Changing Patterns in the Clinical Characteristics of Korean Patients With Breast Cancer During the Last 15 Years

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Hypothesis: Breast cancer has become the most common cancer in Korean women in recent years, with continuously increased incidence rates attributed to westernized lifestyles.

Design: Retrospective case series evaluating the changing patterns of clinical characteristics in breast cancer during the last 15 years.

Setting: Hospitalized patients with breast cancer in a university medical center.

Patients: A total of 5001 breast cancer patients who underwent surgery between July 1989 and March 2004 at the Asan Medical Center.

Main Outcome Measure: Clinicopathologic data were collected using the online Korea Breast Cancer Registration Program, including factors such as age, symptoms, stage, surgery, reconstruction, risk factors, and survival.

Results: The median age of patients slightly increased from 44 years in 1991 to 46 years in 2003. The most frequent age group was the fifth decade (41.7%) and premenopausal women younger than 50 years (64.9%). The proportion of asymptomatic patients detected by screening mammography increased from 3.8% in 1991 to 21.0% (P<.001). The proportion of early breast cancer (stages 0 and I) increased from 34.2% in 1991 to 48.8% in 2003 (P=.013). Breast-conserving surgery has increased continuously from 5.1% in 1991 to 39.1% in 2003 (P<.001). Twelve percent of all patients who underwent mastectomies had immediate reconstruction, and the proportion showed an increasing trend, especially in skin-sparing mastectomy and transverse rectus abdominis myocutaneous flap reconstruction. Five-year observed survival rates were 84.1%. Five-year survival rates according to stages were as follows: (1) 98.5%, stage 0; (2) 95.3%, stage I; (3) 86.0%, stage II; (4) 65.0%, stage III; and (5) 29.3%, stage IV. The number of patients with specific risk factors, such as early menarche and late first delivery, significantly increased. Of 263 high-risk patients examined for the BRCA mutation, mutations were found in 20 patients (7.6%), with 13 cases with BRCA1 and 7 cases with BRCA2.

Conclusions: The present study showed a continuous increase in the number of patients with breast cancer; the proportion of young patients, asymptomatic patients, early breast cancer, breast-conserving surgery, and immediate reconstruction after mastectomy; and the number of patients with risk factors. These results suggest that the clinical characteristics of Korean breast cancer patients reflect the patterns of Western countries.

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through the nationwide multicenter survey on an annual basis.\textsuperscript{6,7} In 2002, the Asan Medical Center performed surgery for 754 cases of primary breast cancer, which represented 10.0\% of all Korean breast cancer cases. The purposes of this study are to determine the clinical and epidemiologic characteristics of breast cancer and to analyze the changing patterns of breast cancer during the last 15 years in Korea (1989-2004).

### Methods

The clinical data of 5001 patients who were diagnosed as having breast cancer and had undergone surgery between July 1989 and March 2004 at the Asan Medical Center in Korea were collected retrospectively by medical records and the online Korea Breast Cancer Registration Program. The clinical data included age distribution, clinical manifestations, staging according to the American Joint Committee on Cancer (AJCC)\textsuperscript{9} classification, surgical methods, survival rate, and risk factors. The clinical data and changing patterns of the clinical characteristics were analyzed.

The immunohistochemical demonstration of estrogen receptor and progesterone receptor expression was performed in accordance with intensity (0 indicates negative; 1, weakly positive; 2, intermediate positively; and 3, strongly positive) and staining percentage (1 indicates <10\%; 2, 10\% to one third; 3, one third to two thirds; and 4, more than two thirds). The immunoreactive score determined by totaling intensity and percentage scores was divided into 4 groups (negative [0-1], weak-positive [2-3], intermediate-positive [4-5], and strong-positive [6-7]), with intermediate- and strong-positive regarded as positive expression.

We used the \( \chi^2 \) test to compare the results of 1991 and 2003. For comparisons, \( P<.05 \) was considered statistically significant. The survival curve was plotted using the Kaplan-Meier method.

