EJGO European Journal of Gynaecological Oncology

Biological and pathological features in pregnancy-associated breast cancer: a matched case-control study

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Summary

Background: The prognosis for breast cancer has been considered to be worsened by the coexistence of pregnancy. However, to date, significant controversy still exists regarding the pathological tumor features and prognosis of patients diagnosed with pregnancy-associated breast cancer (PABC). The aim of the present study was to analyze the different prognostic factors and outcome in PABC subset versus a non-PABC control group matched for age and year of diagnosis. *Materials and Methods:* A total of 56 PABC cases were diagnosed from 1990 to 2008, for whom 73 non-PABC patients were identified. Pathological characteristics, immunohistochemical features, and differences in overall and disease-free survival were compared between both groups. *Results:* Compared to non-PABC controls, PABC patients presented more advanced disease (31% *vs* 13%, $p = 0.024$) and greater lymph node involvement (53% *vs* 34%, $p = 0.034$). Pathological and tumor features tended to present poorer prognostic factors in the PABC subset. Survival was poorer in the PABC patients (five-year DFS 68% in PABC *vs* 86% in non-PABC, $p = 0.12$). However, analysing survival adjusted for stage and age, the authors did not find significant differences between both groups. *Conclusions:* PABC patients tended to be diagnosed in advanced breast disease and presented tumors with adverse pathological prognostic factors. While the authors found a poorer outcome in PABC group, no significant differences were observed with stage-matched analysis. The present results may suggest that the poorer prognosis observed within PABC women could not be due to pregnancy itself, but with a delay in diagnosis and tumor subtype pathological features.

Key words: Breast cancer; Pregnancy; Prognostic factors; Outcome; Pathological features.

Introduction

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within one year after delivery [1]. PABC is a rare situation, but represents a real challenge, with a prevalence of 0.2% to 3.8% of all breast cancers (7.3% of breast cancers in patients younger than 40 years) and an incidence of one in 3,000 to one in 10,000 pregnancies [2, 3]. However, since more women are becoming pregnant later due to cultural and social developments, its diagnosis is likely to increase in clinical practice [4, 5].

The prognosis for breast cancer has been considered to be worsened by the coexistence of pregnancy. To date, some explanations have been proposed for the poorer outcome in PABC subset. Firstly, a hypervascularity process, both in blood flow and lymphatic drainage [6]. Secondly, pregnancy is also characterized by an increase of estrogen and progesterone levels related to the development of breast cancer; therefore, a high concentration of hormones could increase the proliferation of breast cancer cells [7, 8]. Following, the inflammatory-like activity that occurs during pregnancy could affect the microenvironment and promotes tumor cells [9, 10]. Finally, some published studies found datas suggesting a delay in diagnosis and treatment that are related to advanced tumor stage [11].

Today, significant controversy still exists regarding the pathological tumor features and the prognosis of patients diagnosed with PABC. Several studies have described a poorer outcome in PABC patients compared to non-PABC, highlighting pregnancy as an independent prognostic factor [12-16]. Recently, Azim *et al.* concluded a poorer survival in PABC even after adjustment for age and stage (five-year, 52% *vs* 74%, $p = 0.01$) [15]. Conversely, others authors showed equivalent survival controlling for age, tumor subtype, and stage [5, 17].

Knowledge about prognostic factors in PABC patients still remains clinically relevant, as it will allow us to define an appropriate therapeutic strategy and distinguish those patients at high risk of relapse. The present authors performed a retrospective review of patients diagnosed with PABC in their hospital. The aim of the present study was to analyze and compare the different prognostic factors, as well as the outcome in PABC patients versus non-PABC age-matched controls.

