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ORIGINAL ARTICLE

Chronological Improvement in Survival of Patients with Breast Cancer: A Large-Scale, Single-Center Study

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Purpose: This study aimed to chronologically evaluate survival of patients with breast cancer in Korea and investigate the observed changes during the last 20 years. We also sought to determine factors that may influence outcomes and changes in the duration of survival over time. **Methods:** We retrospectively analyzed a total of 10,988 patients with breast cancer who were treated at our institution between January 1993 and December 2008. We divided the study period into three periods (P1, 1993–1997; P2, 1998–2002; and P3, 2003–2008). We retrospectively reviewed the collected data from the Asan database, including age at diagnosis, clinical manifestations, pathology report, surgical methods, types of adjuvant treatment modalities, type of recurrence, and follow-up period. **Results:** At a median follow-up of 8.2 years, we observed that survival outcomes have improved recently. The 5-year breast cancer-specific survival (BCSS) rate also increased from 82.8% in P1 to 92.6% in P3 ($p<0.001$). The survival rate in patients with tumors at each stage increased in similar patterns in all patients, and, remarkably, there was a significant survival improvement in patients with stage III breast cancer (P1 vs. P3: 5-year BCSS, 57.4% vs. 80.0%, $p<0.001$). The time period was a significant prognostic factor in multivariate analysis (P1 vs. P2: hazard ratio [HR], 0.83, $p=0.035$; P1 vs. P3: HR, 0.75, $p=0.015$). **Conclusion:** The study results suggest an improvement in breast cancer survival in Korea, which is consistent with the development of treatments and early detection.

Key Words: *Breast neoplasms, Prognosis, Recurrence, Survival*

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in women, with a 12% lifetime risk of diagnosis, and the leading cause of cancer death among women, accounting for 14% of cancer deaths worldwide [1,2]. Trends in the incidence of breast cancer and death rates due to the disease differ among countries. Korea has one of the lowest breast cancer incidence rates (50.7 per 100,000 women-years in 2012) [3-5]; however, this incidence is rising rapidly, and breast cancer is now the second-most common cancer among women in Korea [3,6,7]. However, like many other developed countries, the age-adjusted death rate in Korean patients with breast cancer has been decreasing [8]. Many reports have provided possible relevant explanations for the recent improvement in survival in patients with breast cancer. These explanations include nationwide screening programs with improved early detection of breast cancer [9], increases in the proportion of less aggressive cancers [8], and advances in adjuvant treatment, such as aromatase inhibitors for hormone receptor-positive tumors and trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive tumors [10-12]. However, almost all of these studies have been from Western countries, and there are limited data to explain the improved breast cancer survival outcomes in Korea. To discriminate the influences on survival between tumor stage and time period, we analyzed survival outcome according to time at a single institution using our database of > 10,000 patients.

Although improvement in the treatment outcomes, such as overall survival (OS) and disease-free survival (DFS), has been achieved on the strength of developed adjuvant treat-

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ments, patients with breast cancer can still experience any type of recurrence. Patients with breast cancer follow a variety of clinical courses depending on tumor characteristics such as size, lymph node metastasis status, and biological subtype. Some relapse a few months after their initial operation, while others may relapse many years later. Therefore, identification of prognostic factors for relapse and death and predictive factors for recurrence is very important to predict patient outcomes and determine the optimal form of adjuvant treatment.

The primary endpoint of this study was to analyze the changing patterns of survival and recurrence in Korean patients diagnosed with breast cancer over the course of 16 years (1993–2008). We also analyzed the data to determine the factors possibly influencing outcomes and changes in the duration of survival over time.

METHODS

Patients and clinical data

We reviewed 11,119 patients with breast cancer who were treated at the Asan Medical Center, Seoul, Korea, between January 1993 and December 2008. We excluded 83 patients with a malignant phyllodes tumor, lymphoma, or sarcoma and 48 patients who underwent neoadjuvant chemotherapy, ultimately enrolling 10,988 patients. We divided the study period into three phases, according to significant changes in anti-hormonal therapy and chemotherapy, as follows: P1, 1993–1997; P2, 1998–2002; and P3, 2003–2008. We analyzed the database of patients with primary breast cancer in each period. All patient information and tumor characteristics were retrieved from our prospectively collected database, including age, clinical manifestations, clinical and pathologic data, surgical methods, type of adjuvant treatment modality, type of recurrence, and follow-up period. We performed stage migration according to the American Joint Committee on Cancer 7th classification. Nodal stage was re-classified according to the number of metastatic lymph nodes for patients diagnosed before 2002. Cases with 1–3, 4–9, and ≥10 metastatic lymph nodes were designated as N1, N2, and N3, respectively. Patients who had a metastatic supraclavicular lymph node and no distant metastasis, who were previously regarded as having M1 disease, were designated as having N3 disease (Supplementary Tables 1-4, available online). This study was reviewed and approved by the Institutional Review Board of Asan Medical Center (20150185). Informed consent was waived because the study was based on retrospective clinical data.

Pathological data

Pathological data were evaluated in the Department of Pathology at the Asan Medical Center. Estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 status were determined immunohistochemically. ER and PR were considered to be positive if >10% of cells showed positivity. For HER2 overexpression analysis, cases graded 0, 1+ or 2+ were considered to be negative. Cases graded 2+ were evaluated by fluorescence *in situ* hybridization, and cases graded 3+ were regarded as positive.

