Journal of Breast Cancer

J Breast Cancer 2018 December; 21(4): 425-432 https://doi.org/10.4048/jbc.2018.21.e58

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ORIGINAL ARTICLE

Neoadjuvant Chemotherapy and Prognosis of Pregnancy-Associated Breast Cancer: A Time-Trends Study of the Korean Breast Cancer Registry Database

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Purpose: Pregnancy-associated breast cancer (PABC) is rare, and its cause and prognosis are not well known. Additionally, treatment is limited with respect to the risk to the fetus. The purpose of this study was to investigate the characteristics and treatment trends of PABC and the survival rate according to the treatment. **Methods:** In the Korean Breast Cancer Society Registry database, women younger than 50 years and who were diagnosed with breast cancer from 1996 to 2015 were included. PABC was defined as breast cancer diagnosed during pregnancy or within 1 year after delivery. **Results:** We examined 411 patients with PABC and 83,381 patients with non-PABC. Over time, the proportions of patients undergoing breast-conserving surgery and sentinel lymph node biopsy increased, and neoadjuvant chemotherapy and radiation therapy administration rates also increased. In the past, the overall survival of patients with PABC was poorer than that of patients with non-PABC, but there was no difference in overall survival rates in more recent years. There was no difference in overall survival rates between patients who received neoadjuvant chemotherapy (hazard ratio [HR], 1.28; 95% confidence interval [CI], 0.66–2.49; $p=0.459$), but PABC conferred poorer prognosis than non-PABC in patients receiving adjuvant chemotherapy (HR, 1.63; 95% CI, 1.27–2.08; $p<0.001$). **Conclusion:** There was no difference in the prognosis between patients with PABC and those with non-PABC receiving neoadjuvant chemotherapy. The increase in neoadjuvant chemotherapy according to current treatment guidelines is expected to improve the survival rate of patients with PABC.

Key Words: *Breast neoplasms, Drug therapy, Pregnancy, Prognosis*

INTRODUCTION

Pregnancy-associated breast cancer (PABC) is generally defined as breast cancer diagnosed during pregnancy or within 12 months after delivery. Breast cancer is one of the most common cancers in pregnant women. Cancer is diagnosed in approximately 1 of 1,000 pregnancies [1], and PABC is diagnosed in approximately 1 of 3,000 pregnancies [2]. The incidence, which ranges from 0.2% to 0.4% of all breast cancers, is very low [3,4].

Because of the low incidence and lack of prospective studies, little is known about PABC. Although there are studies that show no difference in the survival rates between PABC and non-PABC [5,6], recent meta analyses and review articles suggest that the prognosis is worse than that in non-PABC [7-9].

In previous reports, PABC was characterized by a large size and more advanced stage, and delayed diagnosis could be related to the poor prognosis [10,11]. The limitation in treatment for fetal safety during pregnancy was thought to affect prognosis. Recent guidelines and treatment trends suggest that chemotherapy is safe starting from the second trimester of pregnancy [8,12], and this change in treatment direction is expected to improve the prognosis of patients with PABC.

Recent studies have shown that hormone receptor expres-

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This article was supported by the Korean Breast Cancer Society.

This work was supported by the National Research Foundation of Korea (2017R1D1A1B03028103) and Korea University Grant (K1813171).

Received: May 28, 2018 **Accepted:** November 15, 2018

sion is low, and human epidermal growth factor receptor 2 (HER2) overexpression is high in PABC [8,9,13]. This suggests that the biologic characteristics of the PABC tumor or its microenvironment due to pregnancy may be related to the prognosis, in addition to delayed diagnosis or treatment.

The frequency of PABC is likely to increase due to delayed marriage and childbirth [14,15]. The purpose of this study was to analyze the characteristics of PABC and the prognosis according to treatment modalities using the Korean Breast Cancer Society Registry (KBCSR) database.

METHODS

Korean Breast Cancer Society Registry

Since 1996, the Korean Breast Cancer Society has analyzed and reported the nationwide breast cancer data to evaluate the chronological changes in characteristics of breast cancer in Korean patients [16]. In 2001, the KBCSR Program was established via the Internet (http://registry.kbcs.or.kr/ecrf/login.php), and more than 100 hospitals (74 university hospitals, 24 general hospitals, and six private breast clinics) are currently participating. The database includes clinicopathological factors; age; sex; type of surgery; diagnosis at delivery; family history; parity; age of menarche; stage (according to the 7th American Joint Committee on Cancer classification); histology; presence of the biological markers estrogen receptor, progesterone receptor, and HER2; methods of treatment (i.e., chemotherapy, radiotherapy, endocrine therapy); types of chemotherapy; and date and cause of death. Further details of the KBCSR database were described in a previous report [17].

