Clinicopathological markers associated with recurrence in ductal carcinoma *in situ* of breast by age group

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Purpose: In the present study, factors related to the recurrence of breast ductal carcinoma *in situ* (DCIS) in Korean patients were identified, and the prognostic factors for each age group were explored.

Methods: The subjects were 226 patients who were diagnosed with DCIS by histopathologic examination, and the effect of representative prognostic factors that are known already, including estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2) status, Ki-67 levels, and adjuvant therapy on the recurrence of DCIS was analyzed by using the Cox proportional hazard model.

Results: Among the 226 subjects, 11 patients underwent the recurrence of breast cancer. The average follow-up period was 52.7 ± 23.5 months. The average age of the subjects was 50.6 ± 9.3 years. Among the DCIS patients, the recurrence of breast cancer was significantly higher in the ER negative patients and those who have a Ki-67 level over 20%. However, the PR and HER2 status did not significantly affect breast cancer recurrence. The result also showed that only ER negative was a significant factor before the age of 50 years and that only the Ki-67 level over 20% was a significant factor to the patients 50 years of age or older.

Conclusion: DCIS patients should be appropriately treated and managed depending on their age and clinicopathological factors to prevent the recurrence of DCIS.

Keywords: Breast, Ductal carcinoma *in situ*, Recurrence, Age

INTRODUCTION

Breast cancer is the cancer showing the second highest early incidence rate among Korean women (75.1 cases out of 100,000 women, 2015), following thyroid cancer [1]. The incidence rate of breast cancer is ranked fifth in the entire population including men and women and increased by 16.6% in comparison with 2005, and the number of deaths and the mortality are also increasing continu-

ously [2]. In addition, according to a report published by the Korean Breast Cancer Society in 2006 [3], about 20% to 30% of breast cancer patients have experienced a recurrence, and about 71% of the patients who had already undergone a surgery after a recurrence have experienced a second recurrence within 3 years.

Ductal carcinoma *in situ* (DCIS), a noninvasive cancer, has rapidly increased with the recent advancement in the breast cancer diagnosis. According to a study recently conducted in the United States, DCIS accounts for about 25% of total breast cancer incidents [4-6]. The incidence rate of DCIS in Korea is also increasing steadily [7].

The prognostic factors of breast cancer that are conventionally known include the tumor size, lymph node metastasis, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status, and Ki-67 levels [8,9]. As the incidence of DCIS is significantly increasing, the prognostic factors of the DCIS have been investigated. According to a study

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conducted with 458 subjects in 2013, the survival rate was low in triple negative patients who were found negative in all ER, PR, and HER2 [10]. Williams et al. [11] reported in 2015 that the recurrence rate of all subtypes of invasive cancers, except the luminal A type with positive ER and PR and negative HER2, was increased as the Ki-67 level was increased.

In Korea, few studies have been conducted on the prognostic factors of DCIS. The study conducted with 381 DCIS patients in 2010 showed that the local recurrence rate was higher in young, and ER positive patients who have not undergone tamoxifen treatment [12]. The present study was conducted to identify the factors related to the recurrence of DCIS and to explore the prognostic factors for each age group.

METHODS

Study population

The subjects of the present study were 226 patients who were finally diagnosed with DCIS by histopathologic examination at the Department of Surgery in Gachon University Gil Medical Center from January 2007 to December 2015. The information about the patients' age at the diagnosis, family history of breast cancer, menopausal status, the number of childbirth, surgical method, the ER, PR and HER2 status, Ki-67 levels, adjuvant chemotherapy, adjuvant hormone therapy, and adjuvant radiotherapy were collected from their medical records.

Statistical methods

The final endpoint was defined as the recurrence of breast carcinoma *in situ* or invasive breast cancer following the diagnosis of breast DCIS. The time variable in the patient with recurrence was defined as the period from the date of diagnosis until the confirmed date for recurrence. The breast cancer patients who did not have the confirmed evidence on recurrence were censored at the date of final observation. A log-rank test was performed to compare the recurrence considering with the period to the recurrence according to basic characteristics, including the age at diagnosis categorized by the age of 50 when menopausal usually occurs, family history of breast cancer, menopausal, the number of childbirth (less than two times or two times or more), surgical method, and adjuvant therapy. In addition, an age-adjusted Cox proportional hazard model was used to analyze the effect of prognostic factors of breast cancer, including ER and PR, which are the known prognostic factors, as well as the hormone receptor status where only those who are found negative in both the ER and PR levels are defined as negative, the HER2 status and a prior defined categories of Ki-67 level [13]. To explore the age-specific prognostic factors,

the subjects were stratified by the age of 50 years for the analysis. All the analyses were performed by using SPSS. The P-value less than 0.05 was defined as a level of significance.

