Pregnancy-Associated Breast Cancer Compared to Invasive Ductal Carcinoma Less Than 40 Year-Old of Age

임신성 유방암과 40세 미만의 유방암과 비교

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초 록

목적 : 본 연구는 임신성 유방암의 임상병리학적 특징과 예후를 조사하여 임신이 임신성 유방암에 미치는 영향을 평가하고자 하였다.

방법 : 1987년부터 2007년 사이에 치료받은 14명의 임신성 유방암 환자들의 임상병리적 특성, 치료방법, 생존율을 855명의 40세 미만 침윤성 유방암 환자들과 chi-square 검정, Kaplan-Meier 방법, 그리고 Cox's hazards 모델을 이용하여 비교하였다. 임신성 유방암은 임신기간 중 또는 출산 후 1년 이내에 진단된 유방암으로 정의하였다.

결과 : 14명의 임신성 유방암 환자 중, 7명은 임신 중에 진단되었으며, 7명은 산후 1년 내에 진단되었다. 평균 증상기간은 7.6개월이었고, 임신성 유방암과 40세 미만 유방암 환자들의 평균 나이는 각각 32.6세, 34.6세였다 (p=0.044). 임신성 유방암은 모두 유관암이었으며, 병기, 호르몬 수용체 발현, 치료방법은 임신성 유방암과 40세 미만 유방암 사이에 통계적 차이를 보이지 않았다. 임신성 유방암 환자의 5년 무병 생존율과 전체 생존률은 57.1%, 70.0% 였으며, 생존율은 두 그룹 사이에 통계적 차이는 없었다. 다변량 분석에서도 임신 여부는 생존율에 영향을 주지 않았다. 임신성 유방암 환자 중 출산 전과 후에 따른 생존율은 통계적으로 유의한 차이를 보이지 않았다.

결론 : 젊은 유방암 환자와 비교하여 임신성 유방암은 임상병리학적 특성과 예후는 차이가 없었으며, 임신성 유방암 환자와 태아를 위해 적극적인 진단과 다학제적인 치료가 필요하다.

중심단어 : 유방암, 임신, 예후, 생존

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INTRODUCTION

In Korea, the incidence of breast cancer has been increasing significantly in recent years and the absolute number of young breast cancer patients less than 40 years of age has also been increasing.[1)] Pregnancy and breast cancer have become a significant concern for not only young women but also clinicians. Breast cancer is the most commonly diagnosed malignancy during pregnancy.[2)] The incidence has been reported to be from 1:3,000 to 1:10,000 pregnancies and from 0.2% to 3.8% of breast cancer patients whose age was less than 50 years.[3,4)] Pregnancy-associated breast cancer (PABC) is generally defined as breast cancer diagnosed during pregnancy or within the first year after delivery. Recent trends in delaying childbearing may elicit a further increase in the incidence of PABC.

Traditionally pregnancy has been considered to decrease a woman's lifetime risk of developing breast cancer, but more detailed analyses suggest that pregnancy itself transiently increases the risk of breast cancer.[3,5)] Delay in diagnosis of breast cancer during pregnancy, promotional effects of gestational hormones on tumor, and undetermined aggressive intrinsic tumor biology of PABC make pregnant women with breast cancer presenting with more advanced stage breast cancer, and subsequently show a poorer prognosis.[5,6)] On the contrary, it has been reported that the survival of PABC patients is not significantly different from that of non-PABC patients

when the stage of disease was matched.[7,8] Diagnosis and management of PABC are additional challenge for a clinician because not only the treatment of pregnant woman herself but also the safety of the fetus should be considered. There are many issues to be determined regarding pregnancy and breast cancer in younger women.

The aims of this study were to investigate clinicopathological characteristics and outcomes of PABC compared to those of invasive breast cancer patients aged less than 40 years, and to evaluate whether pregnancy itself is an independent prognostic factor and whether the survival of the patients diagnosed before and after their delivery is different among younger Korean breast cancer patients in association with PABC.

PATIENTS AND METHODS

Study population

Patients were selected from the Yonsei Hospital Breast Cancer Registry Database containing clinicopathological information, treatment modalities, and details of outcomes. A total of 1,106 patients under 40 years of age were treated for breast cancer at the Department of Surgery, Yonsei University College of Medicine, Seoul, Korea, between January 1987 and December 2007, and the exclusion criteria were as follows (n=237): pure in situ breast carcinoma, recurrent or metastatic disease, non-PABC patients with special histological types including lobular carcinoma, and tumors of non-epithelial origin such as phyllodes tumor, lymphoma, or sarcoma. PABC was defined as breast cancer diagnosed during pregnancy or during the first postpartum year. A total of 14 patients fulfilled the above criteria. Clinicopathological characteristics, treatment patterns, and survival outcomes were compared to those of 855 invasive ductal carcinoma not otherwise specified (IDC) patients less than 40 years of age.