Patients

Of the patients who were diagnosed with breast cancer between 1996 and 2015 and were enrolled in the KBCSR, women between 20 and 49 years of age were included in the study. PABC was defined as being diagnosed within 1 year after pregnancy or delivery and was compared with non-PABC. Non-PABC was defined as breast cancer in patients who were not currently pregnant and had not delivered within the previous year. Among patients with non-PABC, 114 patients who were of the same age at diagnosis of breast cancer and at delivery were excluded.

Statistical methods

The clinicopathological characteristics were compared between patients with PABC and those with non-PABC. The study period was divided into four intervals of 5 years each (1996–2000, 2001–2005, 2006–2010, and 2011–2015), and the difference in clinicopathological characteristics according to the time was analyzed (Figure 1).

The clinicopathological characteristics were analyzed using Pearson chi-square test. The overall survival (OS) was based on the dates of diagnosis and death; the latter was recorded from the data of the Ministry of Health and Welfare, Republic of Korea. The Kaplan-Meier curve was used for univariate analysis, and the Cox proportional hazards model (95% confidence interval, CI) was used for multivariate analysis. The probability of significance was $p<0.05$. The statistical program used was IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, USA).

This study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No: 2018AN0036). For this type of study, informed consent was not required.

RESULTS

Clinicopathological characteristics of patients with pregnancy-associated breast cancer

Of a total of 83,792 patients, there were 411 patients with PABC (0.5%) and 83,381 patients with non-PABC (99.5%). As shown in Table 1, the percentage of patients in their 30s at the time of diagnosis was higher than that in the past, and the proportion of patients in their 20s decreased. The proportion of patients with early menarche (≤13 years) increased, and the percentage of patients giving birth for the first time after 30 years of age increased over time.

Histology showed that more than 95% of the patients had

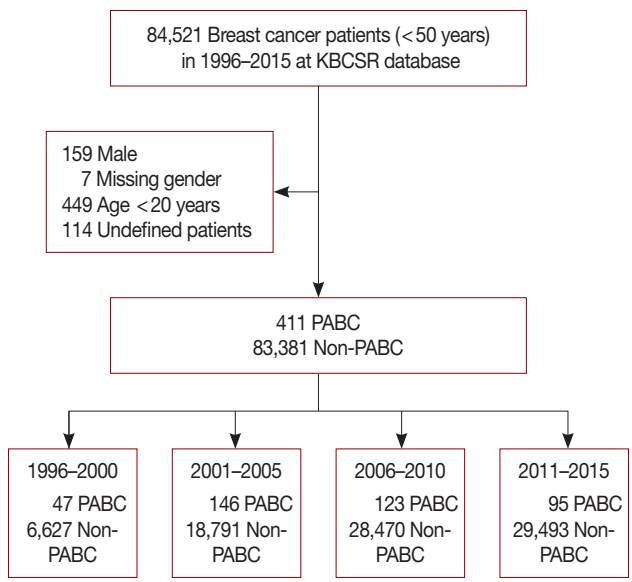

Figure 1. Study flow diagram.
KBCSR=Korean Breast Cancer Society Registry; PABC=pregnancy-associated breast cancer.