Adjuvant treatment

Treatment varied for each patient. Considering each patient's general condition, treatments were administered based on the phenotype of the tumor. Endocrine therapy, such as aromatase inhibitors, tamoxifen, or a luteinizing hormone-releasing hormone (LHRH) analog, was administered to hormone receptor-positive patients. For triple-negative tumors, chemotherapy was administered. Adjuvant chemotherapy included an anthracycline or taxane. In the present study, chemotherapy was divided into cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or anthracycline-based; anthracycline- and taxane-based regimens were the most commonly used chemotherapeutic agents. After 2007, the use of trastuzumab in the adjuvant setting for advanced breast cancer was covered by the Korean National Health Insurance. After adjuvant therapy, all patients had routine follow-up, including clinical examinations, laboratory tests, chest radiography, and mammography every 6 months during the first 5 years and annually thereafter until the first recurrence of their disease.

Statistical analysis

Data analysis was performed with SPSS version 18.0 (SPSS Inc., Chicago, USA). Linear regression analysis and a chi-square test were used to determine the trends in each parameter over time. OS was defined as the time from the initial surgery to the time of death, and breast cancer-specific survival (BCSS) was defined as the time from the initial surgery to the time of breast cancer-specific death, based on the Korean registry cause-of-death code. DFS was defined as the time from the date of the initial surgery to the date of the first appearance of an initial relapse (locoregional or systemic) or cancer-specific death without any type of relapse. When more than one site was involved, patients were classified according to the dominant site of the metastasis. Survival curves were generated using the Kaplan-Meier method, and the significance of survival differences among selected variables was verified using the log-rank test. A multivariate Cox regression analysis with a backward elimination method was used to estimate hazard ratios and identify independent prognostic factors. All reported *p*-values are two-sided, and a value <0.05 was con-

Table 1. Clinicopathologic characteristics according to period at diagnosis of the 10,988 enrolled patients

Factor	1993–1997 (n=1,051) No. (%)	1998–2002 (n=2,703) No. (%)	2003–2008 (n=7,234) No. (%)	Total (n=10,988) No. (%)	*p*-value	Linear association
Age at diagnosis (yr)					<0.001	0.001
<31	41 (3.9)	82 (3.0)	203 (2.9)	326 (3.0)		
31–40	279 (26.5)	616 (22.8)	1,395 (19.3)	2,290 (20.8)		
41–50	378 (36.0)	1,156 (42.8)	3,245 (44.9)	4,779 (43.5)		
51–60	234 (22.3)	557 (20.6)	1,560 (21.6)	2,352 (21.4)		
61–70	84 (8.0)	217 (8.0)	633 (8.8)	934 (8.5)		
71–80	31 (2.9)	68 (2.5)	178 (2.5)	277 (2.5)		
>80	4 (0.4)	7 (0.3)	20 (0.3)	30 (0.3)		
BMI (kg/m^2)					<0.001	<0.001
<18.5	48 (4.8)	98 (3.7)	260 (3.6)	406 (3.7)		
18.5–22.9	433 (43.0)	1,215 (45.3)	3,290 (45.9)	4,938 (45.5)		
23–24.9	235 (23.3)	663 (24.7)	1,700 (23.7)	2,598 (23.9)		
≥25.0	291 (28.9)	705 (26.3)	1,918 (26.8)	2,914 (26.8)		
Unknown	44	22	66	132		
Operation method					<0.001	<0.001
BCS	168 (16.0)	682 (25.2)	3,721 (51.4)	4,571 (41.6)		
Mastectomy	834 (79.4)	1,935 (71.6)	3,361 (46.5)	6,130 (55.8)		
Biopsy	49 (4.7)	86 (3.2)	152 (2.1)	287 (2.6)		
Stage					<0.001	<0.001
0	73 (7.0)	198 (7.3)	726 (10.0)	997 (9.1)		
I	279 (26.8)	841 (31.3)	2,888 (40.0)	4,008 (36.6)		
II	407 (38.9)	1,005 (37.4)	2,414 (33.5)	3,826 (34.9)		
III	236 (22.7)	563 (20.9)	1,049 (14.5)	1,848 (16.9)		
IV	48 (4.6)	84 (3.1)	148 (2.0)	280 (2.5)		
Unknown	8	12	9	29		
T stage					<0.001	<0.001
Tis	74 (7.2)	198 (7.4)	727 (10.1)	999 (9.2)		
T1	372 (36.2)	1,119 (42.1)	3,641 (50.6)	5,132 (47.2)		
T2	451 (43.8)	1,121 (42.1)	2,388 (33.2)	3,960 (36.4)		
T3	90 (8.7)	140 (5.3)	280 (3.9)	510 (4.7)		
T4	42 (4.1)	83 (3.1)	158 (2.2)	283 (2.6)		
Unknown	22	42	40	104		
Node metastasis					<0.001	<0.001
Negative	577 (57.2)	1,551 (58.8)	4,558 (63.4)	6,686 (61.7)		
Positive	432 (42.8)	1,087 (41.2)	2,635 (36.6)	4,154 (38.3)		
Unknown	42	65	41	148		
Histologic grade					<0.001	<0.001
G1	78 (11.3)	147 (7.6)	432 (7.1)	657 (7.6)		
G2	308 (44.4)	897 (46.1)	3,444 (56.8)	4,649 (53.4)		
G3	307 (44.3)	900 (46.3)	2,186 (36.1)	3,393 (39.0)		
Unknown	358	759	1,172	2,289		
Nuclear grade					<0.001	<0.001
G1	22 (7.5)	73 (6.5)	463 (6.9)	558 (6.9)		
G2	174 (59.6)	495 (43.8)	3,807 (57.0)	4,476 (55.3)		
G3	96 (32.9)	563 (49.8)	2,407 (36.0)	3,066 (37.9)		
Unknown	759	1,572	557	2,888		
Lymphovascular invasion					<0.001	<0.001
Negative	1 (9.1)	368 (67.4)	4,771 (74.8)	5,140 (74.1)		
Positive	10 (90.9)	178 (32.6)	1,608 (25.2)	1,796 (25.9)		
Unknown	1,040	2,157	855	4,052		