Patients were treated with either total mastectomy or breast-conserving surgery and sentinel lymph node biopsy or axillary lymph node dissection. Sentinel lymph node was detected using radioisotope technique with 18.5 MBq (0.5 mCi) ^{99m}Tc Phytate Kit (Korea Atomic Energy Research Institute, Daejeon, Korea). After surgery, local radiotherapy or adjuvant systemic treatment was conducted if the patient was able to tolerable it. Among the whole study population, 95 (10.9%) patients with locally advanced breast cancer received preoperative chemotherapy containing anthracycline with or without taxane regimen. Clinical follow-up included history taking, physical examination, laboratory tests, and radiological imaging tests every 6-12 months for detection of relapse. Tumor stage was based on the American Joint Committee on Cancer staging criteria (6th edition). Histological grade was assessed by the modified Bloom-Richardson classification. Tumors with ≥ 10% nuclear-stained cells were considered positive for estrogen (ER) and progesterone receptors (PR). HER2/neu immunohistochemical staining was scored from 0 to 3+ according to the guidelines for the HercepTest™ (Dako, Glostrup, Denmark).[9] Because fluorescence in situ hybridization (FISH) test had not been performed routinely during most of the study period, HER-2 staining was considered positive when strong (3+) membrane staining was observed, whereas cases from 0 to 2+ were regarded as negative.

Study endpoints and statistics

Locoregional recurrence was defined as tumor recurrence in the ipsilateral breast, chest wall, and regional lymph node. Any recurrence at a distant site including contralateral axillary or supraclavicular lymph nodes was considered as a distant metastasis. Disease-free survival (DFS) was measured from the date of the first curative surgery to the date of the first locoregional or systemic recurrence, or death before any type of relapse. Locoregional relapse-free survival (LRRFS) was calculated from the date of the first operation to the date of the first locoregional relapse or death without any type of recurrence. Distant relapse-free survival (DRFS) was

measured from the date of the first operation to the date of the first distant metastasis or death without any type of recurrence. Overall survival (OS) was calculated from the date of the first surgery to the date of the last follow-up or death from any cause.

The differences between the groups were evaluated by a chi-square test. Fisher's exact test was used when appropriate. Continuous variable was compared using two-sample t-test. Survival curve was plotted using the Kaplan-Meier method and group differences in survival times were investigated by a log-rank test. A Cox's proportional hazards model was used to identify the variables that were independently associated with survival. All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL) was used for all statistical analysis.

RESULTS

During the study period, 14 patients were diagnosed with PABC, which constituted 0.3% of all 4,335 IDC patients treated at our institution irrespective of age at diagnosis, 0.6% of 2,541 IDC patients aged less than 50 years, and 1.6% of 869 IDC patients under 40 years. The mean age of the whole study population at diagnosis was 34.6 years [standard deviation (SD), 3.8]. The mean follow-up duration was 69.4 months (SD, 45). Among 14 patients with PABC, 7 were diagnosed with breast cancer during pregnancy: 3 were in the first trimester of pregnancy and 4 in the third trimester. The 7 rest of the patients (7 of 14 patients) were diagnosed with breast cancer during postpartum period. Thirteen patients showed a chief complaint of breast lump and bloody nipple discharge present in one patient. The mean symptom duration was 7.6 months (SD, 7.7; range 0.5-24) in 14 patients with PABC. The mean symptom duration of the patients diagnosed during pregnancy and during postpartum period was 4.5 and 10.7 months, respectively. However, there was no statistical significance (p=0.143, two-sample t-test). The mean tumor size of the patients diagnosed during pregnancy and during postpartum period was 3.0cm (SD, 1.3) and 2.3cm (SD, 1.2), respectively, which was not significantly different (p=0.331, t-test). Three patients diagnosed during the first trimester underwent therapeutic abortion with simultaneous treatment of breast cancer.

