Can cancer-associated epigenetic changes be detected from semiquantitative ER/PgR expression in 1180 patients with invasive ductal breast cancers?

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OBJECTIVE

Model of cancer-associated epigenetic changes (Kurbel S. Tumour Biol 2013;34:2011-7) proposes that, beside in the ER^+PgR^- breast cancers, dysfunctional ERs are also present in some ER^+PgR^+ tumours with weak PgR expression.

METHODS

- 1180 consecutive patients with ductal invasive breast cancers (regardless of stage) were included. All patients were diagnosed and treated in Osijek University Hospital during the time period from January 2004 to December 2012.
- All specimens were excisional biopsy specimens, or mastectomy specimens.
- According to immunohistochemical features, tumours were divided into the following five groups:
- Luminal A (ER^+ and/or PgR^+, HER2-negative, low Ki-67)
- Luminal B1 (ER^+ and/or PgR^+, HER2-negative, high Ki-67)
- Luminal B2 (ER^+ and/or PgR^+, HER2-positive)
- HER2 (ER^-, PgR^-, HER2-positive)
- triple-negative (ER^-, PgR^-, HER2-negative).
- ER and PgR positivity were semiquantitatively classified in four groups: "0" means no positive cells; "1+" <10% positive cells; "2+" 11-30% positive cells; and "3+" 31-100% positive cells.
- Collected data were organized in 2×2 tables and differences from expected frequencies were checked by χ^2 tests. Model prediction calculation methods are described in the published papers (references).

RESULTS

Table 1: Age and Ki-67 as factors that affect distributions of ER nad PgR. Fully functional ERs were more common among younger Luminal A cancer patients (p=0.034). PgR expression in Luminal B1 and B2 cancer patients was age unrelated.

Semiquantative steroid receptor expression	Ki-67 <=20%			Ki-67 >20%		
	Age <55 years	Age >54 years	Total	Age <55 years	Age >54 years	Total
Breast cancer type	**Luminal A**			**Luminal B1**		
ER^{0-2+}	16	10	26	12	8	20
ER^{3+}	104	310	414	76	167	243
Total	120	320	440	88	175	263
χ^2(p)	16.36 (0.0001)			6.85 (0.0089)		
PgR^{0-2+}	18	78	96	24	64	88
PgR^{3+}	102	242	344	64	111	175
Total	120	320	440	88	175	263
χ^2(p)	4.50 (0.034)			2.27 (0.1316)		
Breast cancer type	**Luminal B2**					
ER^{0-2+}	5	3	8	5	6	11
ER^{3+}	21	52	73	34	72	106
Total	26	55	81	39	78	117
χ^2(p)	3.76 (0.0524)			0.80 (0.3703)		
PgR^{0-2+}	10	23	33	15	41	56
PgR^{3+}	16	32	48	24	37	61
Total	26	55	81	39	78	117
χ^2(p)	0.08 (0.7741)			2.07 (0.1500)		

Table 2. Incidences of the $ER^{3+}PgR^{3+}$ phenotype combination in breast tumour types according to the age. Among patients older than 54, Luminal A and B1 tumours were frequently ER^{3+} (p<0.01), while PgR^{3+} tumours were more common among Luminal A patients younger than 55 (p=0.034), suggesting that in older Luminal A or B1 patients, high ER and low PgR expression is common. Nothing similar was found among Luminal B2 cancer patients.

Semiquantative steroid receptor expression		Age <55 years			Age >54 years			All patients		
		PgR^{0-2+}	PgR^{3+}	Total	PgR^{0-2+}	PgR^{3+}	Total	PgR^{0-2+}	PgR^{3+}	Total
Luminal A	ER^{0-2+}	2	14	16	5	5	10	7	19	26
	ER^{3+}	16	88	104	73	237	310	89	325	414
	Total	18	102	120	78	242	320	96	344	440
	χ^2(p)	0.09 (0.7635)			3.68 (0.0522)			0.42 (0.5159)		
Luminal B1	ER^{0-2+}	6	6	12	7	1	8	13	7	20
	ER^{3+}	18	58	76	57	110	167	75	168	243
	Total	24	64	88	64	111	175	88	175	263
	χ^2(p)	3.62 (0.0572)			9.37 (0.0022)			9.67 (0.0019)		
Luminal B2 Ki-67 <=20%	ER^{0-2+}	3	2	5	2	1	3	5	3	8
	ER^{3+}	7	14	21	21	31	52	28	45	73
	Total	10	16	26	23	32	55	33	48	81
	χ^2(p)	1.21 (0.2707)			0.81 (0.3695)			1.74 (0.1870)		
Luminal B2 Ki-67 >20%	ER^{0-2+}	2	3	5	6	0	6	8	3	11
	ER^{3+}	13	21	34	35	37	72	48	58	106
	Total	15	24	39	41	37	78	56	61	117
	χ^2(p)	0.01 (0.9396)			5.87 (0.0154)			3.01 (0.0829)		

Table 3: An attempt to estimate how much of the here presented patients might have acquired steroid receptors during cancerogenesis, beside the already recognized dysfunctional ER in the ER^+PgR^- phenotype. The model predicted share of dysfunctional ERs was 7.32% (for Luminal A), 11.26% (B1), 12.62% (B2 & Ki-67<20%) and 14.73% (B2 & Ki-67>20%). The predicted values matched well with the found shares of $ER^{3+}PgR^{1+}$ tumours within these three types (p>0.10).