(*Continued to the next page*)

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Table 1. *Continued*

Factor	1993–1997 (n=1,051) No. (%)	1998–2002 (n=2,703) No. (%)	2003–2008 (n=7,234) No. (%)	Total (n=10,988) No. (%)	*p*-value	Linear association
Estrogen receptor					<0.001	<0.001
Negative	379 (45.1)	1,029 (40.8)	2,673 (37.7)	4,081 (39.1)		
Positive	462 (54.9)	1,491 (59.2)	4,413 (62.3)	6,366 (60.9)		
Unknown	210	183	148	541		
Progesterone receptor					<0.001	<0.001
Negative	355 (42.3)	1,242 (49.3)	3,200 (45.2)	4,797 (45.9)		
Positive	485 (57.7)	1,277 (50.7)	3,882 (54.8)	5,644 (54.1)		
Unknown	211	184	152	547		
HER2 (IHC)					<0.001	<0.001
Negative	412 (84.6)	1,502 (65.8)	5,275 (75.3)	7,189 (73.6)		
Positive	75 (15.4)	780 (34.2)	1,727 (24.7)	2,582 (26.4)		
Unknown	564	421	232	1,217		
Subtype					<0.001	<0.001
HR+/HER2–	241 (53.7)	1,093 (47.9)	3,901 (55.7)	5,235 (53.8)		
HR+/HER2+	41 (9.1)	425 (18.6)	788 (11.3)	1,254 (12.9)		
HR–/HER2+	31 (6.9)	355 (15.6)	938 (13.4)	1,324 (13.6)		
HR–/HER2–	136 (30.3)	408 (17.9)	1,373 (19.6)	1,917 (19.7)		
Unknown	602	422	234	1,258		
Chemotherapy					<0.001	0.327
Yes	558 (56.1)	1,809 (67.8)	4,482 (62.9)	6,849 (63.5)		
No	437 (43.9)	861 (32.2)	2,646 (37.1)	3,944 (36.5)		
Unknown	56	33	106	195		
Radiation therapy					<0.001	<0.001
Yes	268 (27.0)	960 (36.2)	4,479 (62.7)	5,707 (52.9)		
No	724 (73.0)	1,691 (63.8)	2,669 (37.3)	5,084 (47.1)		
Unknown	59	52	86	197		
Anti-hormonal therapy					<0.001	<0.001
Yes	583 (60.7)	1,687 (64.0)	4,807 (67.7)	7,077 (66.1)		
No	378 (39.3)	948 (36.0)	2,297 (32.3)	3,623 (33.9)		
Unknown	90	68	130	288		
Chemotherapy regimen					<0.001	<0.001
CMF	170 (80.6)	282 (23.2)	11 (0.3)	463 (8.3)		
Anthracyclin based	36 (17.1)	757 (62.3)	2,160 (51.8)	2,953 (52.8)		
Anthracyclin and taxane based	1 (0.5)	72 (5.9)	1,763 (42.3)	1,836 (32.8)		
Others	4 (1.9)	104 (8.6)	236 (5.7)	344 (6.1)		
Unknown	347	594	312	1,253		
Anti-hormonal therapy agent					<0.001	<0.001
AI	0	7 (0.4)	575 (12.0)	582 (8.3)		
SERM	568 (100)	1,643 (99.5)	3,466 (72.4)	5,677 (81.1)		
SERM+LHRH analogue	0	1 (0.1)	743 (15.5)	744 (10.6)		
Unknown	15	36	23	74		

BMI=body mass index; BCS=breast-conserving surgery; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; HR=hormone receptor; HR+=estrogen receptor positive or progesterone receptor positive; CMF=cyclophosphamide+methotrexate+fluorouracil; AI=aromatase inhibitor; SERM=selective estrogen receptor modulator; LHRH=luteinizing hormone releasing hormone.

sidered statistically significant.