https://doi.org/10.4048/jbc.2018.21.e58

Table 1. Clinicopathological characteristics of total patients by period

Characteristic	1996–2000		*p*-value	2001–2005		*p*-value	2006–2010		*p*-value	2011–2015		*p*-value
	Non-PABC (n=6,627) No. (%)	PABC (n=47) No. (%)		Non-PABC (n=18,791) No. (%)	PABC (n=146) No. (%)		Non-PABC (n=28,470) No. (%)	PABC (n=123) No. (%)		Non-PABC (n=29,493) No. (%)	PABC (n=95) No. (%)	
Age (yr)			<0.001			<0.001			<0.001			<0.001
20–29	246 (3.7)	12 (25.5)		522 (2.8)	24 (16.4)		696 (2.4)	9 (7.3)		593 (2.0)	5 (5.3)	
30–39	2,222 (33.5)	31 (66.0)		5,123 (27.2)	98 (67.1)		6,887 (24.2)	102 (82.9)		6,396 (21.7)	82 (86.3)	
40–49	4,159 (62.8)	4 (8.5)		13,146 (70.0)	24 (16.4)		20,887 (73.4)	12 (9.8)		22,504 (76.3)	8 (8.4)	
Breast op.			<0.001			0.001			<0.001			0.379
Mastectomy	4,744 (72.7)	34 (72.3)		10,262 (56.0)	83 (56.9)		11,343 (40.0)	46 (37.4)		9,687 (33.0)	36 (39.1)	
BCS	1,733 (26.5)	9 (19.1)		7,924 (43.3)	58 (39.7)		16,728 (59.0)	70 (56.9)		19,564 (66.5)	56 (60.9)	
No	51 (0.8)	4 (8.5)		134 (0.7)	5 (3.4)		271 (1.0)	7 (5.7)		138 (0.5)	0	
LN op.			0.008			0.621			0.624			0.056
ALND	5,953 (91.4)	37 (78.7)		14,124 (78.4)	117(80.2)		13,100 (46.5)	62 (50.4)		4,230 (14.3)	19 (20.0)	
SLNB	205 (3.2)	4 (8.5)		2,110 (11.7)	18 (12.3)		11,731 (41.7)	49 (39.8)		23,061 (78.2)	74 (77.9)	
No	352 (5.4)	6 (12.8)		1,792 (9.9)	11 (7.5)		3,333 (11.8)	12 (9.8)		2,197 (7.5)	2 (2.1)	
Stage			0.001			<0.001			<0.001			<0.001
0	384 (5.9)	0		1,703 (9.2)	5 (3.5)		3,629 (13.1)	8 (6.6)		4,243 (14.9)	3 (3.4)	
I	1,661 (25.7)	9 (19.1)		5,901 (32.1)	31 (21.5)		9,958 (36.1)	22 (18.0)		11,818 (41.6)	30 (33.7)	
II	3,503 (54.1)	26 (55.4)		7,996 (43.5)	69 (47.9)		9,967 (36.1)	53 (43.4)		9,460 (33.3)	38 (42.7)	
III	782 (12.1)	7 (14.9)		2,534 (13.8)	34 (23.6)		3,619 (13.1)	30 (24.6)		2,552 (9.0)	14 (15.7)	
IV	144 (2.2)	5 (10.6)		251 (1.4)	5 (3.5)		436 (1.6)	9 (7.4)		317 (1.1)	4 (4.5)	
ER			0.011			<0.001			<0.001			<0.001
Positive	2,450 (56.1)	14 (35.9)		9,847 (62.4)	48 (38.4)		18,161 (70.1)	46 (39.0)		19,994 (78.3)	35 (39.8)	
Negative	1,916 (43.9)	25 (64.1)		5,931 (37.6)	77 (61.6)		7,753 (29.9)	72 (61.0)		5,545 (21.7)	53 (60.2)	
PR			<0.001			<0.001			<0.001			<0.001
Positive	2,405 (55.3)	11 (28.9)		9,513 (60.3)	41 (33.1)		17,376 (67.1)	43 (36.4)		17,638 (70.7)	31 (35.2)	
Negative	1,947 (44.7)	27 (71.1)		6,252 (39.7)	83 (66.9)		8,529 (32.9)	75 (63.6)		7,299 (29.3)	57 (64.8)	
HER2			0.094			0.650			0.090			0.001
Positive	495 (30.8)	5 (29.4)		2,982 (24.5)	27 (26.5)		4,578 (20.9)	29 (27.6)		4,594 (20.1)	30 (35.3)	
Negative	1,114 (69.2)	12 (70.6)		9,207 (75.5)	75 (73.5)		17,288 (79.1)	76 (72.4)		18,271 (79.9)	55 (64.7)	
Chemotherapy			0.371			<0.001			<0.001			<0.001
Yes	3,520 (78.4)	40 (85.1)		12,084 (79.4)	128 (92.8)		16,881 (69.6)	101 (87.8)		14,946 (59.6)	76 (84.4)	
No	967 (21.6)	7 (14.9)		3,133 (20.6)	10 (7.2)		7,390 (30.4)	14 (12.2)		10,114 (40.4)	14 (15.6)	
Chemotherapy			0.017			0.174			<0.001			<0.001
NAC	28 (1.0)	0		319 (2.8)	6 (4.8)		1,365 (8.5)	22 (22.5)		2,790 (19.7)	33 (44.6)	
Adjuvant	2,836 (97.3)	36 (92.3)		10,839 (96.0)	115 (92.8)		14,446 (90.4)	74 (75.5)		11,301 (79.7)	40 (54.0)	
Palliative	50 (1.7)	3 (7.7)		132 (1.2)	3 (2.4)		176 (1.1)	2 (2.0)		85 (0.6)	1 (1.4)	
Radiotherapy			0.171			0.926			0.184			0.228
Yes	1,607 (39.1)	13 (28.3)		7,831 (53.9)	66 (54.5)		16,098 (68.2)	82 (74.5)		17,855 (72.9)	69 (79.3)	
No	2,498 (60.9)	33 (71.7)		6,710 (46.1)	55 (45.5)		7,504 (31.8)	28 (25.5)		6,630 (27.1)	18 (20.7)	

Missing data are not shown in this table and are not included in the statistical analysis.
PABC=pregnancy-associated breast cancer; op.=operation; BCS=breast-conserving surgery; LN=lymph node; ALND=axillary lymph node dissection; SLNB=sentinel lymph node biopsy; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; NAC=neoadjuvant chemotherapy.

invasive ductal carcinoma and approximately 1% had invasive lobular carcinoma. There was no difference over time. In terms of the stage, the proportion of patients with stage III or IV decreased and the proportion of patients with stage 0–II increased.