Steroid receptor positive breast cancer types				Luminal A	Luminal B1	Proposed Ki-67/Luminal B2 subgroups	
						<=20%	>20%
Steroid hormone receptor phenotypes	tissue or tumor associated	ER^+PgR^+	Ph_1	**405**	**229**	**69**	**96**
	tumor associated	ER^+PgR^-	Ph_2	29	29	12	21
		ER^-PgR^+	Ph_3	6	5	0	0
	Total		C	440	263	81	117
Probability of tissue or tumor associated PgR expression *(D)*			Ph_1/C	0.9205	0.8707	0.8519	0.8205
Predicted breast cancers with **tissue associated ER^+PgR^+** phenotypes							
Predicted breast cancers with **tissue associated ER^+PgR^+** phenotypes	Predicted share (%)		D^2	84.72%	75.82%	72.57%	67.32%
	Predicted number of patients with functional ER		$D^{2*}C$	**372.8**	**199.4**	**58.8**	**78.8**
Observed frequencies of ER^+PgR^+ phenotypes with full PgR expression							
Number of patients with:	ER^{3+} and PgR^{3+} phenotype			325	168	45	58
	ER^{2+} and PgR^{3+} phenotype			8	4	3	1
	ER^{1+} and PgR^{3+} phenotype			5	3	0	2
Total				**338**	**175**	**48**	**61**
Predicted breast cancers with **tumor associated ER^+PgR^+** phenotypes							
Predicted breast cancers with **tumor associated ER^+PgR^+** phenotypes	Predicted share (%)		$E=D-D^2$	7.32%	11.26%	12.62%	14.73%
	Predicted number of patients with potentially dysfunctional ER *($dysf._{pred}$)*		$E*C$	**32.2**	**29.6**	**10.2**	**17.2**
Observed frequencies of ER^+PgR^+ phenotypes with reduced PgR expression							
Number of patients with:	ER^{3+} and PgR^{1+} phenotype			40	26	11	24
	ER^{3+} and PgR^{2+} phenotype			23	24	6	6
	ER^{2+} and PgR^{1+} phenotype			2	2	1	2
	ER^{2+} and PgR^{2+} phenotype			0	0	2	1
	ER^{1+} and PgR^{1+} phenotype			2	0	1	1
	ER^{1+} and PgR^{2+} phenotype			0	2	0	1
Total ($dysf._{obs}$)				**67**	**54**	**21**	**35**
Ratio observed/predicted number of patients with reduced PgR expression			$dysf._{obs}/dysf._{pred}$	2.08	1.82	2.05	2.03

Table 4: Patients with weak PgR phenotypes. These data are not far from the predicted tumors with potentially dysfunctional ERs, suggesting that recognizing subtle difference in ER & PgR expression in breast tumors might be important.

Comparison of model predicted numbers of tumors with functional or dysfunctional ER expression with observed cancer phenotypes		Luminal A	Luminal B1	Proposed Ki-67/Luminal B2 subgroups		χ^2 value (p)
				<=20%	>20%	
Predicted number of patients with functional ER		373	199	59	79	
ER^{3+} and PgR^{3+} phenotype	observed data	325	168	45	58	19.91 (<0.001)
	χ^2 test calculation	6.18	4.83	3.32	5.58	
ER^{1-3+} and PgR^{3+} phenotype	observed data	338	175	48	61	12.33 (<0.01)
	χ^2 test calculation	3.28	2.89	2.05	4.10	
Predicted number of patients with potentially dysfunctional ER		32	30	10	17	
ER^{3+} and PgR^{1+} phenotype	observed data	40	26	11	24	5.52 (>0.10)
	χ^2 test calculation	2.00	0.53	0.10	2.88	
ER^{3+} and PgR^{2+} phenotype	observed data	23	24	6	6	12.45 (<0.01)
	χ^2 test calculation	2.53	1.20	1.60	7.12	

CONCLUSSIONS

- **The results support heterogeneity among ER^+PgR^+ tumours.**
- **Future studies of ER^+PgR^+ phenotype variants are required since hypothetical dysfunctional ERs in some ER^+PgR^+ breast cancer patients might alter their endocrine treatment outcomes.**

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