RESULTS

Patient characteristics

Table 1 presents the clinicopathologic features of the enrolled patients. The most prevalent range of age at diagnosis was 41 to 50 years old. The proportion of breast-conserving surgery performed increased from P1 to P3 (16.0% in P1 vs. 51.4% in P3, $p<0.001$). The proportion of radiation therapy also increased from P1 to P3 (27.0% in P1 vs. 62.7% in P3, $p<0.001$). Additionally, the proportion of patients diagnosed

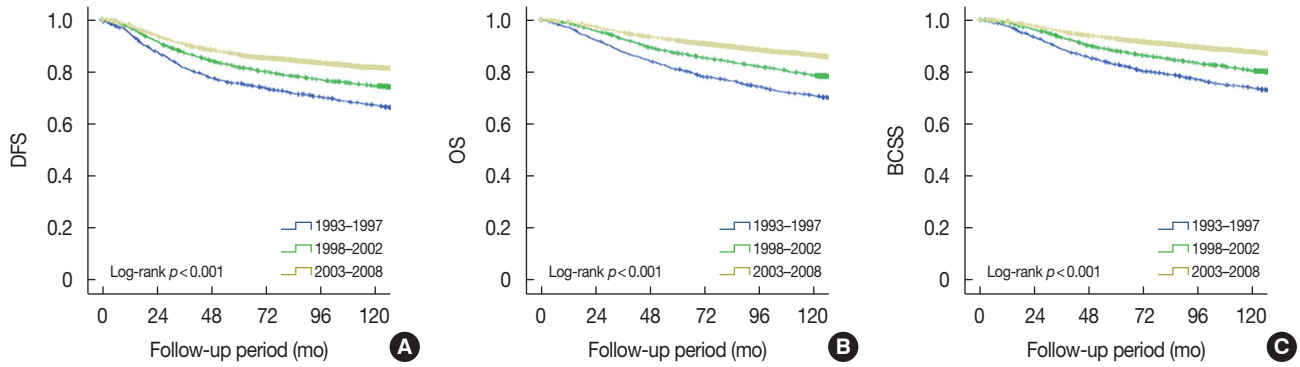

Figure 1. Chronological changes of survival in patients with primary breast cancer. Disease-free survival (DFS) (A), overall survival (OS) (B), and breast cancer-specific survival (BCSS) (C) of breast cancer according to periods at diagnosis in overall series.