In terms of the period-specific surgical techniques, the proportion of patients with PABC who underwent breast-conserving surgery (BCS) increased to 60.6% and the proportion of sentinel lymph node biopsies (SLNB) increased to 77.9%, as in patients with non-PABC.

The rate of radiation therapy also increased to approximately 80% between 2011 and 2015. Chemotherapy was adminis-

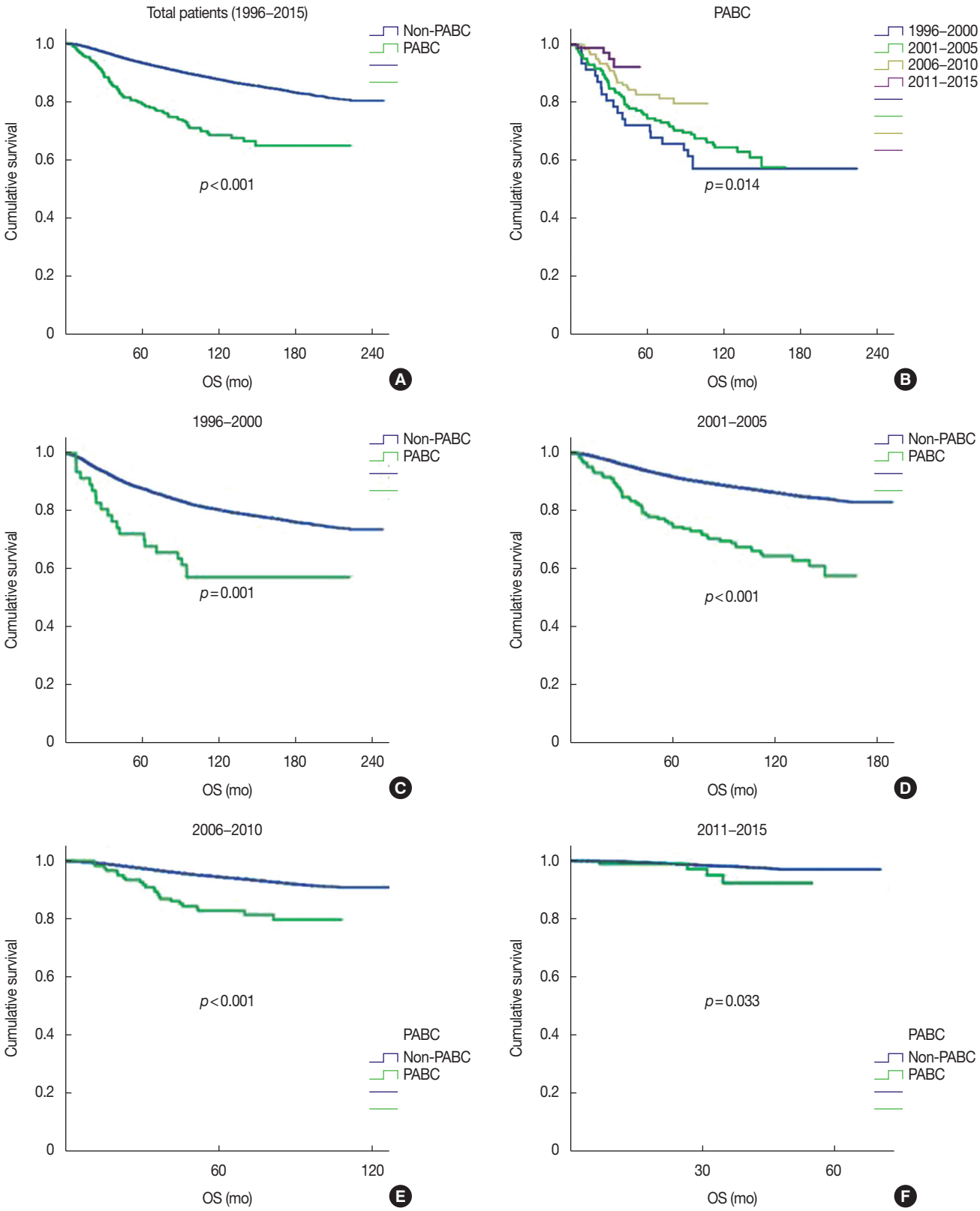

Figure 2. Overall survival (OS) of pregnancy-associated breast cancer (PABC) patients and non-PABC patients by period. (A) Total patients (1996–2015). (B) PABC patients (1996–2015). (C) 1996–2000. (D) 2001–2005. (E) 2006–2010. (F) 2011–2015.