### Results

#### SEX AND AGE DISTRIBUTION

Of the 5001 patients, 4973 (99.4\%) were women and 28 (0.6\%) were men. The most frequent age group was in their fifth decade (2088 cases; 41.7\%), followed by the sixth (1150 cases; 23.0\%), fourth (1024 cases; 20.5\%), seventh (428 cases; 8.6\%), eighth (154 cases; 3.1\%), third (130 cases; 2.6\%), ninth (25 cases; 0.5\%), and second decades (2 cases; <0.1\%). The median age of patients was 46.0 years, with ages ranging from 18 to 92 years. Premenopausal women younger than 50 years constituted 64.9\% (Table 1). The median age showed little change during the last 15 years (from 45.0 years in 1991 to 46.0 years in 2003) (Figure 1).

#### CLINICAL MANIFESTATIONS

The most common clinical symptom was painless breast mass (51.7\%), followed by painful breast mass (10.5\%), change in breast skin and nipple retraction (7.5\%), nipple discharge (5.0\%), breast pain (4.0\%), and palpable axillary mass (3.9\%). The proportion of asymptomatic patients whose breast cancer was detected through screening mammograms or ultrasonography was 14.5\% and showed an increasing pattern from 3.8\% in 1991 to 21.0\% in 2003 (\( P<.001 \)) (Figure 2).

#### SURGICAL METHODS

Of 4999 patients (excluding 2 patients whose operation method data were unavailable), modified radical mastectomy was the most frequently performed method, con-
ducted in 3355 cases (67.1%). Breast-conserving surgery was performed in 1272 cases (25.4%), simple mastectomy in 200 cases (4.0%), and radical mastectomy in 26 cases (0.5%). Of the 1272 patients treated with breast-conserving surgery, 1080 of these had lumpectomy or quadrantectomy with axillary dissection performed (21.6%); in 192 cases, tumor resection only or segmentectomy without axillary dissection was performed (3.8%). Tissue biopsy was performed in 83 cases (1.7%), and other pathologic methods were used in 63 cases (1.3%).

The proportion of mastectomy has decreased, whereas breast-conserving surgery has increased continuously from 5.1% in 1991 to 39.1% in 2003 ($P<.001$) (Figure 3). This increasing trend of breast-conserving surgery is more prominent in stage I (from 42.4% in 1991 to 57.6% in 2003; $P=.007$) and stage II (from 2.8% in 1991 to 29.4% in 2003; $P<.001$).

**IMMEDIATE RECONSTRUCTION AFTER MASTECTOMY**

Since 1993, immediate reconstruction has been performed in 428 (12%) of all 3581 patients who have undergone mastectomy in our center. The types of mastectomy of the 428 patients who underwent reconstruction surgery are as follows: 304 (8.5%) with skin-sparing mastectomy, 21 (0.6%) with nipple-areola–sparing mastectomy, and 103 (2.9%) with conventional mastectomy. Skin-sparing mastectomy and nipple-areola–sparing mastectomy showed a recent increasing pattern (Figure 4).

The types of reconstruction of the 428 patients who received reconstructive surgery were as follows: 102 (23.8%) with insertion of a tissue expander, 20 (4.7%) with insertion of direct implant, 3 (0.7%) with a latissimus dorsi flap, and 303 (70.8%) with a transverse rectus abdominis myocutaneous (TRAM) flap. During the last 2 years, TRAM flap reconstruction has shown greatly increasing patterns (Figure 5).

**STAGING ACCORDING TO AJCC CLASSIFICATION**

Excluding patients with uncertain cancer stages or other breast malignancies, such as malignant phyllodes tumor and lymphoma (76 cases), the breast cancer staging according to AJCC classification of 4925 patients was as follows: stage 0 in 294 (7.5%), stage I in 1155 (29.5%), stage II in 1118 (28.5%), stage IIB in 871 (22.2%), stage IIIA in 278 (7.1%), stage IIIB in 82 (2.1%), stage IV in 123 (3.1%) until 2002 (according to the AJCC Cancer Staging Manual, fifth edition), stage 0 in 114 (11.3%), stage I in 363 (36.0%), stage II in 253 (25.2%), stage IIIB in 101 (10.1%), stage IIIA in 85 (8.5%), stage IIIB in 3 (0.3%), stage IIC in 60 (6.0%), and stage IV in 26 (2.6%) since 2003 (according to the AJCC Cancer Staging Manual, sixth edition).