Comparison of clinicopathological characteristics between PABC and IDC under 40 years of age is shown in Table 1. The mean age at diagnosis of PABC and IDC under 40 years of age was 32.6 (range, 24-39) and 34.6 (range, 20-39) years, respectively. The patients with PABC were younger at diagnosis than those with IDC less than 40 years old (p=0.044, t-test). All PABCs were ductal

Table 1. Clinicopathological Characteristics

Factor	PABC	IDC less than 40 yrs of age	*p*-value
Age (yrs)			
Mean±SD (range)	32.6 (24-39)	34.6 (20-39)	0.044*
<35	9 (64.3)	338 (39.5)	0.061
35~39	5 (35.7)	517 (60.5)	
Tumor size			
≤ 2cm	6 (42.9)	369 (43.2)	0.982
> 2cm	8 (57.1)	486 (56.8)	
Node stage			
N0	9 (64.3)	431 (50.4)	0.739†
N1	4 (28.6)	257 (30.1)	
N2	0 (0.0)	84 (9.8)	
N3	1 (7.1)	83 (9.7)	
Histologic grade (n=649)			
I	3 (27.3)	116 (18.2)	0.541†
II	5 (45.5)	355 (55.6)	
III	3 (27.3)	167 (26.2)	
Estrogen receptor (n=720)			
Negative	6 (50.0)	286 (40.4)	0.560†
Positive	6 (50.0)	422 (59.6)	
Progesterone receptor (n=706)			
Negative	7 (58.3)	294 (42.4)	0.267
Positive	5 (41.7)	400 (57.6)	
HER2 (n=496)			
Negative	5 (55.6)	372 (76.4)	0.228†
Positive	4 (44.4)	115 (23.6)	

*Two-sample t-test; †Fisher's exact test.

Abbreviations: PABC, pregnancy-associated breast cancer; IDC, invasive ductal carcinoma; SD, standard deviation; HER2, human epidermal growth factor receptor 2.

carcinoma without lobular or special type. Tumor and node stage was not significantly different between PABC and IDC under 40 years of age. Among the patients with PABC, 11 (78.6%) were in stage II, 2 (14.3%) in stage I, and 1 (7.1%) in stage III, respectively. No significant difference in histological grade was found between two groups. Among the patients who were available for ER (n=720) and PR (n=706), PABC subgroup showed higher frequency of ER- and PR-negative tumor, but there was no statistical significance. The patients with PABC were determined to present higher proportion of HER2-positive tumor. However, too many missing values and no FISH analysis make our results subject to be validated using independent dataset.

Treatment modalities of the patients with PABC were compared to those of IDC under 40 years of age (Table 2). Three patients with PABC received neoadjuvant chemotherapy using FAC (fluorouracil, anthracycline, and cyclophosphamide) or AT (anthracycline and taxane) regimens. Seven patients with PABC underwent breast-conserving surgery. Sentinel lymph node biopsy using radioisotope and subsequent axillary node dissection were performed in four patients with PABC. Among them, two patients were in the third trimester of pregnancy. After breast surgery with sentinel node biopsy, they delivered a healthy baby. There was no significant difference of treatment patterns including systemic chemotherapy or endocrine therapy between PABC and IDC under 40 years of age.

The Kaplan-Meier curves for DFS, LRRFS, DRFS, and OS are demonstrated in Fig. 1. Five-year DFS, LRRFS, DRFS, and OS of the patients with PABC was 57.1%, 71.3%, 56.4%, and 70.0%, respectively. Survival between PABC and IDC under 40 years of age was not significantly different. In the Cox's regression models adjusting for age at diagnosis, tumor and node stage, grade, ER, and the use of chemotherapy and endocrine therapy, PABC was not associated with survival outcomes (Table 3). Age at diagnosis, tumor stage, node status, and the use of chemotherapy were determined to be independent

Table 2. Treatment Patterns

Factor	PABC	IDC less than 40 yrs of age	*p*-value
Neoadjuvant chemotherapy			
Not done	11 (78.6)	763 (89.2)	0.190*
Done	3 (21.4)	92 (10.8)	
Type of surgery			
Breast-conserving surgery	7 (50.0)	225 (26.3)	0.064*
Total mastectomy	7 (50.0)	630 (73.7)	
Radiotherapy (n=835)			
Not done	5 (35.7)	457 (55.7)	0.137
Done	9 (64.3)	364 (44.3)	
Chemotherapy (n=860)			
Not done	2 (14.3)	116 (13.7)	>0.999*
Done	12 (85.7)	730 (86.3)	
Endocrine therapy (n=836)			
Not done	8 (57.1)	449 (54.6)	0.851
Done	6 (42.9)	373 (45.4)	

*Fisher's exact test

Abbreviations: PABC, pregnancy-associated breast cancer; IDC, invasive ductal carcinoma.