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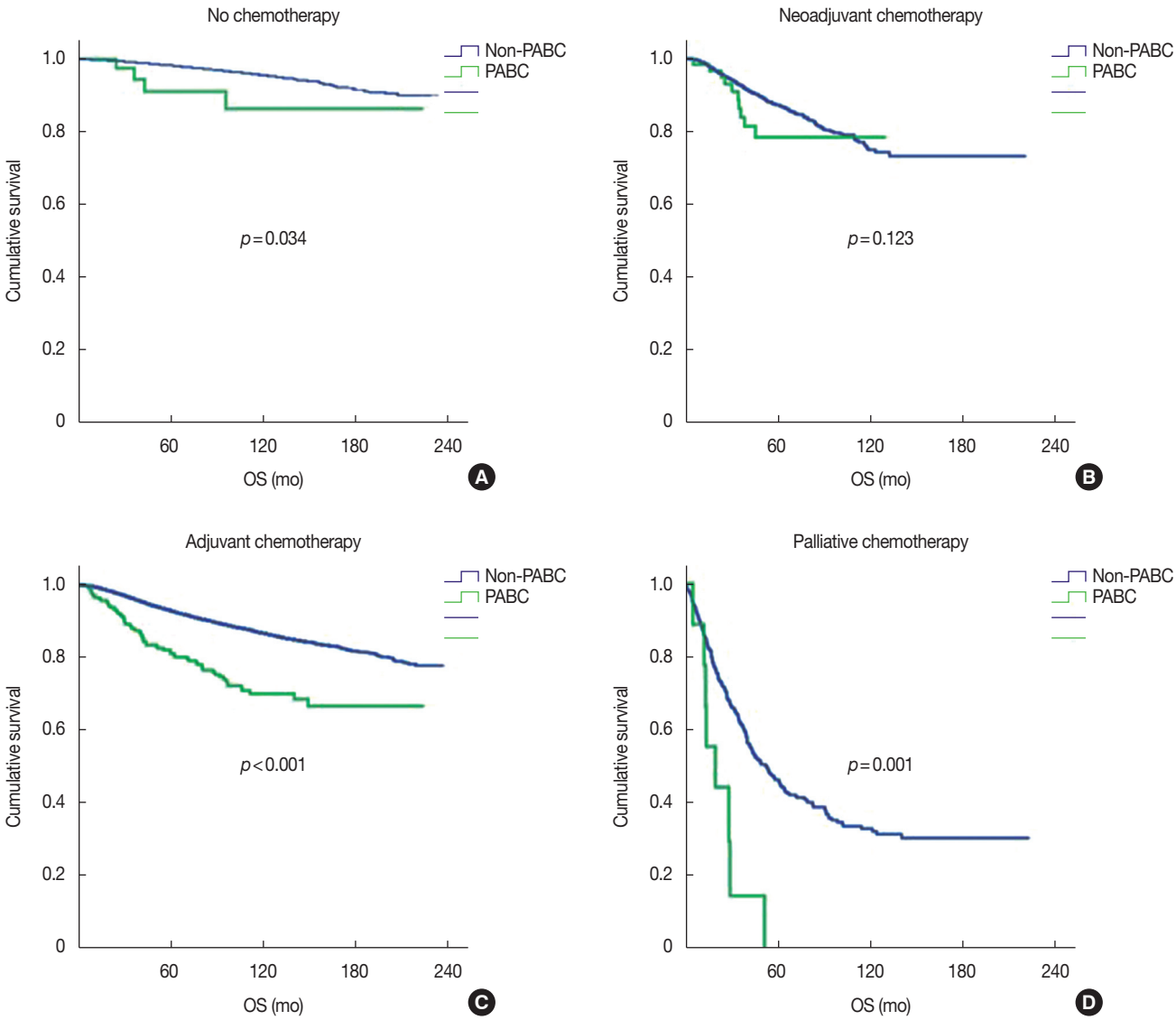

Figure 3. Overall survival (OS) of pregnancy-associated breast cancer (PABC) patients and non-PABC patients by chemotherapy. (A) No chemotherapy. (B) Neoadjuvant chemotherapy. (C) Adjuvant chemotherapy. (D) Palliative chemotherapy.

tered to 88.8% of the total patients. The proportion of patients who had received neoadjuvant chemotherapy increased to 44.6% from 0%, and the proportion of patients who had received adjuvant chemotherapy decreased to 54.1% from 92.3%.

Overall survival

The survival analysis showed that the difference in survival rates between patients with and non-PABC gradually decreased over time; the 3-year OS increased to 92.4% in 2011–2015 from 78.7% in 1996–2000 (Figure 2). In the subgroup analysis according to the type of chemotherapy (Figure 3), of patients who received adjuvant chemotherapy, 265 patients with PABC and 39,529 patients with non-PABC showed a significant difference in OS (10-year OS, PABC 70.1% vs. non-PABC 86.8%; $p<0.001$). In the patients who received neoadjuvant chemotherapy, there were no significant differences in OS between the 4,506 patients with non-PABC and the 61 patients with PABC (10-year OS, PABC 78.5% vs. non-PABC 75.1%; $p=0.123$). In multivariate analysis, there was no difference in OS rates between patients who received neoadjuvant chemotherapy (hazard ratio [HR], 1.28; 95% CI, 0.66–2.49; $p=0.459$), but PABC conferred poorer prognosis than non-PABC in patients receiving adjuvant chemotherapy (HR, 1.63; 95% CI, 1.27–2.08; $p<0.001$) (Table 2).