The present study was approved by the Institutional Review Board of the Gil Medical Center (IRB No. GAIRB2018-178). The informed consent was waived.

RESULTS

Table 1 shows the recurrence according to basic characteristics of the subjects. Among the 226 subjects, 11 patients underwent the recurrence of breast cancer. The average follow-up period was 52.7 ± 23.5 months. The average age of the subjects was 50.6 ± 9.3 years. The average age of the subjects at recurrence was 46.6 ± 7.4 years. The age groups categorized by the age of 50 years showed no difference in the recurrence and the recurrence period. The family history of breast cancer, menopausal, number of times of childbirth categorized by two times of childbirth, surgical method, and adjuvant therapy show no difference in the recurrence and the re-

Table 1. Basic characteristics according to recurrence status

Characteristics	Total (n = 226)	Recurrence (n = 11)	P-value ^{a)}
Follow-up duration (mo)	52.7 ± 23.5	25.7 ± 12.5	
Age (yr)	50.6 ± 9.3	46.6 ± 7.4	0.151
< 50	117 (51.8)	8 (72.7)	
≥ 50	109 (48.2)	3 (27.3)	
Familial history of breast cancer			0.584
No	204 (90.3)	11 (100.0)	
Yes	15 (6.6)	0	
Menopausal status			0.174
No	144 (63.7)	10 (90.9)	
Yes	60 (26.5)	1 (9.1)	
No. of childbirth	2.0 ± 0.9	1.7 ± 0.8	0.395
< 2	42 (18.6)	1 (9.1)	
≥ 2	180 (81.4)	10 (90.9)	
Surgery method			0.121
Excision	4 (1.8)	0	
BCS	164 (72.6)	11 (100.0)	
Mastectomy	58 (25.7)	0	
Adjuvant hormone therapy			0.298
No	52 (23.0)	4 (36.4)	
Yes	174 (77.0)	7 (63.6)	
Adjuvant radiotherapy			0.629
No	121 (53.5)	5 (45.5)	
Yes	105 (46.5)	6 (54.5)	

Values are presented as mean ± standard deviation or number (%). The proportion of missing values was not presented.

BCS, breast-conserving surgery.

^{a)}Log-rank test for categorical variables.

Table 2. Clinicopathological characteristics for the 11 patients underwent the recurrence

Characteristics	1	2	3	4	5	6	7	8	9	10	11
Invasive/noninvasive	DCIS	IDC	DCIS	IDC	ILC	DCIS	LCIS	DCIS	IDC	Page's disease	DCIS
Site of primary breast cancer	L	L	L	R	L	L	R	L	R	L	L
Site of recurrence	L	L	R	R	L	R	L	L	L	L	L
Estrogen receptor	N	N	P	P	P	N	P	N	P	N	N
Progesterone receptor	N	P	N	P	P	N	P	N	P	N	N
Hormone receptor	N	P	P	P	P	N	P	N	P	N	N
HER2 status	N	P	P	P	N	P	N	P	P	N	P
Ki-67 level (%)	5	30	30	5	15	30	0.5	25	5	25	10

DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma *in situ*; L, left; R, right; P, positive; N, negative; HER2, human epidermal growth factor receptor 2.

Table 3. Associations of hormone receptors status, HER2 status, and Ki-67 level with recurrence of breast cancer in 226 DCIS patients

Characteristics	Total (n = 226)	Recurrence (n = 11)	Crude HR	(95% CI)	Age-adjusted HR	(95% CI)
Estrogen receptor						
Positive	174 (77.0)	5 (45.5)	1.00	Reference	1.00	Reference
Negative	50 (22.1)	6 (54.5)	4.45	(1.36–14.59)	4.97	(1.50–16.48)
Progesterone receptor						
Positive	144 (63.7)	5 (45.5)	1.00	Reference	1.00	Reference
Negative	80 (35.4)	6 (54.5)	2.40	(0.73–7.86)	3.07	(0.90–10.50)
Hormone receptor						
Positive	175 (77.4)	6 (54.5)	1.00	Reference	1.00	Reference
Negative	50 (22.1)	5 (45.5)	3.05	(0.93–9.99)	3.42	(1.03–11.33)
HER2 status						
Positive	99 (43.8)	7 (63.6)	1.00	Reference	1.00	Reference
Negative	127 (56.2)	4 (36.4)	0.45	(0.13–1.54)	0.44	(0.13–1.52)
Ki-67 (%)						
≤ 10	155 (68.6)	5 (45.5)	1.00	Reference	1.00	Reference
11–20	36 (15.9)	1 (9.1)	0.86	(0.10–7.35)	0.98	(0.11–8.50)
> 20	35 (15.5)	5 (45.5)	5.33	(1.54–18.43)	5.16	(1.48–17.93)

