

Review Article

The Prognostic Role of Protein Expression in Pregnancy-Associated Breast Cancer: A Literature Review

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Received: 18 February 2020; **Accepted:** 11 March 2020; **Published:** 06 July 2020

Citation: Anna-Maria Korakiti, Despoina Kalapanida, Meletios-Athanasios Dimopoulos, Flora Zagouri. The Prognostic Role of Protein Expression in Pregnancy-Associated Breast Cancer: A Literature Review. Journal of Cancer Science and Clinical Therapeutics 4 (2020): 189-194.

Abstract

Background: Breast cancer is one of the most common malignancies diagnosed during gestation. Pregnancy-associated breast cancer is characterized by poor prognostic outcome.

Objectives: This literature review aims to synthesize all available data and evaluate the prognostic role of protein expression in pregnancy-associated breast cancer.

Search strategy: All articles were retrieved from Medline/PubMed database using an algorithm that

consisted of a predefined combination of the keywords: breast, cancer, pregnancy, protein.

Conclusion: The prognostic role of estrogen and progesterone receptors, HER-2 expression, PD-1, PDL-1 and CTLA-4, RANK and RANKL, p63 and WT-1, EGFR, cyclins D1 and E is meticulously analyzed. Further research on the biological characteristics of pregnancy-associated breast cancer consists an urgent need.

Keywords: Pregnancy; Breast Cancer; Protein; Prognosis

Abbreviations: PABC-Pregnancy-Associated Breast Cancer; ER-Estrogen Receptors; PR-Progesterone Receptors; HER-2-Human Epidermal Growth Factor Receptor-2; PD-1-Programmed Cell Death Protein-1; PDL-1-Programmed Death-Ligand-1; CTLA-4-Cytotoxic T-Lymphocyte Associated Protein-4; RANK-Receptor Activator For Nuclear Factor K β ; RANKL-RANK Ligand; WT-1-Wilms' tumor-1; EGFR-Epidermal Growth Factor Receptor; TNBC-Triple Negative Breast Cancer; YWBC-Young Women With Breast Cancer (≤ 40 years of age); DFS-Disease-Free Survival; OS-Overall Survival; BCSS-Breast Cancer-Specific Survival.

1. Introduction

Pregnancy-associated breast cancer (PABC) is generally defined as breast cancer diagnosed anytime during gestation, lactation or within one year after delivery. Along with melanoma and cervical cancer they are the most frequent types of pregnancy related cancer [1]. Its incidence is estimated to be 1;3,000-10,000 gestations and it represents only 0.2-3.8% of overall breast cancer [1, 2]. Due to the fact that most women delay marriage and childbearing in industrialized societies, there is an expected increase in PABC rate. PABC exhibits particularly aggressive behavior and adverse prognostic characteristics; advanced T stage in diagnosis, lymph node involvement, high histologic grade, negative estrogen (ER) and progesterone (PR) status and HER-2 overexpression [2, 3]. Significant controversy exists in many studies regarding the influence of pregnancy on breast cancer prognosis as the mechanism of PABC is still not well understood [4]. In addition, the coexistence of pregnancy with breast cancer adds many restrictions on treatment recommendations, as both the mother and the fetus may be severely affected. PABC management is considered to be a challenge because of its low incidence and the lack of strong data.

Consequently, the limited therapeutic strategies may also be related to poor prognostic outcome [5]. This review aims to analyze the prognostic role of protein expression in pregnancy-associated breast cancer while integrating all information from literature.

2. Method

The Medline/PubMed database was searched using an algorithm that consisted of a predefined combination of the keywords: breast, cancer, pregnancy, protein. Studies focusing mainly on clinicopathological tumor characteristics in PABC cases and on the prognostic role of protein expression were meticulously selected. A total of 12 articles were retrieved. Reference lists of identified articles were also investigated for additional articles resulting in 16 to be included in this literature review.

