The Impact of Diabetes Mellitus on Prognosis of Early Breast Cancer in Asia

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ABSTRACT

Background. Diabetes mellitus (DM) has been implicated in influencing the survival duration of patients with breast cancer. However, less is known about the impact of DM and other comorbidities on the breast cancer–specific survival (BCS) and overall survival (OS) outcomes of Asian patients with early-stage breast cancer.

Patients and Methods. The characteristics of female patients with newly diagnosed, early-stage breast cancer were collected from the Taiwan Cancer Registry database for 2003–2004. DM status and other comorbidities were retrieved from Taiwan's National Health Insurance database. The BCS and OS times of patients according to DM status were estimated via the Kaplan–Meier method. Cox's proportional hazard model was used to estimate adjusted hazard ratios (HRs) for the effects of DM, comorbidities, and other risk factors on mortality.

Results. In total, 4,390 patients were identified and 341 (7.7%) presented with DM. The 5-year BCS and OS rates were significantly worse in DM patients than in non-DM patients (BCS, 85% versus 91%; OS, 79% versus 90%). Furthermore, after adjusting for clinicopathologic variables and comorbidities, DM remained an independent predictor of shorter BCS (adjusted HR, 1.53) and OS (adjusted HR, 1.71) times. Subgroup analyses also demonstrated a consistent prognostic influence of DM across different groups.

Conclusion. In Asian patients with early-stage breast cancer, DM is an independent predictor of lower BCS and OS rates, even after adjusting for other comorbidities. The integration of DM care as part of the continuum of care for early-stage breast cancer should be emphasized. *The Oncologist* 2012;17:485–491

INTRODUCTION

The incidence of breast cancer is rising rapidly in Asian countries and is accompanied by a higher diagnostic rate of early-stage breast cancer [1, 2]. With early diagnosis and

improvements in adjuvant therapy, the life expectancy of breast cancer patients has been significantly prolonged. For example, the 5-year survival rates of patients with stage I and stage II breast cancer are >95% and >90%, respectively [3, 4].

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The prolonged survival time complicates the care of patients with early-stage breast cancer, because other chronic diseases also contribute to mortality [5].

Diabetes mellitus (DM) has been associated with a higher mortality rate among patients with breast cancer in western countries [6–10]. The association between DM and breast cancer prognosis in Asia has been also explored. A meta-analysis by Liao et al. [11] found that the relative risk for mortality for patients with breast cancer was twofold greater in patients with DM than in those without DM. In China and Korea, DM was also associated with a shorter survival time after a diagnosis of breast cancer [12, 13]. However, patients with all stages of breast cancer were analyzed in these studies. Thus, the influence of DM in the prognosis of early-stage breast cancer patients in Asia is unclear.

DM is associated with other comorbidities, such as metabolic disorder, cardiovascular disease, and renal disease [7, 14, 15], and thus, the prognostic influence of DM is affected when other comorbidities are present [9, 14, 16]. To date, no Asian studies have adjusted for the effects of other comorbidities when assessing the influence of DM on the breast cancer-specific survival (BCS) and overall survival (OS) outcomes of patients with early-stage breast cancer.

Thus, the present study, which was based on nationwide databases, focused on evaluating the individual effect of DM on both BCS and OS rates in Asian patients with early-stage breast cancer while taking into account other comorbidities.

PATIENTS AND METHODS

Data Source

This population-based study assessed newly diagnosed primary breast cancer patients in 2003–2004 in the Taiwan Cancer Registry (TCR) database. The TCR is managed by the Department of Health in Taiwan from the Bureau of Health Promotion (BHP) [17–19]. All major cancer care providers are obligated to report on the data gathered on newly diagnosed cancer patients, who represent ~78% of new cancer patients in Taiwan. Information regarding patient demographics, their clinicopathologic status, and details regarding the first treatment course were obtained from the database. Data were then linked to the claims database of Taiwan's National Health Insurance (NHI) to identify whether or not the patients presented with DM and other comorbidities. The NHI program is a mandatory single-payer health insurance in Taiwan. More than 98% of the total Taiwanese population is covered by the program [20]. All medical claims are submitted and captured electronically [21]. The complete history of diagnosis, which includes the International Classification of Disease Ninth Revision Clinical Modification code (ICD-9-CM code), prescriptions, procedures, and examinations ordered for every patient, could be identified. The complete claim records of each patient were retrieved as far as 1 year prior to the diagnosis of breast cancer to provide baseline information. Patients were followed up until their date of death or the end of the study on December 31, 2009. The patients' records were then linked to the National Death Registry (NDR) to identify mortality outcomes in 2003–2009. To comply with personal electronic data privacy regulations, personal identities were encrypted and all data were analyzed anonymously. The study data were approved for re-

lease by the Data Release Review Board of the BHP. The study protocol was approved by the Research Ethics Committee of the College of Public Health, National Taiwan University (protocol #201105022RC).