Values are presented as number (%). The proportion of missing values was not presented.

HER2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma *in situ*; HR, hazard ratio; CI, confidence interval.

currence period, either.

Table 2 presents the status of clinicopathological characteristics for the 11 patients of recurrence group. Five of patients recurred with DCIS and three with invasive ductal carcinoma (IDC), and there were also one of lobular carcinoma *in situ*, invasive lobular carcinoma, and Page's disease, respectively. Seven of patients recurred in the same site and four of patients recurred in the contralateral breast. In the recurrence group, ER and PR were negative in six patients, and hormone receptor status was negative in five patients, and HER2 status was negative in four patients. The Ki-67 level was found to be more than 20% in five, more than 10% in two, and less than 10% in four patients.

Table 3 shows the association of the ER, PR, hormone receptors and HER2 status, and Ki-67 level with the recurrence in the total

DCIS patients. The breast cancer recurrence rate was significantly higher in the ER negative patients or the patients with a Ki-67 level over 20%. The significance was preserved also in the age-adjusted Cox proportional hazard model. In contrast to the ER status and the Ki-67 level, the PR and HER2 status did not show a significant effect on the breast cancer recurrence. However, the age-adjusted analysis suggested that the hormone receptor status may increase the risk of breast cancer recurrence.

In Table 4 stratifying all the subjects by the age of 50 years, only the ER status showed a significant effect on the recurrence in the patients younger than 50 years. In the patients 50 years or older, only the Ki-67 level over 20% significantly increased the risk of recurrence.

Table 4. Associations of hormone receptors status, HER2 status, and Ki-67 level with recurrence of breast cancer according to age 50 years in 226 DCIS patients

Characteristics	Total (n = 226)	Recurrence (n = 11)	Crude HR	(95% CI)	Age-adjusted HR	(95% CI)
Age < 50 yr						
Estrogen receptor						
Positive	94 (80.3)	4 (50.0)	1.00	Reference	1.00	Reference
Negative	22 (18.8)	4 (50.0)	4.51	(1.13–18.06)	4.60	(1.14–18.52)
Progesterone receptor						
Positive	89 (76.1)	5 (62.5)	1.00	Reference	1.00	Reference
Negative	27 (23.1)	3 (37.5)	2.12	(0.51–8.88)	1.37	(0.31–6.19)
Hormone receptor						
Positive	95 (81.2)	5 (62.5)	1.00	Reference	1.00	Reference
Negative	21 (17.9)	3 (37.5)	2.79	(0.67–11.70)	2.83	(0.67–11.89)
HER2 status						
Positive	51 (43.6)	6 (75.0)	1.00	Reference	1.00	Reference
Negative	66 (56.4)	2 (25.0)	0.26	(0.05–1.29)	0.26	(0.05–1.28)
Ki-67 (%)						
≤ 10	82 (70.1)	4 (50.0)	1.00	Reference	1.00	Reference
11–20	15 (12.8)	1 (12.5)	1.29	(0.14–11.54)	1.41	(0.15–13.16)
> 20	18 (17.1)	3 (37.5)	3.52	(0.79–15.74)	3.39	(0.74–15.55)
Age ≥ 50 yr						
Estrogen receptor						
Positive	80 (73.4)	1 (33.3)	1.00	Reference	1.00	Reference
Negative	28 (25.7)	2 (66.7)	6.07	(0.55–66.95)	6.18	(0.56–68.52)
Progesterone receptor						
Positive	55 (50.5)	0	1.00	Reference	1.00	Reference
Negative	53 (48.6)	3 (100.0)	–	–	–	–
Hormone receptor						
Positive	80 (73.4)	1 (33.3)	1.00	Reference	1.00	Reference
Negative	29 (26.6)	2 (66.7)	5.82	(0.53–64.21)	5.86	(0.53–64.81)
HER2 status						
Positive	48 (44.0)	1 (33.3)	1.00	Reference	1.00	Reference
Negative	61 (56.0)	2 (66.7)	1.55	(0.14–17.10)	1.58	(0.14–17.46)
Ki-67 (%)						
≤ 10	73 (67.0)	1 (33.3)	1.00	Reference	1.00	Reference
11–20	21 (19.3)	0	–	–	–	–
> 20	14 (13.7)	2 (66.7)	12.19	(1.11–134.48)	15.86	(1.24–203.67)

Values are presented as number (%). The proportion of missing values was not presented.