Revised manuscript accepted for publication December 11, 2014

Table 1. — *Clinical patients' characteristics.*

	PABC cases (%)	Non-PABC cases (%)	*p*
Total cases	56 (100)	73 (100)	Match
Age (years)	35.39 (27-50)	37.31 (27-52)	Match
Year of diagnosis	1990-2008	1990-2008	Match
Term in diagnosis			
1st trimester	6 (12)		
2nd trimester	4 (8)		
3rd trimester	9 (18)		
Puerperium	34 (62)		
Laterality			
RB	48.2 (27)	53.4 (39)	0.62
LB	51.8 (29)	46.6 (34)	

Table 2. — *Pathological and tumor features in PABC and non-PABC groups.*

	PABC cases (%)	Non-PABC cases (%)	*p*
T stage			
T1 (2cm or less)	22 (44)	32 (52)	0.03
T2 (>2 -5cm)	14 (28)	25 (40)	
T3 (>5cm)	7 (14)	4 (6)	
T4 (skin/muscle)	7 (14)	1 (2)	
NA	6	11	
TNM stage			
Early (I+II)	33 (69)	52 (87)	0.024
Advanced (III+IV)	15 (31)	8 (13)	
NA	8	13	
Histology			
Invasive ductal carcinoma	38 (76)	52 (74)	0.58
Invasive lobular carcinoma	6 (12)	6 (9)	
Others	6 (12)	12 (17)	
NA	6	3	
Histological tumor grade			
Grade I	8 (24)	17 (45)	0.17
Grade II	16 (49)	15 (39)	
Grade III	9 (27)	6 (16)	
NA	23	35	
Lymph node involvement	28 (53)	24 (34)	0.03
Estrogen receptors			
Positive	26 (67)	42 (78)	0.23
Negative	13 (33)	12 (22)	
NA	17	19	
Progesterone receptors			
Positive	20 (51)	41 (76)	0.01
Negative	19 (49)	13 (24)	
NA	17	19	
Her2			
Positive	10 (35)	9 (31)	0.78
Negative	19 (65)	20 (69)	
NA	27	44	
Tumor subtype			
HR+/Her2-	14 (48)	19 (66)	0.17
Her2+	10 (35)	9 (31)	
Triple -	5 (17)	1 (3)	

NA: not assigned.

Materials and Methods

The authors recorded the experienced of PABC over years at Quirón Dexeus Univeristy Hospital, Barcelona. From 1990 to 2008, 56 patients were diagnosed with PABC and matched 1:1.5 to non-PABC controls by age and date at diagnosis (73 controls). All patients were identified from the authors' prospective Breast Cancer Database.

The PABC criteria included only patients diagnosed with invasive breast cancer during or within one year after delivery. All patients were pathologically diagnosed at the present center. Before 2007 the diagnosis was performed by fine-needle aspiration and beyond 2007 by core biopsy. All cases were subsequently pathologically confirmed in the surgical specimens.

Since 2002 sentinel lymph node biopsy was introduced as a part of the axillary staging protocol, therefore patients treated later did not undergo an axillary lymphadenectomy if the sentinel node was negative.

Clinical and pathological data such as hormone receptors status, Her2Neu, histological tumor grade, histological tumor type, lymph node involvement, tumor size were retrieved from medical and pathological records.

Histological and immunohistochemical study

Histological grade was performed according to the Elston and Ellis modification of the Scarff-Bloom-Richardson grading system [18]. Hormone receptors were analyzed by immunohistochemistry. Determination of estrogen receptors (clone 6F11), progesterone receptors (clone 16), and Her2Neu (clone CB11) was performed by IHC using, in all cases, the manufacturer's prediluted antibody. A tumor considered positive for estrogen or progesterone receptors was defined as having 10% or more of stained tumor cells nuclei. Positive Her2 was considered as overexpression 3 + or 2 + if FISH technique was positive. Ki67 was not reported in the study since it had not been routinely recorded at that time.

Statistical analysis

The description of quantitative variables was performed using median, mean, range (minimum and maximum), and standard deviation. The qualitative variables were presented by means of the description of proportions. Quantitative variables were compared with Wilcoxon Mann-Whitney or Student's *t*-test, and categorical variables were analyzed with either the Pearson chi-square or Fisher's exact test. Survival was estimated using Kaplan-Meier curves. A Cox regression model was performed for the stage-adjusted survival subanalysis. All statistical analysis were performed using the SPSS Statistics 20.0 program. All tests were two-sided and the significance level was set at 0.05.