Study Population

Newly diagnosed breast cancer patients (ICD-O-3, C50) [22] were identified using the following inclusion criteria: (a) an initial diagnosis of breast cancer as a primary tumor; (b) the presence of stage I–III disease, according to the American Joint Committee on Cancer staging system (sixth edition) criteria [23]; and (c) age ≥ 40 years. Patients with the following characteristics were excluded: (a) the presence of multiple primary cancers; (b) the presence of lymphoma (ICD-O-3 morphology code, 9590–9989), Kaposi's sarcoma (ICD-O-3 morphology code, 9140), or phyllodes tumor (ICD-O-3 morphology code, 9020); (c) having received any other treatment prior to surgery; (d) a positive cancer margin after surgical treatment; or (e) not fulfilling the DM diagnostic criteria of the present study, despite having received anti-DM medication.

Study Variables and Endpoint Definitions

Patients were classified as either with or without DM according to the NHI claim database diagnostic code (ICD-9-CM code, 250.x) during the 1 year period prior to their diagnosis of breast cancer. Patients who had DM as the principle diagnosis at least three times during their outpatient clinic visits or at least once during a hospital admission were considered to be diabetic in our study. To increase the accuracy of the DM diagnoses, patients repeatedly diagnosed with DM within a single month were not classified as having DM in our study. In addition to DM, comorbidities defined by the Deyo's Charlson Comorbidity Index [24] were examined using a revised mapping algorithm cited by Quan et al. [25]. Each comorbidity was coded and analyzed separately as a dichotomized variable (i.e., yes or no). The following ICD-9-CM codes were used: myocardial infarction, 410.x, 412.x; congestive heart failure, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x; peripheral vascular disease, 093.0, 437.3, 440.x, 441.x, 443.1–443.9, 47.1, 557.1, 557.9, V43.4; cerebrovascular disease, 362.34, 430.x–438.x; coronary artery disease, 414.0; hyperlipidemia, 272.0–272.4; dementia, 290.x, 294.1, 331.2; chronic pulmonary disease, 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8; hemiplegia or paraplegia, 334.1, 342.x, 343.x, 344.0–344.6, 344.9; renal disease, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x; mild liver disease, 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7; moderate or severe liver disease, 456.0–456.2, 572.2–572.8; rheumatologic disease, 446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x; and peptic ulcer disease, 531.x–534.x. Patients were followed from the day of breast cancer diagnosis until either death resulting from breast cancer (BCS), death resulting from any cause (OS), or the last follow-up date of the NDR database (i.e. December 31, 2009).

Statistical Analysis

The means or frequencies of the baseline characteristics of the two study groups were compared using one-way analysis of variance for continuous variables and a χ^2 test for categorical variables. The BCS and OS times of patients according to their DM status were estimated via the Kaplan–Meier method and compared using the log-rank test. Data from patients who died from causes other than breast cancer or survived until the last date in the NDR database (i.e., December 31, 2009) were analyzed as censors for the BCS time on the date of the last follow-up. Cox’s proportional hazard model was used to estimate the adjusted hazard ratio (HR) and the associated 95% confidence interval (95% CI) to evaluate the effects of DM and other risk factors on mortality. Patient demographics, tumor stage, estrogen receptor (ER) status, progesterone receptor (PR) status, lymph node involvement status, type of surgical treatment, adjuvant treatment status, and comorbidities were all included in the Cox’s model for adjustment. For parsimonious results, backward elimination of variables with a p -value $>.05$ was performed. Adjusted HRs for DM on mortality in subgroups defined by age (<55 years, 55–69 years, or 70+ years old), tumor stage (I, II, or III), ER status (positive or negative), lymph node involvement (positive or negative), adjuvant chemotherapy (yes or no), and adjuvant hormone therapy (yes or no) were determined to test if the effects of DM on mortality were consistent across the different patient populations. A two-sided p -value $\leq .05$ was considered statistically significant. The statistical package SAS, version 9.2 (SAS Institute Inc., Cary, NC), was used to perform the analyses.