Table 2. Multivariate analysis for overall survival of total patients and subgroup analysis by type of chemotherapy

Parameter	B	Standard error	Wald	*p*-value	HR	95% CI	
						Lower	Upper
Total patients							
PABC	0.478	0.102	21.931	<0.001	1.613	1.321	1.971
Stage	1.115	0.015	5,554.546	<0.001	3.048	2.960	3.139
Age	–0.035	0.002	261.458	<0.001	0.966	0.962	0.970
No chemotherapy							
PABC	0.383	0.506	0.571	0.450	1.466	0.543	3.955
Stage	1.185	0.052	517.541	<0.001	3.271	2.954	3.623
Age	–0.033	0.008	16.195	<0.001	0.968	0.953	0.983
Neoadjuvant chemotherapy							
PABC	0.251	0.339	0.549	0.459	1.285	0.662	2.497
Stage	0.893	0.060	220.252	<0.001	2.444	2.172	2.750
Age	–0.030	0.008	13.552	<0.001	0.970	0.954	0.986
Adjuvant chemotherapy							
PABC	0.488	0.126	14.952	<0.001	1.630	1.272	2.087
Stage	1.018	0.024	1,770.352	<0.001	2.768	2.640	2.902
Age	–0.037	0.003	161.856	<0.001	0.964	0.958	0.969
Palliative chemotherapy							
PABC	0.727	0.380	3.670	0.055	2.070	0.983	4.357
Stage	0.772	0.107	52.181	<0.001	2.164	1.755	2.668
Age	–0.014	0.012	1.367	0.242	0.986	0.963	1.010

HR = hazard ratio; CI = confidence interval; PABC = pregnancy-associated breast cancer.

DISCUSSION

PABC is uncommon, but its incidence is expected to increase as the age of marriage and childbirth increases. Analysis of the KBCSR database showed that the frequency of first delivery after 30 years of age had increased, which is a risk factor along with early menarche for PABC, as demonstrated in previous studies [18].

As shown in the results for each period, the frequency of undergoing mastectomy decreased and that of BCS and SLNB increased over time. This could be the result of earlier diagnosis as shown by the change in stage distribution, which may have resulted in improved survival. In general, surgical treatment for patients with breast cancer during pregnancy is similar to that for nonpregnant patients [15]. However, SLNB using blue dye is not recommended because of anaphylactic maternal reactions [19], and the detection rate is lower than cited in previous literature [20]. In terms of radioactivity concern, ^{99m}Tc-sulfur colloid lymphoscintigraphy is evaluated as safe because it uses a small dose that is rapidly released, and the amount absorbed by the fetus is less than 20 μGy [21].

A major change in the treatment method over the study period was the increase in neoadjuvant chemotherapy. Organogenesis occurs in the first 2–8 weeks of pregnancy. At this time, fetal malformations occur at an approximate frequency of 14%, but the subsequent risk decreases to approximately 3%. Therefore, chemotherapy is administered after the first trimester [22]. The anticancer drugs considered are doxorubicin, cyclophosphamide, and taxane, as with nonpregnant patients with breast cancer [23]. The administration of neoadjuvant chemotherapy during pregnancy may increase the rate of BCS after delivery, and this in turn would lead to an increase in the proportion of patients undergoing radiation therapy.

Because the placenta is not completely developed until approximately 20 weeks, chemotherapy during early pregnancy increases the rate of small-for-gestational-age births [24], whereas in the case of late-pregnancy chemotherapy, the rate of malformations does not differ from that in the general population [25]. Because it is not possible to administer chemotherapy in the first trimester, it is difficult to decide whether therapeutic abortion should be considered or not. There is no evidence that termination of pregnancy affects prognosis in the first and second trimesters [26]. The risk of spontaneous abortion in the first trimester increases as a result of general anesthesia [27]. Moreover, initiating treatment during pregnancy is considered to be appropriate for both the patient and fetus because full-term delivery is important in terms of neuropsychological outcomes [15].

Recent guidelines and treatment trends suggest that chemotherapy is safe from the second trimester of pregnancy [8,12], and this change in treatment direction is expected to improve the prognosis of PABC. In this study, the prognosis of patients

https://doi.org/10.4048/jbc.2018.21.e58

who received neoadjuvant chemotherapy was not different among those with non-PABC, whereas PABC conferred poor prognosis in patients who received adjuvant chemotherapy or in patients who had not received chemotherapy during the entire period. This might be because it was possible to reduce the delay in treatment due to neoadjuvant chemotherapy. Of course, we must confirm the difference in prognosis according to when treatment is initiated.

