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Controversy

Estrogen receptor-negative progesterone receptor-positive breast cancer – “Nobody's land“ or just an artifact?

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ABSTRACT

The estrogen receptor α (ER) and the progesterone receptor (PgR) are one of the most important prognostic and predictive immunohistochemical markers in breast cancer. Breast cancers may express various profiles of hormone receptors: ER(+)/PgR(+), ER(−)/PgR(−), ER(+)/PgR(−) and ER(−)/PgR(+). The existence of the latter profile is a matter of controversy since PgR expressions is induced by ER-dependent pathways in breast cancer cells. One of the most extensively propagated hypotheses trying to explain the origin of ER(−)/PgR(+) breast cancers claims that they are technical artifacts dependent on the immunohistochemical procedure. On the other hand, in recent years there is a growing body of evidence, suggesting that such cancers create a unique group with distinct molecular and clinical features. In the following review, we present background theories on the ER(−)/PgR(+) breast cancer origin and their epidemiological and clinicopathological characteristics, including the predictive and prognostic significance of these rare tumors.

Introduction

The St. Gallen surrogate classification for intrinsic breast cancer subtypes defines four entities: luminal-A-like, luminal-B-like, HER2-positive and basal-like [1]. They are assessed by the immunohistochemical evaluation of estrogen receptor α (ERα – later also referred to as ER), progesterone receptor (PgR), human epidermal growth factor receptor type 2 (HER2) and Ki-67. Triple-negative breast cancer is closely related to the basal intrinsic phenotype and is characterized by lack of expression of ER, PgR and no overexpression of HER2. Luminal tumors are defined as ER and/or PgR positive, therefore, such tumors may have three distinct profiles: ER(+)/PgR(+), ER(+)/PgR(−), ER(−)/PgR(+). Luminal A-like tumors are characterized by a high expression of ER and/or PgR, whereas luminal B-like cases demonstrate a lower expression of hormone receptors and a higher proliferation rate. Prat et al. suggested the cut-off of > 20% PgR expressing cells best correlates with luminal-A phenotype. Until the 2015 edition, the ER(−)/PgR(+) phenotype had not been included in the surrogate definitions of intrinsic subtypes of breast cancer proposed by the St. Gallen consensus and in the 2017 guidelines the subtype allocation of ER(−)/PgR(+) cancers between luminal A-like and luminal B-like phenotype is still not clearly defined [2]. The use of the reference method, gene-expression profiling (Prediction Analysis of Microarray 50, PAM50) showed that these tumors are mostly basal-like (50–60%) and luminal-A (15–30%), suggesting a significant molecular heterogeneity within the group [3–5]. Extensive research has shown that PgR expression is dependent on ER activity [6]. Therefore, the ER(−)/PgR(+) profile in breast cancer is hard to explain on biological grounds and for this reason some pathologists and oncologists put its existence into question. On the other hand, in recent years there is growing body of evidence that such cancers create a unique group with distinct molecular and clinical features.

In 2004 Olivotto started a debate on the significance of PgR expression evaluation in breast cancer patients. He declared that PgR testing in breast cancer management should be discontinued, due to its negligible role in altering therapeutic decisions [7]. This article has aroused many controversies and initiated worldwide discussion. In response, some authors have raised an important issue: PgR status in ER(−) tumors may provide an important predictive information and PgR positivity may indicate which patients are more likely to respond to adjuvant endocrine treatment [8]. Others pointed out the prognostic value of PgR expression in breast cancer, especially if determined by appropriate immunohistochemical methods [9].

This paper aims to present the possible origin, epidemiology and prognostic/predictive significance of the ER(−)/PgR(+) breast cancer phenotype.

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Table 1
Main studies addressing ER(−)/PgR(+) breast cancers.