RESULTS

Patient Characteristics

There were 7,595 patients with newly diagnosed breast cancer registered in the TCR in 2003–2004. In total, 4,390 patients who had stage I–III breast cancer and received curative surgery fulfilled the eligibility criteria of the present study (Fig. 1). Of these, only 341 patients (7.7%) had DM, whereas 4,049 (92.3%) patients did not have DM. Compared with patients without DM, patients with DM were older (mean age, 62.7 years versus 53.0 years; $p < .01$) and were more likely to have stage III disease ($p = .03$) and other comorbidities (supplemental online Table 1). DM patients were also less likely to receive adjuvant chemotherapy than non-DM patients ($p < .01$). Lymph node involvement, ER and PR status, and the percentages of patients receiving adjuvant hormone therapy, adjuvant radiotherapy, and surgery were not significantly different between the two study groups.

Survival Analysis

Within the median follow-up period of 67.2 months, 79 (23.2%) patients in the DM group and 462 (11.4%) patients in the non-DM group died. Patients with DM also had a significantly lower BCS rate than patients without DM (Fig. 2A) ($p < .01$). The BCS rates at 2 years for the DM group and non-DM group were 94% and 98%, respectively, and at 5 years, the BCS rates were 85% and 91%, respectively. Patients with DM also experienced significantly shorter OS times than patients without DM (Fig. 2B) ($p <$

Figure 1. Patient flow diagram.
Abbreviation: DM, diabetes mellitus.

.01). The OS rates at 2 years for the DM group and non-DM group were 92% and 97%, respectively, and at 5 years, the OS rates were 79% and 90%, respectively.

After adjusting for age, tumor stage, ER status, lymph node involvement, adjuvant chemotherapy, adjuvant hormone therapy, and comorbidities in the multivariate analysis, DM remained an independent predictor of a lower BCS probability (adjusted HR, 1.53; 95% CI, 1.14–2.05; $p < .01$) and OS probability (adjusted HR, 1.71; 95% CI, 1.33–2.19; $p < .01$) (Table 1).

Subgroup analyses demonstrated that the prognostic influence of DM was consistent across the different subgroups, including age, tumor stage, lymph node status, ER and PR status, and adjuvant chemotherapy and hormone treatment status. The ranges of the adjusted HRs were 1.2–2.1 for breast cancer–specific mortality and 1.3–2.3 for overall mortality among the subgroups analyzed (Fig. 3). There was no obvious heterogeneity between the HRs of different subgroups.

DISCUSSION

The present study demonstrated that DM is an independent predictor of BCS and OS outcomes in Asian patients with early-stage breast cancer. Furthermore, the prognostic influence of DM was consistent across multiple subgroups, including age, tumor stage, and ER status. This study is the first of its kind to investigate the association between DM and survival in an Asian population that consisted of a nationwide cohort of only early-stage breast cancer patients.

Although previous studies also reported that DM is a prognostic predictor of BCS and OS outcomes [10, 16, 26], the specific influence of DM in early-stage breast cancer was controversial because their findings were based on data from all

Figure 2. Survival of stage I–III breast cancer patients by diabetes mellitus (DM) diagnosis status. **(A):** Breast cancer specific survival. **(B):** Overall survival.

stages of breast cancer. A questionnaire-based study found that DM predicted a worse survival rate in patients with early-stage breast cancer [26], whereas another single-institution study demonstrated that DM was not a significant prognostic factor for the OS time via a multivariate analysis [16]. Our nationwide, population-based cancer registry and health insurance medical data allowed us to accurately evaluate the impact of DM on the survival outcomes of early-stage breast cancer patients.

Aside from DM, other comorbidities also play an important role in the prognosis of patients with early-stage breast cancer, and thus may interfere with the true impact of DM on BCS and OS outcomes. The effects of comorbidities on sur-

vival are commonly assessed via indices that sum up the multiple diseases and conditions [27, 28]. Nevertheless, the specific prognostic effects of each comorbidity may be lost during condensation. Considering each comorbidity separately, Patnaik et al. [6] demonstrated that patients with stage I and stage II breast cancer and an additional comorbidity had a survival trend similar to that of patients with stage III and stage IV disease not having any of these comorbidities. In the present study, renal disease and cerebrovascular disease were found to be associated with the BCS rate. Renal disease was previously reported to influence the prognosis of breast cancer patients [6, 9]. The reasons for this association are likely to be multifacto-

Table 1. Multivariate analysis of potential factors predicting breast cancer–specific mortality and overall mortality