The low hormonal receptor and high HER2 expression levels are characteristic of PABC; these were demonstrated not only in our study, but also in several other studies [28,29], and they did not differ with the time period (Supplementary Table 1, available online). This also means that the survival rate is improved through earlier diagnosis and treatment. Therefore, it is suggested that further research should target the characteristics of PABC itself. PABC is characterized by high HER2 overexpression, and trastuzumab is not recommended because of adverse effects during pregnancy [30]. When administering pertuzumab, the rate of pathologic complete remission is higher, but there are no data on its administration during pregnancy. Tamoxifen also cannot be recommended to patients during pregnancy.

In conclusion, neoadjuvant chemotherapy during pregnancy appears to improve the survival rate. According to the current guidelines, treatment should be administered from the second trimester without any delay in gestational therapy. However, in order to improve the fetal and maternal risks in first-trimester pregnant women, further research is needed. In addition, the administration of drugs such as tamoxifen and trastuzumab is still limited, and the development of drugs that can be administered during pregnancy is needed.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. Am J Obstet Gynecol 2003;189:1128-35.
2. Parente JT, Amsel M, Lerner R, Chinea F. Breast cancer associated with pregnancy. Obstet Gynecol 1988;71(6 Pt 1):861-4.
3. Lee YY, Roberts CL, Dobbins T, Stavrou E, Black K, Morris J, et al. Incidence and outcomes of pregnancy-associated cancer in Australia, 1994-2008: a population-based linkage study. BJOG 2012;119:1572-82.
4. Stensheim H, Møller B, van Dijk T, Fosså SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol 2009;27:45-51.
5. Amant F, von Minckwitz G, Han SN, Bontenbal M, Ring AE, Giermek J, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol 2013;31:2532-9.
6. Litton JK, Warneke CL, Hahn KM, Palla SL, Kuerer HM, Perkins GH, et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. Oncologist 2013;18:369-76.
7. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat 2016;160:347-60.
8. Azim HA Jr, Peccatori FA, Brohée S, Branstetter D, Loi S, Viale G, et al. RANK-ligand (RANKL) expression in young breast cancer patients and during pregnancy. Breast Cancer Res 2015;17:24.
9. Azim HA Jr, Brohée S, Peccatori FA, Desmedt C, Loi S, Lambrechts D, et al. Biology of breast cancer during pregnancy using genomic profiling. Endocr Relat Cancer 2014;21:545-54.
10. Kroman N, Mouridsen HT. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. Breast 2003;12:516-21.
11. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. Arch Surg 2003;138:91-8.
12. Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso MJ, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast 2017;35:203-17.
13. Johansson AL, Andersson TM, Hsieh CC, Jirström K, Cnattingius S, Fredriksson I, et al. Tumor characteristics and prognosis in women with pregnancy-associated breast cancer. Int J Cancer 2018;142:1343-54.
14. Eibye S, Kjær SK, Mellemkjær L. Incidence of pregnancy-associated cancer in Denmark, 1977-2006. Obstet Gynecol 2013;122:608-17.
15. Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. JAMA Oncol 2015;1:1145-53.
16. Min SY, Kim Z, Hur MH, Yoon CS, Park EH, Jung KW, et al. The basic facts of Korean breast cancer in 2013: results of a nationwide survey and breast cancer registry database. J Breast Cancer 2016;19:1-7.
17. Ahn SH, Son BH, Kim SW, Kim SI, Jeong J, Ko SS, et al. Poor outcome of hormone receptor-positive breast cancer at very young age is due to tamoxifen resistance: nationwide survival data in Korea: a report from the Korean Breast Cancer Society. J Clin Oncol 2007;25:2360-8.
18. Kim YG, Jeon YW, Ko BK, Sohn G, Kim EK, Moon BI, et al. Clinicopathologic characteristics of pregnancy-associated breast cancer: results of analysis of a nationwide breast cancer registry database. J Breast Cancer 2017;20:264-9.
19. Raut CP, Daley MD, Hunt KK, Akins J, Ross MI, Singletary SE, et al. Anaphylactoid reactions to isosulfan blue dye during breast cancer lymphatic mapping in patients given preoperative prophylaxis. J Clin Oncol 2004;22:567-8.
20. Gropper AB, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. Ann Surg Oncol 2014;21:2506-11.
21. Pandit-Taskar N, Dauer LT, Montgomery L, St Germain J, Zanzonico PB, Divgi CR. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. J Nucl Med 2006;47:1202-8.
22. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol 2004;5:283-91.

