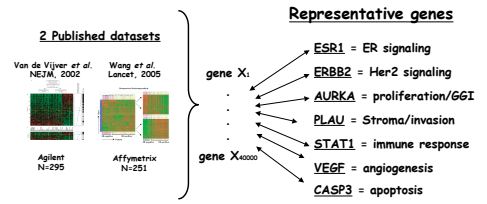
Introduction

We have recently developed several gene expression indices related to hallmarks of breast cancer involving various biological processes such as tumor invasion, impairment of immune response, sustained angiogenesis, evasion of apoptosis and self-sufficiency in growth signal, and investigated their impact on clinical outcome. Here, we aim to refine our biological understanding and the prognostic impact of these indices according to the previously described molecular subtypes based on the estrogen (ER) and ERBB2 receptors.

Materials & Methods

·Selection of prototype genes related to several biological processes in breast cancer (hallmarks of cancer) such as ER and ERBB2 signalling, proliferation, fully captured by the gene expression grade index, stroma/invasion, angiogenesis, apoptosis and immune response.

2 Published datasets

Van de Vijver et al. NEJM, 2002 — Agilent N=295

Wang et al. Lancet, 2005 — Affymetrix N=251

gene X$_i$ ... gene X$_{40000}$

Representative genes

ESR1 = ER signaling
ERBB2 = Her2 signaling
AURKA = proliferation/GGI
PLAU = Stroma/invasion
STAT1 = immune response
VEGF = angiogenesis
CASP3 = apoptosis

A model selection procedure is fitted to estimate the contribution of each prototype for the prediction of the expression of each gene on the arrays

computed on several publicly available microarray studies totaling over 2100 BC patients
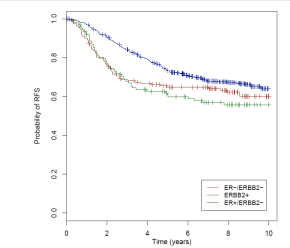
Prototype	Nr of genes associated with the prototype*	Nr of genes *specifically* associated with the prototype**
ESR1	990	468 (47%)
ERBB2	158	27 (17%)
AURKA	730	228 (31%)
PLAU	241	67 (28%)
STAT1	480	94 (20%)
VEGF	307	13 (4%)
CASP3	76	9 (12%)

Defining Molecular Subtypes
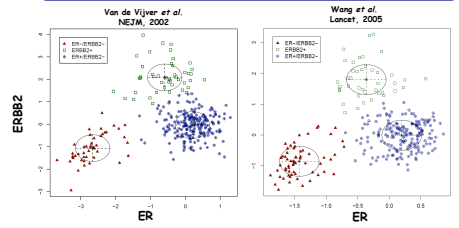
Van de Vijver et al. NEJM, 2002

Wang et al. Lancet, 2005

Clinical Outcome

Survival Analysis RFS

ER-/ERBB2-   ERBB2+   ER+/ERBB2-
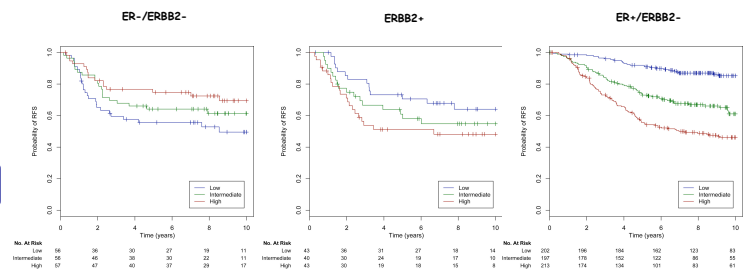
Prognostic signatures by molecular subtype

	ESR1-/ERBB2-			ERBB2+			ESR1+/ERBB2-		
	HR (95% CI)	p-value	Nr of patients	HR (95% CI)	p-value	Nr of patients	HR (95% CI)	p-value	Nr of patients
GENE70	1.12 (0.73-1.72)	6.04 E-01	154	1.29 (0.75-2.20)	3.60 E-01	120	2.11 (1.67-2.66)	3.26 E-10	566
GENE76	1.30 (0.78-2.15)	3.17 E-01	99	0.81 (0.49-1.34)	4.19 E-01	85	1.52 (1.24-1.88)	2.28 E-5	422
P53	1.01 (0.42-2.42)	9.83 E-01	163	1.04 (0.51-2.11)	9.15 E-01	126	2.23 (1.64-3.03)	3.53 E-07	605
WOUND	0.90 (0.65-1.26)	5.40 E-01	160	1.24 (0.79-1.93)	3.48 E-01	126	1.48 (1.25-1.75)	4.62 E-06	598
GGI	0.78 (0.44-1.36)	3.76 E-01	165	0.79 (0.40-1.53)	4.81 E-01	126	3.16 (2.46-4.06)	1.91 E-19	598
ONCOTYPE	0.86 (0.36-2.08)	7.44 E-01	156	1.00 (0.50-2.02)	9.99 E-01	126	4.79 (3.43-6.68)	2.56 E-20	605
IGS	1.08 (0.73-1.61)	7.04 E-01	169	0.96 (0.63-1.46)	8.49 E-01	126	2.12 (1.73-2.60)	6.24 E-13	605

Conclusions

Although proliferation seems to be the strongest parameter predicting clinical outcome in ER+/ERBB2- subtype, immune response and tumor invasion appear to be the main molecular mechanisms associated with prognosis in the ESR1-/ERBB2- and ERBB2+/ESR1- subgroups respectively.

ER-/ERBB2- — Immune response

ERBB2+ — Tumor invasion Immune response

ER+/ERBB2- — Proliferation