Factor	Breast cancer-specific mortality		All-cause mortality	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
DM versus non-DM	1.53 (1.14–2.05)	<.01	1.71 (1.33–2.19)	<.01
Age, yrs				
40–54		NS	Reference	<.01
55–69			1.13 (0.93–1.38)	
70+			2.00 (1.54–2.59)	
Stage				
I	Reference	<.01	Reference	<.01
II	2.33 (1.56–3.49)		2.02 (1.45–2.82)	
III	7.43 (4.71–11.73)		5.89 (4.00–8.67)	
ER status				
Negative	Reference	<.01	Reference	<.01
Positive	0.41 (0.34–0.50)		0.50 (0.41–0.60)	
Lymph node involvement				
Negative	Reference	<.01	Reference	<.01
Positive	2.23 (1.65–3.01)		2.00 (1.54–2.60)	
Adjuvant chemotherapy	0.69 (0.55–0.86)	<.01	0.67 (0.54–0.82)	<.01
Adjuvant hormone therapy			0.80 (0.65–0.98)	.03
Comorbidity				
Renal disease	2.65 (1.35–5.18)	<.01	3.03 (1.83–4.99)	<.01
Cerebrovascular disease	1.81 (1.15–2.83)	<.01		
Congestive heart failure		NS	1.87 (1.11–3.15)	.02

Using backward selection with the eliminating criterion of *p*-value >.05.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; ER, estrogen receptor; HR, hazard ratio; NS, not significant.

rial. It is known that patients with chronic kidney disease have a higher risk for developing multiple cancers, including breast cancer [29, 30]. Additionally, patients with chronic kidney disease have lower serum levels of vitamin D [31], which has also been associated with a higher risk for metastasis and a poorer prognosis in breast cancer patients [32, 33]. Furthermore, the greater risk for cerebrovascular events may direct patients with cerebrovascular disease to less intensive adjuvant hormone treatment, thereby resulting in a poorer BCS outcome [34, 35].

The subgroup analyses revealed that the prognostic effects of DM on all subgroups, including age, tumor stage, lymph node status, ER and PR status, and adjuvant chemotherapy and hormone treatment status, were similar. However, the negative impact of DM on survival was not prominent in patients who received adjuvant chemotherapy, compared with those who did not receive adjuvant chemotherapy. In contrast, Srokowski et al. [8] showed that the negative impact of DM on BCS outcomes was only observed in breast cancer patients receiving adjuvant chemotherapy. Nevertheless, the study population in our study consisted of patients aged ≥ 40 years, whereas Srokowski et al. [8] assessed patients who were aged ≥ 66 years. In a younger population, colon cancer patients with DM did not have a higher risk for chemotherapy-related complications, except for diarrhea [36]. Additionally, in our subgroup analysis, DM was also not a prognostic factor of

survival in patients with stage I breast cancer. Given that patients with stage I breast cancer tend to live longer, other comorbidities are more likely to influence breast cancer–specific and overall mortality outcomes, and thereby attenuate the effects of DM on BCS and OS rates.

The present study had a few limitations that need to be addressed. First, this study is a retrospective study. However, the use of nationwide databases diminished the likelihood of missing data and observational bias and prevented selection bias inherent to single-institution studies. Furthermore, the severity of DM and reliability of the DM controls were unavailable because the databases used did not report on glycated hemoglobin levels. Thus, whether or not a more severe form of DM had a greater prognostic impact on BCS and OS outcomes could not be explored.

Of note, another metabolic disorder, obesity, was not included in the analysis. Body mass index (BMI) is a common way to evaluate obesity, but the databases used in the study did not have such information. A high BMI, like DM, has been demonstrated to impact survival outcomes of early-stage breast cancer patients [37, 38]. Furthermore, obesity and DM may both exert their prognostic effects via an insulin-related pathway [39], making the true influence of DM on survival more complex. Therefore, the influence of obesity on the prog-

Figure 3. Subgroup analysis of adjusted HR of mortality for DM versus non-DM patients using Cox's proportional hazard model. Each analysis was adjusted for all the other factors not involved in the subgroup, including age, tumor stage, ER status, lymph node involvement, adjuvant chemotherapy, adjuvant hormone therapy, and all other comorbidities.

Abbreviations: CI, confidence interval; DM, diabetes mellitus; ER, estrogen receptor; HR, hazard ratio.

nostic effect of DM in early-stage breast cancer patients should be further evaluated.

In conclusion, our study demonstrated that DM is a significant prognostic factor for BCS and OS outcomes in Asian early-stage breast cancer patients, even after adjusting for other comorbidities.

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Wei-Wu Chen and Yu-Yun Shao contributed equally to this work.

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