23. Bines J, Earl H, Buzaid AC, Saad ED. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014;25:1079-85.
24. Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-96.
25. National Toxicology Program. NTP monograph: developmental effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy. NTP Monogr 2013;(2):i-214.
26. Lenhard MS, Bauerfeind I, Untch M. Breast cancer and pregnancy: challenges of chemotherapy. Crit Rev Oncol Hematol 2008;67:196-203.
27. Molckovsky A, Madarnas Y. Breast cancer in pregnancy: a literature review. Breast Cancer Res Treat 2008;108:333-8.
28. Genin AS, Lesieur B, Gligorov J, Antoine M, Selleret L, Rouzier R. Pregnancy-associated breast cancers: do they differ from other breast cancers in young women? Breast 2012;21:550-5.
29. Cruz GI, Martínez ME, Natarajan L, Wertheim BC, Gago-Dominguez M, Bondy M, et al. Hypothesized role of pregnancy hormones on HER2+ breast tumor development. Breast Cancer Res Treat 2013;137:237-46.
30. Zagouri F, Sergentanis TN, Chrysikos D, Papadimitriou CA, Dimopoulos MA, Bartsch R. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. Breast Cancer Res Treat 2013;137:349-57.

https://doi.org/10.4048/jbc.2018.21.e58

Supplementary Table 1. Clinicopathological characteristics of PABC patients by period

Characteristic		1996–2000 (n=47) No. (%)	2001–2005 (n=146) No. (%)	2005–2010 (n=123) No. (%)	2011–2016 (n=95) No. (%)	*p*-value
Age (yr)	20–29	12 (25.5)	24 (16.4)	9 (7.3)	5 (5.3)	0.001
	30–39	31 (66.0)	98 (67.1)	102 (82.9)	82 (86.3)	
	40–49	4 (8.5)	24(16.4)	12 (9.8)	8 (8.4)	
Opertion (breast)	Mastectomy	34 (72.3)	83 (56.8)	46 (37.4)	36 (39.1)	<0.001
	BCS	9 (19.1)	58 (39.7)	70 (56.9)	56 (60.9)	
	None	4 (8.5)	5 (3.4)	7 (5.7)	0	
Opertion (axillary)	ALND	37 (78.7)	117 (80.1)	62 (50.4)	19 (20.0)	<0.001
	SLNB	4 (8.5)	18 (12.3)	49 (39.8)	74 (77.9)	
	None	6 (12.8)	11 (7.5)	12 (9.8)	2 (2.1)	
FHx	Yes	2 (5.0)	10 (7.5)	19 (17.1)	19 (21.6)	0.005
	No	38 (95.0)	123 (92.5)	92 (82.9)	69 (78.4)	
Menarche (yr)	≤13	10 (27.0)	55 (41.7)	60 (56.1)	48 (58.5)	0.002
	>13	27 (73.0)	77 (58.3)	47 (43.9)	34 (41.5)	
First delivery (yr)	≥30	13 (36.1)	39 (33.6)	45 (45.0)	45 (69.2)	<0.001
	<30	23 (63.9)	77 (66.4)	55 (55.0)	20 (30.8)	
Stage	0	0	5 (3.5)	8 (6.6)	3 (3.4)	0.090
	I	9 (19.1)	31 (21.5)	22 (18.0)	30 (33.7)	
	II	26 (55.3)	69 (47.9)	53 (43.4)	38 (42.7)	
	III	7 (14.9)	34 (23.6)	30 (24.6)	14 (15.7)	
	IV	5 (10.6)	5 (3.5)	9 (7.4)	4 (4.5)	
Chemotherapy	Yes	40 (85.1)	128 (92.8)	101 (87.8)	76 (84.4)	0.214
	No	7 (14.9)	10 (7.2)	14 (12.2)	14 (15.6)	
Chemotherapy	Neoadjuvant	0	6 (4.8)	22 (22.4)	33 (44.6)	<0.001
	Adjuvant	36 (92.3)	115 (92.7)	74 (75.5)	40 (54.1)	
	Palliative	3 (7.7)	3 (2.4)	2 (2.0)	1 (1.4)	
Radiotherapy	Yes	13 (28.3)	66 (54.5)	82 (74.5)	69 (79.3)	<0.001
	No	33 (71.7)	55 (45.5)	28 (25.5)	18 (20.7)	
ER	Positive	14 (35.9)	48 (38.4)	46 (39.0)	35 (39.8)	0.981
	Negative	25 (64.1)	77 (61.6)	72 (61.0)	53 (60.2)	
PR	Positive	11 (28.9)	41 (33.1)	43 (36.4)	31 (35.2)	0.840
	Negative	27 (71.1)	83 (66.9)	75 (63.6)	57 (64.8)	
HER2	Positive	5 (29.4)	27 (26.5)	29 (27.6)	30 (35.3)	0.572
	Negative	12 (70.6)	75 (73.5)	76 (72.4)	55 (64.7)	

PABC=pregnancy-associated breast; BCS=breast-conserving surgery; ALND=axillary lymph node dissection; SLNB=sentinel lymph node biopsy; FHx=familial history; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2.