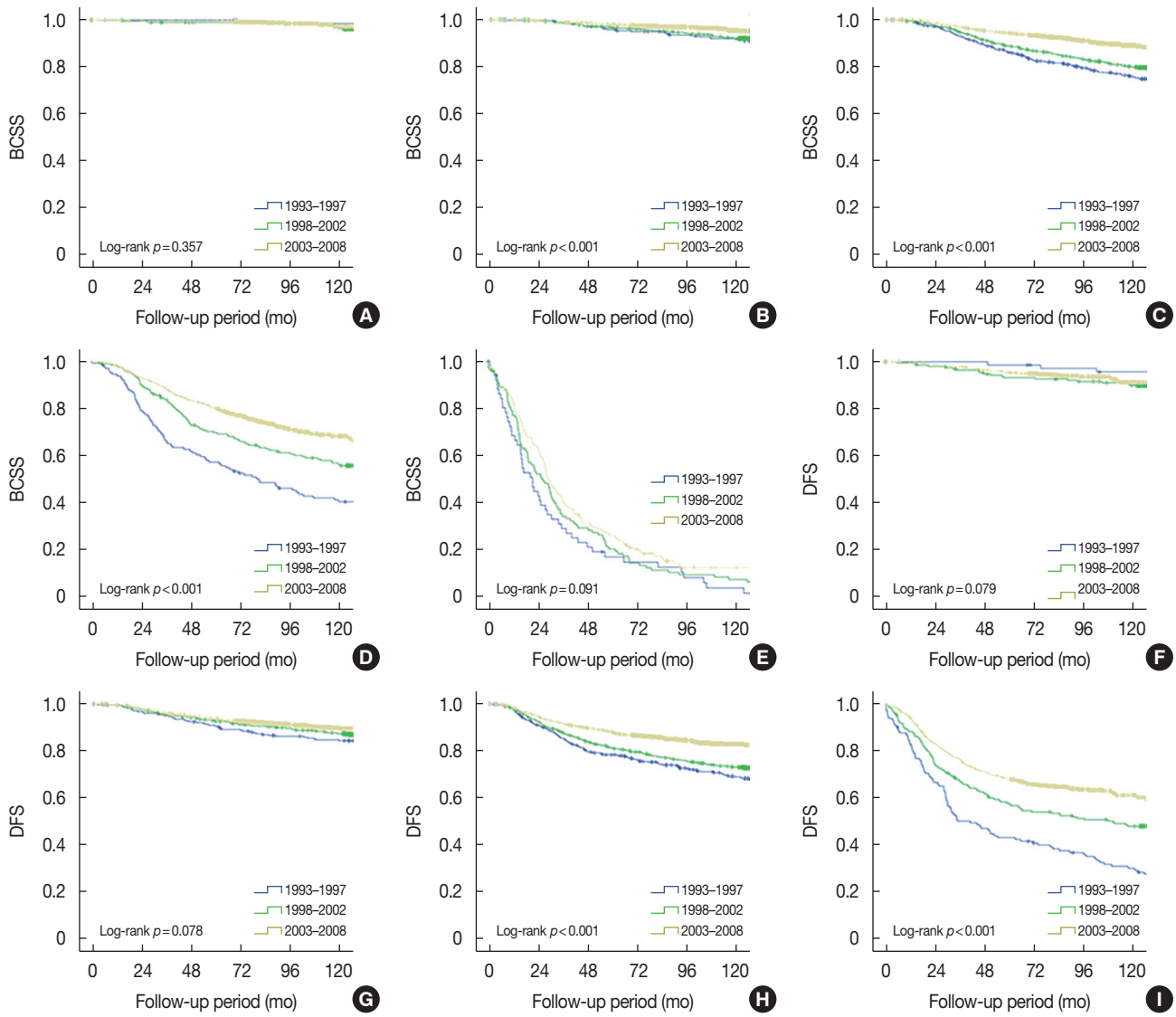

Figure 2. Chronological changes of survival in patients with primary breast cancer according to stage. Subgroup analyses of breast cancer-specific survival (BCSS) by stage, stage 0 (A), stage I (B), stage II (C), stage III (D), and stage IV (E). Subgroup analyses of disease-free survival (DFS) by stage, stage 0 (F), stage I (G), stage II (H), and stage III (I).

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with early stage breast cancer (stages 0 and I), as measured by T stage and nodal status, also increased from P1 to P3 (33.8% in P1 vs. 50.0% in P3, $p<0.001$).

Survival

Survival was examined for 10,988 patients with breast cancer first diagnosed during 1993–2008 and followed up through

Table 2. Multivariate analysis for DFS and BCSS

Factor	DFS			BCSS		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age at diagnosis (yr)			<0.001			<0.001
<35	1.00	Ref.		1.00	Ref.	
35–50	0.59	0.52–0.67	<0.001	0.62	0.53–0.72	<0.001
>50	0.68	0.59–0.79	<0.001	0.88	0.75–1.04	0.122
T stage			<0.001			<0.001
Tis	1.00	Ref.		1.00	Ref.	
T1	1.45	1.31–1.61	<0.001	1.57	1.38–1.78	<0.001
T2	2.34	2.00–2.75	<0.001	2.59	2.17–3.11	<0.001
T3	5.45	4.60–6.45	<0.001	6.90	5.74–8.30	<0.001
T4	0.81	0.65–1.00	0.048	0.83	0.64–1.08	0.160
Node metastasis			<0.001			<0.001
Negative	1.00	Ref.		1.00	Ref.	
Positive	2.72	2.43–3.05		3.53	3.09–4.04	
Histologic grade			<0.001			<0.001
G1	1.00	Ref.		1.00	Ref.	
G2	1.80	1.32–2.46	<0.001	2.48	1.58–3.88	<0.001
G3	1.86	1.35–2.56	<0.001	2.63	1.66–4.14	<0.001
Nuclear grade			0.056			0.051
G1	1.00	Ref.		1.00	Ref.	
G2	1.14	0.81–1.62	0.457	1.18	0.71–1.97	0.519
G3	1.35	0.94–1.94	0.104	1.54	0.92–2.58	0.102
LVI			<0.001			<0.001
No	1.00	Ref.		1.00	Ref.	
Yes	1.72	1.51–1.95		1.67	1.42–1.95	
ER status			0.018			0.073
Negative	1.00	Ref.		1.00	Ref.	
Positive	0.86	0.75–0.97		0.87	0.75–1.01	
PR status			0.009			0.002
Negative	1.00	Ref.		1.00	Ref.	
Positive	0.86	0.76–0.96		0.80	0.70–0.92	
HER2 (IHC) status			0.085			0.162
Negative	1.00	Ref.			Ref.	
Positive	1.10	0.99–1.22		1.10	0.96–1.25	
Adjuvant chemotherapy agent			<0.001			<0.001
None	1.00	Ref.		1.00	Ref.	
CMF	0.70	0.57–0.86	0.001	0.78	0.62–0.98	0.035
Anthracyclin based	0.79	0.68–0.92	0.002	0.87	0.74–1.05	0.172
Anthracyclin and taxane based	0.58	0.48–0.69	<0.001	0.61	0.50–0.76	<0.001
Antihormonal therapy agent			0.411			0.056
None	1.00	Ref.		1.00	Ref.	
AI	0.95	0.76–1.19	0.665	0.89	0.68–1.15	0.358
SERM	0.93	0.82–1.05	0.224	0.83	0.72–0.95	0.009
SERM+LHRH analogue	1.03	0.78–1.36	0.850	0.69	0.44–1.08	0.687
Periods			0.113			0.043
1993–1998	1.00	Ref.		1.00	Ref.	
1999–2002	0.87	0.70–1.09	0.233	0.83	0.70–0.99	0.035
2003–2008	0.86	0.74–0.99	0.038	0.73	0.57–0.94	0.015

DFS = disease-free survival; BCSS = breast cancer-specific survival; HR = hazard ratio; CI = confidence interval; ref. = reference; LVI = lymphovascular invasion; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; CMF = cyclophosphamide+methotrexate+fluorouracil; AI = aromatase inhibit; SERM = selective estrogen receptor modulator; LHRH = luteinizing hormone-releasing hormone.