The proportion of early breast cancer (stages 0 and I) has increased from 34.2% in 1991 to 48.8% in 2003, whereas a decreasing pattern in advanced breast cancer has been observed from 65.8% in 1991 to 51.2% in 2003 (P = .01) (Figure 6). Of all the patients, immunohistochemical expression of the estrogen receptor and progesterone receptor was positive in 57.1% and 50.8%, respectively.

**SURVIVAL RATE**

During 43 months of median follow-up, the 5-year observed overall survival rate was 84.1%. Five-year observed survival rates according to stage were as follows: 98.5% in stage 0, 93.3% in stage I, 86.0% in stage II, 65.0% in stage III, and 29.3% in stage IV (Figure 7).
RISK FACTORS

As a whole, the proportion of patients with risk factors was as follows: early menarche before 13 years of age in 18.3%, late menopause after 55 years of age in 7.5%, late first delivery after 30 years of age in 12.9%, nonbreastfeeding in 18.3%, late menopause after 55 years of age in 7.5%, late first delivery after 30 years of age in 12.9%, no children 13.9%, and being unmarried in 5.6%. Aberrant sized bands were sequenced. The numbers of patients with early menarche (P < .001) and late first delivery after 30 years of age (P = .001) in 2003 was significantly increased compared with 1991 figures (Table 2).

EVALUATION OF BRCA GENE MUTATION

Since 2002, the authors of this study have evaluated the BRCA1 and BRCA2 gene mutations in high-risk breast cancer patients, such as those with a family history of breast cancer, younger patients (age <35 years), and those with bilateral cancer, multiorgan cancer, or male breast cancer, using conformation-sensitive gel electrophoresis. Germline mutations in the entire coding sequences of the BRCA1 and BRCA2 genes were analyzed by the conformation-sensitive gel electrophoresis method, and any aberrantly sized bands were sequenced. The numbers of patients with known BRCA mutations were as follows: 13 patients before 2002, 104 (13.7%) among 757 patients in 2002, 114 (13.8%) among 824 patients in 2003, and 32 (13.8%) among 234 patients until March 2004. Of 263 patients who had a known BRCA mutation, BRCA1 mutations were found in 20 (7.6%): 13 cases with BRCA1 and 7 cases with BRCA2.

COMMENT

The incidence of breast cancer is continuously increasing throughout the world. According to the Ministry of Health and Welfare (Central Cancer Registry Program) in Korea, breast cancer has become the most common primary female cancer in Korean women since 2001. The KBCS has conducted annual nationwide breast cancer surveys since 1996. These surveys have revealed that the number of new patients diagnosed as having breast cancer has continuously increased, from 3801 patients in 1996, 4695 in 1998, 5401 in 2000, to 7551 in 2002. The crude incidence rate has also increased from 16.7 per 100,000 women in 1996, 20.3 per 100,000 women in 1998, 23.0 per 100,000 women in 2000, to 31.4 per 100,000 women in 2002. Although this rate is still low compared with its incidence in Western countries, the number of patients with newly diagnosed breast cancer increased 2-fold from 1996 to 2002, showing a more rapid rate of increase compared with the world average. The characteristics of breast cancer incidence in Western countries include a high incidence in elderly people (>400 per 100,000 women older than 65 years in the United States), a high proportion of elderly women in the population composition, and a high crude incidence rate of breast cancer. In Japan, where a large elderly population exists, the crude incidence rate of breast cancer was 52.2 per 100,000 women in 1998, and the age-adjusted incidence rate was 43.6 per 100,000 women. This rate is higher than the incidence rate of breast cancer in Korea and other developing Asian countries, and these period and cohort effects are due to the changes in the prevalence of risk factors of breast cancer, such as low parity and insufficient breastfeeding. In the present study, the age distribution of breast cancer showed the highest incidence in the fifth decade, followed by the sixth and fourth decades. This age distribution pattern differs from that of Western countries and demonstrates that the peak age of breast cancer is 10 to 20 years younger in Korea. This may be due in part to both a cohort effect of high incidence in the younger generation and relatively easier accessibility to a screening program to detect breast cancer among middle-aged women. We believe that the younger generations of Korean women have been directly affected by the progressive westernization of the Korean lifestyle. According to the biennial report of the KBCS, the proportion of risk factors, such as early menarche, late menopause, high-fat diet, and obesity, was significantly increased among the patients between 1996 and 2000. This shows that the lifestyle of Korean women is becoming westernized. It is likely that educational opportunities for women that lead to delayed childbearing were also increased during the period in our study (data was not shown). In addition, national survey data from the Korea National Statistical Office substantiated the westernized lifestyle of Korean women. The report apparently showed a decrease in birth rate and increases in age at first mar-