3. Estrogen (ER) and Progesterone (PR) Receptors

Several studies have demonstrated that estrogen (ER) and progesterone (PR) negative status is the rule rather than the exception in PABC patients. [3-8]. However, only a few cohort studies have proved that ER and PR negative status represents an independent statistically significant adverse prognostic factor [3, 6]. Johansson et al (2018), one of the most recent studies on tumor characteristics of PABC, analyzed the mediating effect of ER/PR negative status on mortality rates and correlated it with more advanced tumors during pregnancy [6]. Reed et al (2003), while separating the PABC patients in lymph node-positive and lymph node-negative subgroups, demonstrated that the hormone receptors had positive prognostic impact on node-positive cases only. PR status remained a significant prognostic factor in the multivariate analysis as well [3]. In contrast, Bae et al (2018) showed that luminal B subtype of breast cancer (ER and/or PR positive and either HER-2 negative or HER-2 positive) was related to poorer survival in PABC

especially when combined with high Ki-67 levels, as there were worse disease-free survival (DFS) and breast cancer-specific survival (BCSS) rates [5]. The aforementioned results are in concordance with another retrospective matched-case control study by Madaras et al (2013) that demonstrated the poor prognosis of luminal B and triple negative (TNBC) subtypes especially in postpartum cases [7].

4. HER-2

Human epidermal growth factor receptor-2 (HER-2) represents a significant protein promoting cancer cells growth. HER-2 positive patients consist a breast cancer subgroup characterized by HER-2 gene mutation that results in excessive cell growth and aggressive tumor behavior. Today, HER-2 positive patients remain the target of monoclonal antibodies, such as trastuzumab or pertuzumab, improving the prognosis outcome [10]. HER-2 overexpression in PABC remains an independent prognostic factor for DFS and OS according to Wang et al (2019) that recently studied retrospectively the clinicopathological characteristics of PABC in a series of 142 patients. However, in the subgroup analysis of HER-2 positive and HER-2 negative patients, all PABC cases with HER-2 overexpression gained fundamental benefit from trastuzumab targeted therapy and ameliorated significantly five-year DFS [2]. Of note, current guidelines recommend postponing trastuzumab targeted therapy until after delivery as it is associated with pregnancy complications (oligohydramnios and/or anhydramnios) and fetal malformation [2, 10]. Reed et al (2003) demonstrated in subgroup analysis that HER-2 overexpression represents a significantly unfavorable prognostic factor in lymph node-positive PABC patients only [3]. Several other studies have mentioned the high rate of HER-2 expression in comparison to other series of breast cancer, but have not resulted in

statistically significant HER-2 prognosis outcome [4-6, 11]. On the other hand, only a few studies have not noticed significant difference in HER-2 status among PABC and control cases [7, 8, 13].

5. ER/PR & HER-2 Status

When combining ER/PR status with HER-2 expression, TNBC subtype predominates as the most common immunohistochemistry subcategory of PABC. Luminal B subtype represents the second most frequent state. Comparison results regarding the worst prognostic outcome among TNBC and luminal B cases, remain inconsistent as they are both related to poor survival [5-7, 12].

6. PD-1, PD-L1, CTLA-4

Ács et al (2017) compared retrospectively in a matched-case control study of 42 patients the expression of PD-1, PDL-1 and CTLA-4 among PABC and early onset non-PABC (YWBC) patients [12]. As it is well known, programmed death protein-1 (PD-1), expressed on both T and B lymphocytes and on NK cells, is responsible for preventing their lytic activity. Programmed death ligand-1 (PDL-1) on the contrary, while expressed on several tumor cells, is able to block the activity of the immune system. Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), found exclusively on T-lymphocytes, deactivates their activity by protein-phosphatases when interacting with its ligands (CD80, CD86). PD-1/PDL-1 and CTLA-4 remain the target of developing inhibitory antibodies (nivolumab, pembrolizumab) aiming to block the immune-checkpoints related to tumor growth. The aforementioned study by Ács et al, showed no significant difference in the PD-1, PDL-1 and CTLA-4 expression between the two groups of patients. Concerning prognosis though, PDL-1 expressed on tumor cells, intratumoral or peri-tumoral lymphocytes is a significant prognostic factor defining OS. Regarding DFS,

PDL-1 expressed only on tumor cells and on intratumoral lymphocytes can potentially determine unfavorable prognosis. Overall, higher levels of PDL-1 are correlated to adverse prognosis of both OS and DFS in PABC and YWBC cases, whereas PD-1 and CTLA-4 are not included in statistically significant results [12].