Results

A total of 56 PABC patients were diagnosed between 1990-2008, for whom 73 controls non-PABC were identified. In the present center the PABC rate was 1/1230 pregnancies and 1/76 of all breast cancer cases (1.31%).

Patient characteristics are shown in Table 1. The mean age of PABC and non-PABC group was 35.4 ± 4.7 (27-50) years and 37.3 ± 6.6 (27-52), respectively (age-matched). The PABC diagnosis was made during postpartum term in 34 cases (62%), and during pregnancy in 22 patients (38%): six cases in the first trimester (12%), four cases in the second trimester (8%), and nine in the third trimester (18%).

Table 3. — *Recurrence and mortality in PABC and non-PABC patients.*

	PABC cases (%)	Non-PABC cases (%)	*p*
N patients	56 (100)	73 (100)	Match
Locoregional recurrence	4 (7)	5 (4)	0.9
Distant metastasis	5 (9)	7 (10)	0.8
Deaths	7 (13)	0	0.02

Pathological and tumor features are summarized in Table 2. PABC patients presented more advanced tumor stage at diagnosis compared to non-PABC (31% advanced disease in PABC group *vs* 13% non-PABC group, $p = 0.024$). Larger tumors were found within PABC patients (40% T2 stage in PABC *vs* 28% non-PABC ($p = 0.03$). In the present series, lymph node involvement was found in 28 PABC patients (53%) versus 24 non-PABC patients (34%) ($p = 0.034$). No relevant differences were found according tumor histology or laterality between both groups. The majority was diagnosed with invasive ductal carcinoma in both groups, 52 PABC cases (74%) and 38 (76%) in control group ($p = 0.5$).

Regarding immunohistochemical analysis, adverse prognostic factors were found within PABC patients compared to non-PABC group: negative-ER (33% *vs* 22%; $p = 0.23$), negative-PR (49% *vs* 24%; $p = 0.014$) and positive-Her2 (35% *vs* 31%; $p = 0.78$)

The most common tumor subtype in PABC patients was positive-HR/negative-Her2 (48%), but in comparison to non-PABC group, triple negative tumors were found in a high rate (17% vs 3%, $p = 0.17$).

At a median follow-up of 3.6 years (1-14) for PABC subset and 8.8 years (1-31) for the control group, four patients (7.4%) had a locoregional recurrence, five (14%) cases metastasized, and seven (13%) died in PABC group, related to 5 (6.9), 7 (16) and 0 in non-PABC group (Table 3).

Survival in the PABC subset tended to be lower (Figure 1). The five-year DFS was 64% in PABC patients and 86% in non-PABC patients ($p = 0.12$) and five-year OS was 74% and 100%, respectively ($p = 0.21$). However, DFS analysis matching stage did not find significant differences between both groups (Figure 2).

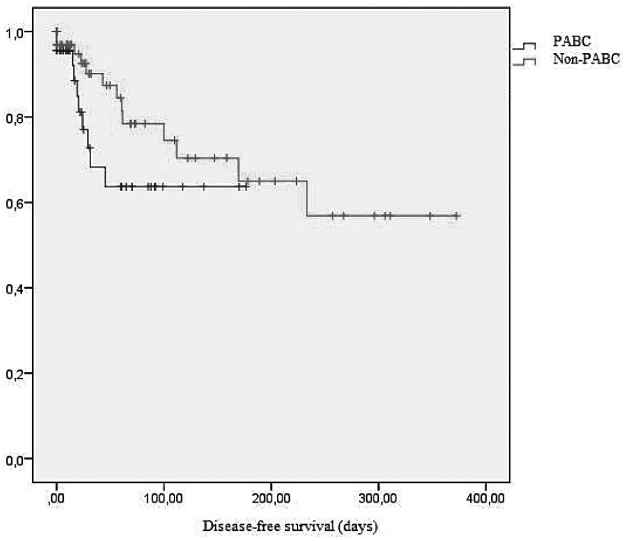

Figure 1. — Disease-free survival between PABC patients and non-PABC matched patients.