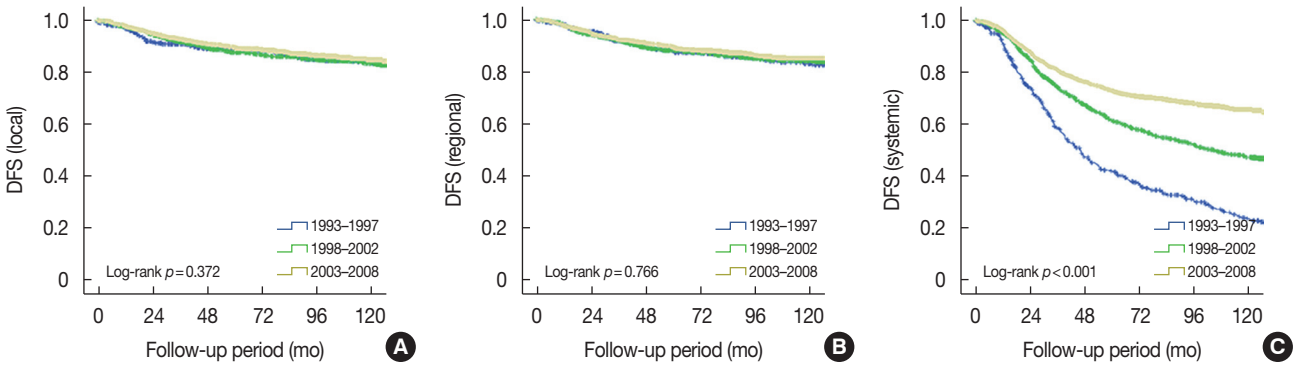

Figure 3. Disease-free survival (DFS) according to recurrence type in patients with breast cancer. DFS according to periods at diagnosis in overall series. Local DFS (A), regional DFS (B), and systemic DFS (C).