HER2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma *in situ*; HR, hazard ratio; CI, confidence interval.

DISCUSSION

Through the follow-up survey for an average period of 4.3 years, we found that different clinicopathological factors affect the recurrence of breast cancer of different age groups. A total of 11 breast cancer recurrences were found during the follow-up. The factor that showed a significant association with the breast cancer recurrence was the ER status in the patients before the age of 50 years and the Ki-67 level in the patients aged 50 years or older.

DCIS is known as non-obligate precursor of invasive breast cancer, and less than 40% of DCIS is progressed to the invasive disease when patients had not been treated [14]. Until recently, the precise

mechanism of the major driver acting on the development of DCIS into invasive breast cancer has not been elucidated. However, previous studies have reported that DCSI and IDC are remarkably similar, and that a series of processes occurs through genetic, epigenetic aberrations in some subsets of DCIS cells and molecular mechanisms associated with micro-environmental factors [15–18].

Clinicopathological factors revealed in the present study were consistently identified in the previous study. In ER, PR, and HER2 status, Roka et al. [19] reported that the recurrence rate was significantly higher in the ER negative patient group than in the ER positive patient group. Kerlikowske et al. [13] conducted a study with 324 DCIS patients and reported that the ER negative status was

not significantly associated with the recurrence as an invasive cancer but significantly increased the recurrence risk of DCIS. They also reported that the recurrence risk of DCIS was even higher in the ER negative, HER2 positive and high level of Ki-67. The effect of the Ki-67 level investigated in the present study was also similar to the results found in previous reports. Chasle et al. [20] reported that the global proliferation factor indicated the level of Ki-67 and cyclin is a predictor of the recurrence of the breast cancer. Barnes et al. [21] reported that the recurrence rate was increased as the Ki-67 level was increased.

The result of the present study additionally suggests that different factors may be involved in the recurrence in different age groups. Previous studies have shown that the recurrence rate was higher in younger age groups, especially higher in the age group below 49 years than in the age group over 50 years [22], or the recurrence rate was higher more than two times in the patients at the age of 40 years or younger [23]. A study conducted in Korea also showed that the recurrence rate was higher in younger patients [12]. Although there were suggestions that the reason for the higher recurrence rate in younger patients may be the lower hormone receptor expression level, which is consistent with our study, an association between the hormone receptor expression level and age group was not found. Further study will be needed to reveal the mechanism of how hormonal receptors are acting in the progression of DCIS.

When interpreting the result of the present study, it should be considered that the number of patients who underwent the DCIS recurrence was extremely small. Thus, we could not divide the recurrence group into invasive and noninvasive breast cancer. However, the recurrence, metastasis, and mortality of the DCIS are known as very low [6]. Therefore, most of the previous studies were also conducted by using the local recurrence, including both invasive and noninvasive breast cancer as an outcome. In addition, the statistical power to capture precise effect of clinicopathological factors on the recurrence of DCIS may be insufficient. However, the present study has the strength of being able to propose the possibility of different prognostic factors of DCIS depending on the age group for the first time. Moreover, in present study, we could not consider the subtype of DCIS. The effect of clinicopathological factors on the prognosis of breast cancer according to subtype of breast cancer should be evaluated in the further study.