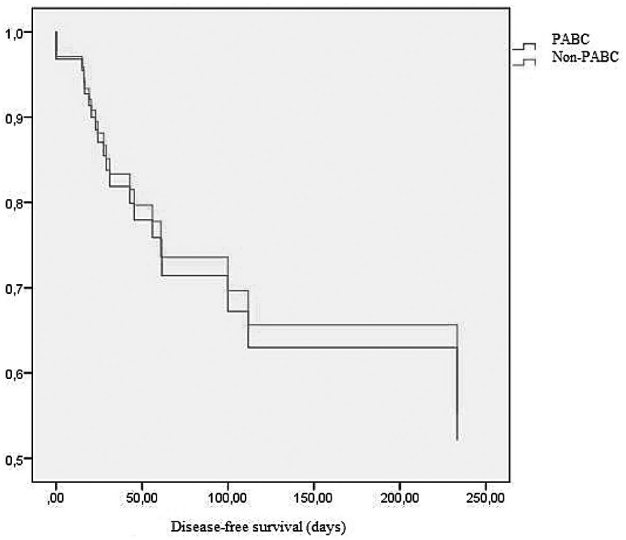

Figure 2. — Disease-free survival adjusted for stage between PABC and non-PABC patients.

Discussion

The overall PABC rate in the present series between 1990-2008 was 1/1230 pregnancies and 1.31% of all breast cancers, higher than the rate described in literature [2]. This is likely due to a delay in pregnancy among patients at our center, with a mean parity age of 34 years.

Classically, PABC has been considered an aggressive disease with a poor outcome, mainly, due to the independent effect of pregnancy. This belief has led it to be considered as an intractable situation in which surgery was not effective [19, 20]. However, in recent years some published datas have suggested a poor prognosis related to the delay in diagnosis and the young age of PABC patients [17, 21, 22].

The current study represents a large series in a single center evaluating the pathological features in PABC group compared with non-PABC patients. The authors found that in the PABC group patients were diagnosed with an advanced TNM stage and presented greater nodal involvement compared to non-PABC patients (31% *vs* 13%, $p < 0.05$; 52% *vs* 34%, $p < 0.05$; respectively). These findings corroborate the observa-

tions by Middleton *et al.* who found a more advanced diseased among PABC patients [23]. This may reflect a delay in diagnosis and treatment due to childbearing. The physiological changes induced by gestation make physical examination more challenging. This difficulty must be added to the lack of attention to breast symptoms (breast pain, nipple discharge, increased mammary density, mastitis) by the obstetrician who can consider them as normal changes in the pregnant breast. All these factors could result in a more advanced PABC diagnosis.

Regarding prognostic factors, the present series showed a high rate of Grade III histological tumor, negative hormone receptors, and positive Her2. These results are in agreement with those previously published where the PABC group had adverse prognostic factors [5, 23-25]. Although the most common tumor subtype within PABC patients was positive-HR/negative-Her2, the present authors found a high rate of triple negative tumors (17% *vs* 3%, $p = 0.17$). This could suggest that the poor outcome is not directly related to pregnancy but to tumor subtypes and its pathological characteristics. Such findings may be attributed to the young age of PABC patients who are more likely to develop breast tumors with such features [23, 26]. However, the present authors' matching process allowed them to correct the impact of age, and they found even a greater percentage of adverse prognostic factors in PABC subset.

In the prognosis and outcome analysis, PABC patients had greater mortality ($p = 0.02$) and poorer survival (five-year DFS 64% *vs* 86%), but the adjustment for age and stage showed no considerable differences between both groups. If pregnancy itself is the main cause of the poorer prognosis within women with PABC, PABC patients would be expected to have more recurrences and greater mortality compared to non-PABC patients with the same stage at the time of diagnosis.

From the present study the authors may conclude that PABC patients are diagnosed with advanced breast cancer. The poorer prognosis observed within PABC women may not be associated with pregnancy itself, but with tumor subtype pathological features and a delay in diagnosis related to advanced disease, as the matched-stage analysis found no major differences in survival between both groups.

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