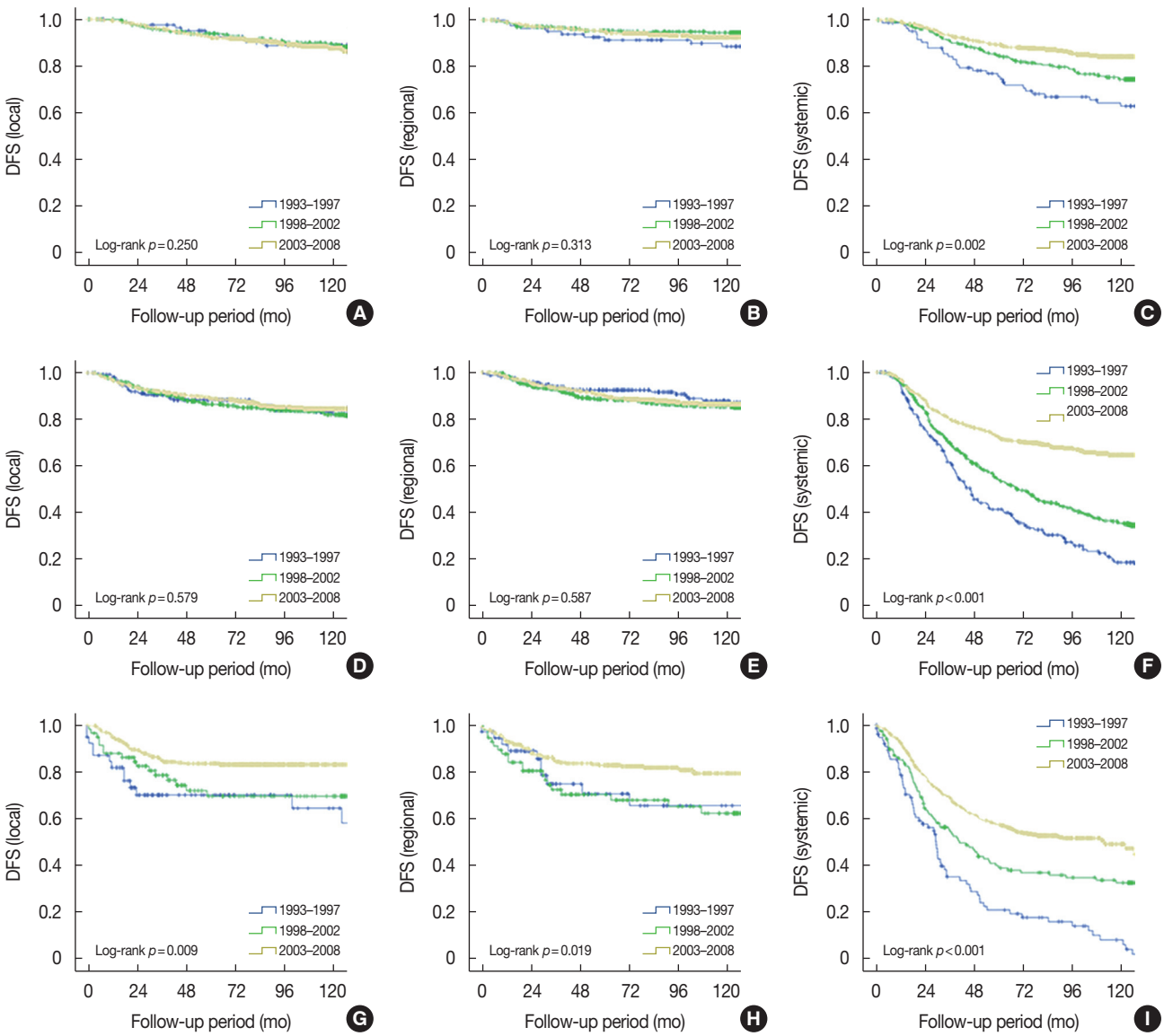

Figure 4. Disease-free survival (DFS) according to recurrence type in patients with breast cancer by stage. DFS according to periods at diagnosis in stage I (A-C), stage II (D-F), and stage III (G-I).

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August 31, 2014. Among the 10,988 patients, 372 were lost to follow-up (3.4%). The follow-up rates at 1 year, 3 years, and 5 years after surgery were 99.6%, 99.1%, and 98.2%, respectively. The median follow-up period for the entire cohort was 98.7 months (range, 0–269.5 months), and the median duration of follow-up during P1, P2, and P3 was 166.7 months, 131.8 months, and 86.8 months, respectively.

During the follow-up period, 1,678 breast cancer-specific mortalities and 200 non-cancer-related deaths occurred. The 5-year OS rate was 89.8% for the entire cohort. We observed that survival outcomes had improved recently (Figure 1). The 5-year DFS increased from 75.6% in P1 to 86.6% in P3 ($p<0.001$). The 5-year OS increased from 81.0% in P1 to 92.0% in P3 ($p<0.001$). The 5-year BCSS also increased, from 82.8% in P1 to 92.6% in P3 ($p<0.001$).

We analyzed survival according to tumor stage to discover the influencing chronological changes on improved survival outcome (Figure 2). An improvement in 5-year BCSS of 80% to 98.0% was observed in all stages. Otherwise, the 5-year DFS was improved in stage II (78.5% in P1 vs. 88.0% in P3) and stage III (43.4% in P1 vs. 68.2% in P3) patients.

We performed multivariate Cox proportional hazards regression analysis to identify the factors influencing DFS and BCSS (Table 2). This analysis demonstrated that the time factor was significantly and independently associated with only BCSS ($p=0.043$). We also observed that age at diagnosis, T stage, node metastasis, histologic grade, lymphovascular invasion (LVI), PR status, and chemotherapeutic agent were associated with DFS and BCSS; ER status was significantly associated with DFS, but not BCSS.

Recurrence

We performed an analysis of DFS according to time period for each type of recurrence (Figure 3). There were no significant differences in local or regional DFS according to time period. However, systemic DFS recently increased to a significant degree. We performed an additional analysis of DFS in each stage according to time period (Figure 4). There were no significant differences in stage 0 patients (data not shown). While distant DFS was improved in all stages, local and regional DFS improved only in stage III patients. We analyzed the changes of adjuvant treatment according to time period in stage III patients. The administration of all adjuvant treatments, including radiotherapy, chemotherapy, and hormonal therapy, increased from P1 to P3. From P1 to P3, radiotherapy administration increased from 47.7% to 94.6%, chemotherapy administration increased from 78.5% to 97.1%, and hormonal therapy administration increased from 55.4% to 63.9%. Moreover, the agents of chemotherapy and hormonal therapy changed. In P1, the most frequently used chemotherapy was CMF (29.4%), but in P3, anthracycline/taxane-based agents (79.9%) were the most used. For hormonal therapy, the use of aromatase inhibitors increased from P1 to P3 (Supplementary Table 5, available online).

DISCUSSION

Our present chronological study indicated improvements in the survival of Korean patients with breast cancer during the study period from 1993 to 2008. The 5-year BCSS was 92.6% during 2003–2008, which was a significant improvement over the earlier periods (Figure 1). In the Surveillance, Epidemiology, and End Results database, the age-standardized 5-year relative survival rate for American patients with breast cancer diagnosed during 2003–2009 was 89.2% [13]. Moreover, the 5-year survival rate of patients with breast cancer diagnosed in 2006–2010 in the Korea central registration statistics was 91.1%, similar to that of the present study [14]. However, the enrolled population in our study was based on a uniform treatment environment at a single center, unlike the population registries in these previous studies.

There are many factors that can influence survival change in patients with breast cancer. Our data showed that more patients were diagnosed with stage I disease since 2003 (40.0%) compared with the earlier periods. We expect that the detection rate of early breast cancer in Korea has increased owing to societal generalization of organized screening programs and the development of early detection systems in cases of opportunistic screening [15]. Therefore, the seeking of treatment in earlier stages of breast cancer may have resulted in better patient outcomes. Although all patients lived longer in later periods, survival also improved significantly more in patients with stage III breast cancer (Figure 2), which can likely be attributed to advancements in adjuvant systemic therapy. CMF was usually administered during P1, but its use gradually decreased over the years between P1 and P3. New drugs, such as taxane- and anthracycline-containing regimens, have become available since the 2000s. Identical results have been reported in previous studies, suggesting that the administration of adjuvant chemotherapy is associated with a better prognosis [10,16,17]. Henderson et al. [17] found that the risk reductions of the addition of paclitaxel to AC (doxorubicin+cyclophosphamide) were 17% for recurrence ($p=0.001$) and 18% for death ($p=0.010$). At 5 years, the DFS was 65% and 70% and the OS was 77% and 80% after AC alone or AC plus paclitaxel, respectively [18]. Our current study was not designed to identify which specific regimens led to survival improvement, but we speculate that advances in adjuvant che-