Author and year	Population	Method	Total cases	Number of ER(−)/PgR(+) (%)	Cut-off	Mean age	Prognostic significance	Response to endocrine therapy	Clinicopathological features
Keshgegian 1994 [74]	US women	LBA	319	18 (5,6)	–	56	High recurrence rate, CRD 3.5x higher than ER(+)/PgR(+) cases	–	Tumor size, grade, and S-phase fraction higher than in ER(+)/PgR(+) tumors
Bernoux 1998 [46]	Operable primary breast cancer	LBA	3000	62 (2)	> 15 fmol/mg protein	49.4	Trend for worse DFS and the metastasis-free survival than in ER(−)/PgR(+) patients	–	Smaller size and more frequently grade I than ER(−)/PgR(−) tumors
Bardou 2003 [58]	PP and SPORE databases	LBA	14,183	298 (2)	–	–	Probably better prognosis than ER(−)/PgR(−) cancers	Probably worse response to tamoxifen than ER(+)/PgR(+)	–
Olivotto 2004 [7]	Victoria, British Columbia	IHC (ER 6F11, PgR 1A6)	192	0 (0)	–	–	–	–	–
Dowsett 2005 [78]	ATAC Trial	IHC	9336	220 (2.4)	Allred score > 2	–	–	Slight benefit from endocrine therapy	–
Grann 2005 [38]	SEER	Various	155,890	5165 (3.3)	Various	–	Higher CRD than patients in the other groups	–	–
Nadji 2005 [17]	South Florida and Latin America	IHC (ER 1D5, PgR 636)	5993	0 (0)	Any positive nuclear reaction	–	–	–	–
Dowsett 2006 [66]	NATO & CRC study	IHC (ER 1D5, PgR 1A6)	813	26 (3)	H-score: ER > 1, PgR > 19	–	–	Substantial benefit from tamoxifen	–
Kiani 2006 [11]	Pakistanian women (Karachi)	IHC (ER 1D5, PgR IA6)	1625	132 (8.12)	H-score > 74	47.04	–	–	More poorly differentiated and larger tumors than in ER(+) PgR(+)
Viale 2007 [42]	BIG 1–98	LBA IHC	6291	8 (0.1)	LBA: > 10 fmol/mg IHC: > 1%	–	–	–	–
Rakha 2007 [30]	Nottingham Tenovus Primary Breast Carcinoma Series	IHC	1944	60 (3.4)	> 1%	48 (median)		Similar response to endocrine therapy as ER(+)/PgR(−)	Larger tumor size, higher expression of p53, P-cadherin, basal CKs and HER-2 compared to ER(+)/PgR(+)
Dunnwald 2007 [52]	SEER	Various	155,175	4896 (3)	Various	–	Increased risk of mortality compared to ER(+)/PgR(+) patients (particularly high if tumor size > 5 cm or high grade)	–	–
Bird 2008 [45]	Kenyan women (Kijabe)	IHC	129	12 (10%)	> 1%	–	–	–	–
Yu 2008 [51]	Chinese women (Shanghai)	IHC	1863	205 (11%)	> 10%	50	Independent prognostic factor for DFS and OS only for axillary node (+)	Less benefits from adjuvant tamoxifen than ER(+)/PgR(+).	No significant differences in stage, pathologic pattern and HER-2 status when compared to ER(+)/PgR(+)
De Maeyer 2008 [18]	Belgian women, primary operable breast cancers	IHC (ER SP1, PgR SP2)	2013	0 (0)	Any nuclear staining	–	–	–	–
Rhodes 2009 [50]	UK women	IHC	4053	131 (3.2)	Various	–	–	–	–
Stuart-Harris 2009 [59]	Metastatic breast cancers from trials: ANA, AR/BC2, AR/BC3	LBA IHC	979	40 (4.1)	Various	–	Median OS worse than in ER(+)/PgR(+), but similar to ER(+)/PgR(−)	No differences in benefit from an AI or a non AI treatment	–
Liu 2010 [56]	Invasive early breast cancer (British Columbia)	IHC	4046	166 (4.1)	> 1%	–	5 year BCSS higher in ER(−)/PgR(+) than in double negative (non-significant at 10 years)	–	–
EBCTCG 2011 [67]	EBCTCG meta-analysis of 20 trials of 5 years of adjuvant tamoxifen	LBA	21,457	1236 (5.8)	> 10 fmol/mg	–	–	No benefit from TAM in ER poor breast cancer, irrespective of PgR	–
Yi 2011 [75]	US women	IHC	3726	93 (2.5)	> 10%	–	5 years DSS worse than all other subgroups	–	–

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