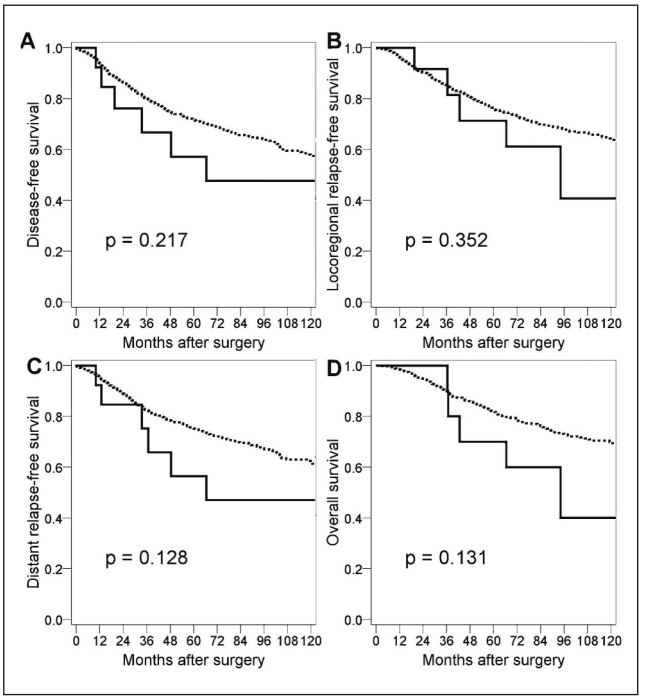

Fig. 1. Disease-free (A), locoregional relapse-free (B), distant relapse-free (C), and overall (D) survival curve.
Solid line represents pregnancy-associated breast cancer and dotted line represents invasive ductal carcinoma less than 40 years of age.

Table 3. Multivariate Analyses for Survival

	DFS			LRRFS			DRFS			OS		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Pregnancy-associated (yes)	1.604	0.584-4.402	0.359	1.289	0.404-4.115	0.668	1.924	0.697-5.314	0.207	1.881	0.581-6.091	0.292
Age (< 35 yrs)	1.696	1.255-2.292	0.001	1.706	1.230-2.367	0.001	1.671	1.214-2.301	0.002	1.741	1.203-2.517	0.003
Tumor size (> 2cm)	1.752	1.252-2.452	0.001	1.708	1.175-2.483	0.005	1.876	1.303-2.699	0.001	1.718	1.121-2.633	0.013
Node status (positive)	2.805	1.973-3.987	<0.001	2.799	1.885-4.156	<0.001	2.984	2.045-4.353	<0.001	3.302	2.070-5.267	<0.001
Grade (II/III)	1.138	0.754-1.719	0.537	1.254	0.785-2.003	0.343	1.244	0.792-1.953	0.344	1.552	0.886-2.717	0.124
ER (negative)	0.909	0.603-1.369	0.647	0.923	0.595-1.434	0.723	0.960	0.622-1.480	0.852	0.898	0.551-1.465	0.668
Chemotherapy (not done)	2.485	1.313-4.704	0.005	2.885	1.458-5.710	0.002	1.858	0.851-4.059	0.120	2.374	0.994-5.672	0.052
Endocrine therapy (not done)	1.216	0.822-1.799	0.327	1.418	0.920-2.186	0.114	1.121	0.740-1.696	0.591	1.486	0.916-2.411	0.109

Abbreviations: DFS, disease-free survival; LRRFS, locoregional relapse-free survival; DRFS, distant relapse-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor.

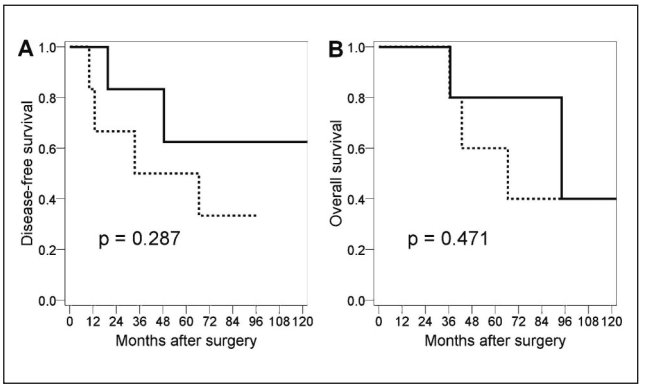

Fig. 2. Disease-free (A) and overall (B) survival of the patients diagnosed before and after delivery.
Solid line represents breast cancer patients diagnosed during antepartum period and dotted line represents those diagnosed during postpartum period.

prognostic factors in our study population of young breast cancer patients. Among the patients with PABC, there was no statistical difference in survival outcomes between the patients diagnosed before and after delivery (Fig. 2).