motherapy in general have contributed to this clear trend. When we performed multivariate survival analysis, the contributions of adjuvant chemotherapy to survival improvement were independent of other important factors such as age, tumor size, nodal status, and hormone receptor status (Table 2). Another factor found to influence survival and recurrence was the use of anti-hormonal therapy. The use of newer endocrine drugs could at least partially explain the increase in survival over time. We initially mainly administered tamoxifen as an anti-hormonal treatment. Aromatase inhibitors and LHRH agonists subsequently gained widespread use in 2003. As expected, there were major differences in the use of new aromatase inhibitors and/or LHRH agonists before and after 2003, because 1% of our patients treated during P1 but 28% treated during P3 received at least one of these drugs. The number of our patients administered aromatase inhibitors as adjuvant therapy was quite small, such that their impact on improvements over time appeared to be minimal. Trastuzumab has also improved the survival of HER2-positive patients [17], although our present findings do not significantly support this because the use of trastuzumab in the adjuvant setting for breast cancer was not covered by the Korean National Health Insurance during the period of this study.

In the second part of our present investigation, in which we analyzed DFS according to the type of recurrence, no change was seen in local and regional recurrence (LRR), but there was a difference in systemic recurrence in all patients among the three periods. Furthermore, there was a difference in systemic recurrence among the three periods in each stage of breast cancer for stages I–III (Figure 4). Hence, our results imply that advanced systemic therapy was sufficient to achieve better long-term survival rates, as mentioned above. Additionally, there was a significant difference in the LRR rates during the investigated period in stage III patients, but there were no significant differences in LRR for stage 0–II patients. These results suggest that advancement in local management may be associated with reduced LRR rates of patients with breast cancer, particularly in patients with locally advanced breast cancer, and may have less of an effect on recurrence in early breast cancer. These outcomes are in line with those of a number of previous studies [19,20].

The survival benefit of post-mastectomy radiotherapy (PMRT) in patients with node-positive breast cancer has been well established through multiple randomized trials [19-21]. The results of the Early Breast Cancer Trialists' Collaborative Group meta-analyses show that PMRT substantially reduces the risk of LRR [22]. These findings are congruent with other studies that confirmed the clinical benefit of adjuvant radiotherapy in patients who underwent breast-conserving surgery [23,24]. There has been a benefit improvement from radiotherapy in patients with early breast cancer, which is assumed to have a relatively low absolute LRR risk (5-year local recurrence rate P1: 1.5%, P2: 1.4%, and P3: 2.0% in stage I; P1: 2.5%, P2: 3.2%, and P3: 2.2% in stage II). To clarify the possibility of erroneous results in our present study in terms of local recurrence according to the type of surgery, we analyzed local recurrence among the subgroups according to surgical method. Although breast-conserving surgery has become more common, we found no significant difference in local recurrence according to the type of surgery (data not shown).

We wanted to identify the factors that exerted considerable influence, so we compared survival and recurrence between the P1, P2, and P3 time periods, including the time factor, by performing multivariate survival analysis. This analysis allowed us to conclude that age at diagnosis, tumor size, nodal status, histologic grade, LVI, and PR status had constant proportional effects on DFS and BCSS (Table 2). In addition, the effect of the period at diagnosis also had strong effects independent of other important factors; there was a 25% improvement in survival over the 16-year period. This increase is most likely a surrogate for improvements in detection, such as increases in screening, greater awareness of breast cancer, better preoperative diagnostic planning, better multidisciplinary decision making, and a thorough pathological investigation. The overall gains from the time effect were most likely due to a combination of other biological and social factors. Unfortunately, we did not have data on these factors and could only evaluate the effect of changes in treatment on survival.

Our present study had a number of limitations that should be considered when interpreting the results. As in all single-institution, retrospective, observational cohort studies, there was a potential for both referral and selection bias. In addition, the bias due to the drastic increase in the number of patients in P3 and the associated change toward lower cancer stage would have had an impact on the survival results. Additionally, we speculated that differences in the follow-up period between the investigated periods might be a limitation; therefore, we adjusted the follow-up period to 87 months (median follow-up duration of patients diagnosed in P3), and similar results were obtained ($p < 0.001$, data not shown).

In conclusion, this study of more than 10,000 patients revealed a marked improvement in survival for patients with breast cancer during the investigated period. Moreover, as the analyzed chronological change in recurrence rates of local, regional, and systemic recurrence differed from previous studies, we identified a reduction in systemic recurrence for patients with stage I–III breast cancer and in the LRR for those with stage III breast cancer during the most recent period. We

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conclude that the recent improvement in Korean breast cancer patient outcomes might be due to therapeutic advances in breast cancer treatment and a time effect, including intricate factors such as widespread screening and developments in diagnostic planning and multidisciplinary decision making.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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