The present study showed that the ER status and the Ki-67 level affect the recurrence in breast DCIS patients, indicating that the prognostic factor is the ER status before the age of 50 years and the Ki-67 level after the age of 50 years. Therefore, the DCIS patients should be treated and managed depending on the age and the clinicopathological marker status to prevent the recurrence in the patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Korean Statistical Information Service. Incidence and the number of cancer by sex in 2015 [Internet]. Daejeon (Korea): Korean Statistical Information Service; c2015 [cited 2018 Jan 15]. Available from: http://kosis.kr/statHtml/statHtml.do?orgId=117&tblId=DT_117N_A00025&vw_cd=&list_id=&scrId=&seqNo=&lang_mode=ko&obj_var_id=&itm_id=&conn_path=E1.
2. Statistics Korea. Incidence and mortality of cancer from 2000 to 2015; c2015 [Internet]. Daejeon (Korea): Statistics Korea; c2015 [cited 2018 Jan 15]. Available from: http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=2770.
3. Son BH, Ahn SH, Kwak BS, Kim JK, Kim HJ, Hong SJ, et al. The recurrence rate, risk factors and recurrence patterns after surgery in 3700 patients with operable breast cancer. *Journal of Breast Cancer* 2006;9:134-44.
4. Frykberg ER. An overview of the history and epidemiology of ductal carcinoma in situ of the breast. *Breast J* 1997;3:227-31.
5. Allegra CJ, Aberle DR, Ganschow P, Hahn SM, Lee CN, Mil-lon-Underwood S, et al. National Institutes of Health State-of-the-Science Conference statement: diagnosis and management of ductal carcinoma in situ September 22-24, 2009. *J Natl Cancer Inst* 2010;102:161-9.
6. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst* 2010;102:170-8.
7. Ko SS; Korean Breast Cancer Society. Chronological changing patterns of clinical characteristics of Korean breast cancer patients during 10 years (1996-2006) using nationwide breast cancer registration on-line program: biannual update. *J Surg Oncol* 2008;98:318-23.
8. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol* 1998;11:155-68.
9. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989;63:181-7.
10. Zhou W, Jirstrom K, Amini RM, Fjallskog ML, Sollie T, Lindman H, et al. Molecular subtypes in ductal carcinoma in situ of the breast and their relation to prognosis: a population-based cohort study. *BMC Cancer* 2013;13:512.
11. Williams KE, Barnes NL, Cramer A, Johnson R, Cheema K, Morris J, et al. Molecular phenotypes of DCIS predict overall and inva-

- sive recurrence. *Ann Oncol* 2015;26:1019-25.
12. Kim JS, Moon HG, Ahn SK, Min JW, Shin HC, Kim HS, et al. Clinicopathological characteristics and factors affecting recurrence of ductal carcinoma in situ in Korean women. *J Breast Cancer* 2010; 13:392-7.
13. Kerlikowske K, Molinaro AM, Gauthier ML, Berman HK, Waldman F, Bennington J, et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. *J Natl Cancer Inst* 2010;102:627-37.
14. Sanders ME, Schuyler PA, Dupont WD, Page DL. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. *Cancer* 2005;103:2481-4.
15. Burkhardt L, Grob TJ, Hermann I, Burandt E, Choschick M, Janicke F, et al. Gene amplification in ductal carcinoma in situ of the breast. *Breast Cancer Res Treat* 2010;123:757-65.
16. Vargas AC, McCart Reed AE, Waddell N, Lane A, Reid LE, Smart CE, et al. Gene expression profiling of tumour epithelial and stromal compartments during breast cancer progression. *Breast Cancer Res Treat* 2012;135:153-65.
17. Hu M, Yao J, Cai L, Bachman KE, van den Brule F, Velculescu V, et al. Distinct epigenetic changes in the stromal cells of breast cancers. *Nat Genet* 2005;37:899-905.
18. Ma XJ, Dahiya S, Richardson E, Erlander M, Sgroi DC. Gene expression profiling of the tumor microenvironment during breast cancer progression. *Breast Cancer Res* 2009;11:R7.
19. Roka S, Rudas M, Taucher S, Dubsky P, Bachleitner-Hofmann T, Kandioler D, et al. High nuclear grade and negative estrogen receptor are significant risk factors for recurrence in DCIS. *Eur J Surg Oncol* 2004;30:243-7.
20. Chasle J, Delozier T, Denoux Y, Marnay J, Michels JJ. Immunohistochemical study of cell cycle regulatory proteins in intraductal breast carcinomas: a preliminary study. *Eur J Cancer* 2003; 39:1363-9.
21. Barnes NL, Khavari S, Boland GP, Cramer A, Knox WF, Bundred NJ. Absence of HER4 expression predicts recurrence of ductal carcinoma in situ of the breast. *Clin Cancer Res* 2005;11:2163-8.
22. Vicini FA, Recht A. Age at diagnosis and outcome for women with ductal carcinoma-in-situ of the breast: a critical review of the literature. *J Clin Oncol* 2002;20:2736-44.
23. Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol* 2001;19:2263-71.