DISCUSSION

The majority of abnormal breast findings during pregnancy or lactation are benign disease including infectious complications. It has been widely recognized that the delay in diagnosis is associated with more advanced disease at diagnosis of women with PABC.[10] Therefore, physicians should be vigilant of any suspicious abnormalities during pregnancy or lactation to avoid a delay in the diagnosis of breast cancer. It has been reported that the average age of patients with PABC is 32-38 years and the average delay in diagnosis in pregnant patients is 5-10 months as compared to 1-4 months in non-pregnant patients.[3] Our mean age at diagnosis and average symptom duration of the patients with PABC was 32.6 years and 7.6 months. In 2006, The Korean Breast Cancer Society reported that 64.5% of newly diagnosed breast cancer patients presented symptom duration of less than 3 months and 15.8% presented symptom duration of 3 to 6 months.[11] These findings suggest that diagnosis of Korean PABC might be delayed similar to the western series.

IDC is the most prevalent histological type of cancer in PABC and these tumors tend to have higher grade and lymphovascular invasion.[3,12] PABC shows typically frequent and larger size axillary node metastasis.[13] Gestational hormones may play an important role for aggressive biology of PABC.[6] A higher percentage of PABC is ER- and/or PR-negative tumor and increased overexpression of HER2 is also common.[8] PABC frequently presents higher Ki-67 proliferative index.[13] However, the majority of these studies are composed of case series with small sample size. The overall histopathological and immunohistochemical findings of PABC are consistent with young patients with breast cancer.[8] In our study, histopathological characteristics and expression of biomarkers are not significantly different between PABC

and IDC under 40 years of age.

Under general anesthesia, breast surgery can be safely performed with little risk to the fetus during any stage of pregnancy.[3] Patients with PABC can be treated with mastectomy or breast-conserving surgery. Elective abortion has been found not to improve survival for PABC patients.[14] Therefore, it is not routinely recommended as a therapeutic approach but should be discussed in case of the early pregnancy period. Radiation therapy is contraindicated during pregnancy due to the increased risk of teratogenesis. However, radiation therapy can be delayed up to 12 weeks without increasing the risk of local recurrence and if adjuvant or neoadjuvant chemotherapy is indicated according to the risk evaluation, the delay in breast irradiation up to 6 months may be possible.[8] Recently, the international panel of experts have recommended that even if patients are treated in the first trimester or early second trimester, radiation therapy can be delayed until after delivery, but local failure rate of PABC patients treated with breast-conserving therapy is not clearly defined.[2] Axillary staging by sentinel lymph node biopsy using 99m-Tc is determined to be safe and accurate in the pregnant women with clinically node-negative disease.[15] However, the use of blue dye is not recommended because of anaphylaxis, teratogenesis, or unknwn effects to the fetus.[3,8]

The decision to administer systemic chemotherapy in a PABC patient should depend on the risk evaluation such as disease stage and clinicopathological features as in a non-pregnant breast cancer patient.[16] Although most chemotherapeutic agents are under the U.S. Food and Drug Administration pregnancy FDA category D, namely positive evidence of human fetal risk exists but benefits in certain situations may make use of the acceptable drug despite its risk. Several recent studies have shown that certain chemotherapy regimens including anthracycline can be safely used during the second and third trimester of pregnancy.[3,16,17] PABC patients should not receive any chemotherapeutic drugs for at least three weeks prior to delivery to allow for correction of myelosuppression in both the mother and fetus.[3] Antiemetic agents such as ondansetron (Zofran®) and granisetron (Kytril®) are rated pregnancy risk category B and are safely used in pregnant women receiving chemotherapy.[16] The short use of dexamethasone for nausea prophylaxis and granulocyte colony-stimulating factor (G-CSF) for neutropenia prophylaxis also can be available.[10,16,17] Endocrine therapy using tamoxifen should be initiated after delivery and completion of chemotherapy if PABC is determined as endocrine-responsive tumor. Although no fetal abnormalities has been described, some cases of anhydramnios or oligohydramnios, which is known to significantly increase the risk of premature delivery, fetal morbidity, and mortality, have been reported by the use of trastuzumab during pregnancy.[18,19] The safety profile of trastuzumab or lapatinib during pregnancy is supported by very limited data, so, targeted agents are not routinely recommended yet.[10,19]