7. RANK, RANKL

Azim et al (2015), triggered by recent studies suggesting an association of RANK/RANKL signaling with young women breast carcinogenesis [15], investigated the difference in expression of RANK/RANKL pathway among 195 pregnant and non-pregnant breast cancer patients. The main hypothesis of their study was that pregnancy would increase RANKL levels due to its fundamental role in mammary gland development. As expected, PABC cases had significantly higher RANKL expression both on tumor cells and adjacent normal tissue. No significant difference in RANK expression was observed between pregnant and non-pregnant patients [13]. In both subgroups, RANKL levels were higher in small, well-differentiated and PR-positive tumors in contrast to RANK expression that remained higher in patients with poorly differentiated and hormone receptor-negative tumors. In addition, RANKL levels were observed to be significantly higher in Luminal A subtype cases with the lowest expression in TNBC tumors, whereas RANK expression was exactly the opposite in terms of subtype correlation. As far as prognosis is concerned, neither RANK nor RANKL had significant impact on the outcome when considering pregnant patients, non-pregnant patients or both groups combined [13]. Consequently, further research is required on RANK/RANKL pathway as a potential target of breast cancer treatment with anti-RANKL antibodies, such as denosumab, focusing on drug efficacy and safety on pregnant and non-pregnant breast cancer patients as well.

8. p63, WT-1

One of the major roles of p63 and Wilms' tumor-1 (WT-1), molecules expressed in breast myoepithelial cells, is to function as paracrine tumor suppressors [16]. Xu et al (2009) correlated the aberrant tumor suppressor expression and the focal disruption in the myoepithelial cell layer with PABC aggressiveness and invasiveness. More particularly, the absence of p63 and WT-1 in PABC cases was demonstrated in the vast majority of the myoepithelial cells of acini and terminal duct and lobular units (TDLU) contributing to cell proliferation and tumor growth. Moreover, epithelial cells with reduced p63 and WT-1 levels were represented by ER and PR negative status that is related to adverse prognosis as already established [14]. The mechanism that explains the abnormal tumor suppressor expression is still not fully understood and requires further investigation in order to draw definite conclusions regarding outcome prediction.

9. EGFR

Epidermal growth factor receptor (EGFR) is part of the oncogenic signaling pathway and is critical for cancer cell proliferation. Aziz et al (2003), while evaluating the prognostic markers in 24 PABC cases, demonstrated the discrepancy in EGFR expression between pregnant and non-pregnant breast cancer patients and attributed it to the young and reproductive age of the PABC subgroup. Despite the markers' variation though, the study revealed no statistically significant difference regarding OS among the two subgroups [8].

10. Cyclin D1 & Cyclin E

Reed et al (2003) examined PABC in a population-based series of 122 patients and correlated the disease with cell cycle modulators such as cyclin E, that is responsible for the transition from G1 to S-phase, and cyclin D1. The

analysis demonstrated that cyclin E expression was significantly higher in lymph node-negative tumors but there was no association with the prognostic outcome of PABC. Cyclin D1 was also meticulously studied but no prognostic significance was established [3].

11. Conclusion

Most of the recent studies on pregnancy-associated breast cancer indicate a poor prognosis for the disease not only because of the advanced stage in diagnosis and the treatment restrictions. Biological characteristics of PABC are highly associated with adverse prognosis and consist the target of the latest therapeutic developments. Current guidelines regarding PABC treatment are based on small retrospective studies and systematic meta-analyses as no randomized or prospective studies have been conducted due to its low incidence. It is more than necessary to develop collaboration registries among specialized centers in Europe for further research of PABC. The combination of existing data from literature with serum and/or breast tissue samples analyses (fresh frozen tissue or paraffin block) would offer the opportunity to extract conclusions regarding optimal diagnostic evaluation, management, survival rates and long-term effects of chemotherapeutic agents on both mothers and developing fetuses. Further research of PABC is an absolutely urgent need as its rate is expected to increase severely in the upcoming years.

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