Figure 6. Proportional trends in early breast cancer.

Figure 7. Observed survival curve according to stage of breast cancer.
rieger, economic opportunities, entrance rates for college or university, and high-fat diet for the past 2 decades. The rate of breast cancer development in Korea is expected to rise with an increase in high-caloric high-fat diet (due to the westernization of the Korean diet), fewer full-term deliveries, and older age at first delivery. We do not know whether a biologic difference exists. The BRCA mutation in high-risk patients was found in 7.6% of patients in the present study. This supports the theory that genetic background alone cannot explain the features of Korean breast cancer incidence.

Because the median age and age proportion of the patients changed little during the last 15 years, more epidemiologic, biologic, or genetic studies are needed to determine why Korean women experience such early onset of breast cancer compared with Western countries. However, the crude age-standardized incidence (patients per 100,000 women) in young Korean women is low so far (4.0 in the 20s, 29 in the 30s, 77.2 in the 40s, 79.8 in the 50s, 47.6 in the 60s, and 24.2 in the 70s). In the present study, the age-specific incidence of breast cancer in Korea was the highest in the fifth decade, gradually decreasing after menopause. On the other hand, the incidence of breast cancer in the United States rises continuously, even after menopause, with a peak incidence in the eighth decade of life. The incidence of male breast cancer in our study was 0.6% (28 cases), lower than the 1% reported in Western countries.

The proportion of patients without symptoms detected by regular screening checks was 14.5% and showed an increasing pattern from 3.8% in 1991 to 21.0% in 2003. However, it is still lower than that in the United States, which has approximately 30% to 40% of breast cancers detected with screening. We expect that the detection rate of early breast cancer in Korea will rise owing to increased awareness and screening mammography. Our data, which show that stage II cancer was the most prevalent (50.7%) until 2002 and stage I cancer was the most prevalent (36.0%) since 2003, support this expectation. Furthermore, the proportion of early breast cancer (stages 0 and I) has increased from 34.2% in 1991 to 48.8% in 2003, whereas a decreasing pattern in advanced breast cancer has occurred, from 65.8% in 1991 to 51.2% in 2003. However, it is still considerably lower compared with that of Western countries, so we believe that more efforts for early detection of breast cancer through screening are necessary.