It has not been clearly established whether pregnancy itself is an independent predictor for outcomes in PABC. The prognosis of PABC had been known to be poor, partly associated with the delay in diagnosis and treatment, higher stage at diagnosis, more favorable microenvironment created during pregnancy, and BRCA1 and BRCA2 germline mutations.[6,20,21] Except for only two patients, our PABC subgroups were diagnosed with stage II disease, although there was no statistical difference between the two groups. However, when pregnant women are age and stage-matched with non-pregnant controls, survival is determined to be equivalent between the two groups.[3,22] This is further supported by our results of no difference in DFS, LRRFS, DRFS, and OS between PABC and IDC less than 40 years of age.

Recently a large population-based study of Swedish women with PABC showed that the elevated mortality among PABC patients varied markedly with timing of diagnosis in relation to delivery.[23] The authors observed nearly 4 times higher peak mortality in women diagnosed

with breast cancer during 4–6 months after delivery and subsequent higher mortality rate in women diagnosed during pregnancy or within 3 months after birth. Since the involution of breast to its pre-pregnant state begins to occur during those periods, they suggest the hypothesis that postpartum changes in the microenvironment of mammary gland may enhance tumor growth and metastasis.[23,24] Although small sample size of our PABC subgroup could not come to solid conclusions, there was no statistical difference in survival outcomes between women diagnosed with breast cancer before and after delivery. It is remained to be determined in the near future.

In conclusion, PABC patients frequently presented breast symptoms such as palpable lump and showed longer symptom duration. Clinicopathological characteristics, treatment patterns, and survival outcomes were not significantly different between PABC and IDC less than 40 years of age. Pregnancy itself did not increase the risk of poorer disease outcome when adjusting for other clinicopathological parameters. Therefore, pregnant or lactating women who present breast symptoms should be urgently evaluated as not to delay the diagnosis and be treated appropriately with multidisciplinary therapeutic modalities once an accurate diagnosis is made. Termination of pregnancy should be discussed along with the implications of pregnancy when dealing with the choice of treatment options, the possible effects on the fetus and the prognosis. Since pregnant or lactating women have been excluded in most prospective clinical trials, ethically supported new randomized trials and basic researches for the biological mechanisms of pregnancy should be developed to determine issues that remain unsettled.

Conflict of interest

The authors have no financial conflicts of interest.

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Pregnancy-Associated Breast Cancer Compared to Invasive Ductal Carcinoma Less Than 40 Year-Old of Age

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Abstract

Purpose : The aims of this study were to investigate clinicopathological characteristics and outcomes of pregnancy-associated breast cancer (PABC) and to determine the implications of pregnancy itself on the prognosis of PABC.

Methods : Clinicopathological features, treatment patterns, and survival of 14 PABC patients were compared to those of 855 invasive ductal carcinoma (IDC) patients under 40 years of age, who were treated between 1987 and 2007, using a chi-square test, the Kaplan-Meier method, and Cox's hazards models. PABC was defined as breast cancer diagnosed during pregnancy or within the first year after delivery.

Results : Among 14 PABCs, 7 were diagnosed during pregnancy and 7, during the first postpartum year. The mean duration of the symptoms was 7.6 months. The mean age at diagnosis of PABC and IDC under 40 years was 32.6 and 34.6 years, respectively (p=0.044). All PABCs were ductal type. Hormone receptors, treatment modalities, and tumor and node stage were not statistically different between PABC and IDC under 40 years. Five-year disease-free, locoregional relapse-free, distant relapse-free, and overall survival of PABC was 57.1%, 71.3%, 56.4%, and 70.0%, respectively. Survival was not significantly different between two groups. In Cox°Øs models, PABC was not associated with survival outcomes. Among PABCs, there was no statistical difference in survival between patients diagnosed before and after delivery.

Conclusion : Pregnancy itself does not increase the risk of poorer outcomes among young breast cancer patients. Vigilant diagnosis and multidisciplinary treatment should be recommended to best manage woman with PABC and her baby.

Key Words : Breast neoplasms, Pregnancy, Prognosis, Survival

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