In our study, although mastectomy was performed most frequently, breast-conserving surgery was performed in 25.4% of total cases and showed an increasing trend from 5.1% in 1991 to 39.1% in 2003. This increasing trend of breast-conserving surgery was more prominent in stage I and stage II cancers. The National Cancer Institute Consensus Conference in 1990 indicated that breast conservation surgery for stage I and II breast cancers resulted in the same overall and disease-free survival rates compared with radical surgery but proved that the technique has fewer surgical complications and a better cosmetic effect. Since 1991, breast conservation surgery has become the accepted form of surgical treatment for early breast cancer. Recently, 2 randomized prospective trials with 20-year follow-up demonstrated no difference in long-term survival rates between breast-conserving surgery and mastectomy, although the locoregional recurrence rates appear to be somewhat higher for breast-conserving treatment than mastectomy. The proportion of breast-conserving surgery in Korea is still considerably lower than that of Western countries, but we believe it is low because of the smaller breast volume of Korean women compared with Western women and the fact that many Korean patients are more concerned about locoregional recurrence than cosmetic effects. According to stage, however, the proportion of breast-conserving surgery is high in early-stage breast cancer. This increase is expected to continue as the growth of the number of patients with breast cancer detected in early stages with mammographic screening increases and awareness of breast cancer among the public is raised.

Immediate reconstruction was performed in 12.0% of all patients who had undergone mastectomy, with increasing patterns of skin-sparing mastectomy and TRAM flap reconstruction. Since the introduction of skin-sparing mastectomy in 1991 by Toth and Lappert, skin-sparing mastectomy with immediate reconstruction has markedly increased. This procedure offers cosmetic results superior to conventional mastectomy and is oncologically safe. We expect that the use of immediate breast reconstruction after mastectomy in cases of breast cancer detected at stages 0 to II by mammography will also increase be-

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*Data are presented as percentage of 5001 patients.
‡Calculated as weight in kilograms divided by the square of height in meters.
cause of the increased interest in the cosmetic effects of reconstructed breasts among Korean women. Epidemiologic studies performed in Korea have shown that advanced age, a family history of breast cancer, early menarche, late menopause, late full-term delivery, and nonbreastfeeding are the primary risk factors of breast cancer, and a 4- to 7-fold reduction in risk was observed in postmenopausal women who experienced a full-term pregnancy and breastfeeding. The nationwide survey in 2000 showed that the incidence of patients with menarche before 13 years of age, menopause after 55 years of age, high-fat diets, and family history of breast cancer were significantly increased compared with the 1996 figures. The present study showed that the incidence of patients with risk factors such as early menarche and late first delivery has significantly increased during the past 15 years. Other risk factors, such as unmarried status, nonbreastfeeding, family history of breast cancer, oral contraceptive use, and hormone therapy show an increasing trend. This trend is consistent with the nationwide data of Korean breast cancer patients reported by the KBCS between 1996 and 2002.

Generally, tests for BRCA mutations are recommended in cases with a 10% or higher prevalence rate of the mutation in a clinical setting. Our previous study of BRCA germline mutations in Korean breast cancer patients showed that BRCA mutation was present in 12.7% of high-risk patients compared with 2.8% of unselected patients. Among high-risk patients, mutations were most prevalent in patients with a family history of breast cancer (22.1%), followed by those with male breast cancer (20%), bilateral breast cancer (20%), multiple organ cancer (22.1%), and younger breast cancer patients (aged <35 years) (8.1%). Moreover, BRCA mutations were detected in 34.8% of patients who had 2 high-risk factors. The study suggests that breast cancer patients with high-risk factors should be tested for BRCA mutations. Characteristically, the phenotype of BRCA mutations in Korea is different from that of Ashkenazi Jewish and other populations and suggests the need for large-scale, population-based studies to establish the clinicopathologic characteristics as well as the genetic conditions related to BRCA mutations in Korean breast cancer patients.

CONCLUSIONS

Our study showed that the clinical characteristics of breast cancer patients in Korea have continuously changed, demonstrating the following: an increase in the incidence rate and number of breast cancer cases, a high proportion of both young and premenopausal patients, an increase in the proportion of asymptomatic screening groups, an increase in the proportion of early breast cancer detection (stages 0 and I), an increase in the proportion of breast-conserving surgery, an increase in the proportion of immediate reconstruction after mastectomy, and an increase in the number of patients with risk factors. The present results suggest that the rate of breast cancer in Korea will continue to increase owing to westernized lifestyles, and the clinical characteristics of Korean breast cancer are now reflecting the patterns of Western countries.

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