Clinicopathological features of breast cancer patients with nipple discharge

WEN-JIN YIN*, GEN-HONG DI*, GUANG-YU LIU, JIONG WU, JIN-SONG LU, QI-XIA HAN, ZHEN-ZHOU SHEN and ZHI-MIN SHAO

Department of Breast Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, P.R. China

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Abstract. The demographic features and prognostic profiles of breast cancer patients with nipple discharge (ND) have not been well elucidated in previous studies. We therefore performed a retrospective study of female unilateral breast cancer patients that underwent surgery. According to the initial symptoms at diagnosis, a total of 3,317 patients were categorized into the ND (2.74%) and non-ND (NND; 97.26%) subgroups. Survival curves were performed with the Kaplan-Meier method and annual recurrence hazard was estimated by the hazard function. The proportion of larger tumors was lower in patients with ND than in the NND subgroup (P=0.019). In addition, 22.22% of patients with ND had positive lymph nodes in the axilla as compared to 51.06% of those without ND (P<0.001). Multivariate logistic regression analysis showed that axillary lymph node (ALN) status (P=0.003) and Cathepsin-D status (P=0.025) were independent prognostic factors for ND. In the univariate survival analysis, a significant difference in recurrence-free survival (RFS) was found between patients with and without ND (P=0.014). As ND and ERBB2 status were time-varying covariates (global test, both P<0.05), the Cox non-proportional hazards regression model was used. In this model, ND status (P=0.028; RR=2.174, 95% CI 1.086-4.351), as well as tumor size (P<0.001; RR=1.779, 95% CI 1.406-2.250), ALN status (P<0.001; RR=2.257, 95% CI 1.886-2.702), ERBB2 status (P=0.011; RR=0.759, 95% CI 0.613-0.940) and use of adjuvant chemotherapy (P=0.048; RR=0.642, 95% CI 0.414-0.995) were independent prognosticators for RFS. Regarding hazard peaks, patients without ND showed an early major recurrence surge peaking at 1.5 years after surgery, while the corresponding peak for the ND subgroup was at 3.5 years. Furthermore, the risk of early recurrence for women with ND was lower than that for the NND subgroup. Our findings suggest that biological behavior and prognostic profiles differ significantly between patients with and without ND. This suggests that further studies are required to elucidate these two distinctive disease entities.

Correspondence to: Dr Zhimin Shao, Department of Breast Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, 399 Ling-Ling Road, Shanghai 200032, P.R. China
E-mail: zhimingshao1962@yahoo.com

*Contributed equally

Abbreviations: ND, nipple discharge; NND, non-nipple discharge; ALN, axillary lymph node; ECG, electrocardiogram; ER, estrogen receptor; PR, progesterone receptor; RFS, recurrence-free survival; HR, hormone receptor; OR, odds ratio; CI, confidence interval; RR, relative risk

Key words: breast cancer, nipple discharge, prognostic factors

Introduction

Among various breast complaints, nipple discharge (ND) ranks third after breast pain and breast lump, accounting for approximately 5% of referrals to breast clinics (1). Unexpected ND causes many women discomfort and anxiety, but is only a symptom of malignant underlying disease on rare occasions. Lesions associated with ND are typically not revealed on mammography or sonography. However, early detection of abnormalities has been made possible through the introduction of techniques for breast imaging such as galactography and ductoscopy (2-4).

Over the past three decades, early detection has resulted in a marked improvement in the prognosis of breast cancer (5). However, it is just the one side of the coin. Adjuvant systemic therapy has also been demonstrated to have a significant survival benefit (6). At present, treatment selection according to various guidelines (7-9) is based on several sufficiently established prognostic factors, exemplified by tumor size and nodal status. In the case of ND, most studies conducted examnied its use in evaluation and diagnosis for the early detection of carcinoma; however, its role in prognosis has not been fully evaluated.

The literature has demonstrated that the status of initial symptoms at diagnosis is associated with a delay in seeking medical care. Rather than ND, breast lump or breast pain are more likely to be distinguished by women as symptoms of breast malignancy, provoking their eventual visit to a doctor (10,11). Several studies have substantiated that a longer

time before receiving medical attention is linked to shorter survival in breast cancer patients (12,13). It is noteworthy that such studies have been conducted among Western populations; similar data is not available for the Chinese population. Recent advances in genomic techniques have brought about a gradual recognition that breast cancer is a heterogeneous disease categorized into different subtypes with distinct biological characteristics (14). Therefore, we hypothesized that different molecular mechanisms may be at work in patients with and without ND. This warranted further investigation of the prognostic value of ND status in Chinese breast cancer patients.

In manifold studies, survival curves rather than hazard function have been applied to delineate prognosis. Nonetheless, the former fails to provide insight into changes in event probability over time. By contrast, the hazard function describes not only the timing, but also the magnitude of the hazard ratio (15). With an increasing number of investigators intrigued by the hazard function, this method has been adopted in clinical trials, such as the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial (16,17). However, scanty data exist on the hazard pattern for patients with ND. Consequently, we sought to gather relevant information so as to obtain a clear picture of the full complexity of this disease entity.

On the basis of the above, a retrospective analysis was carried out at the Fudan University Shanghai Cancer Center (Shanghai, China) to illuminate the clinical features and prognostic patterns for women with ND, with the aim of clarifying the implications of the underlying distinctions in tumor biology between the different subgroups.

Patients and methods

Patients. Patients were retrospectively selected from a large database of individuals that underwent surgery between January 1, 1990 and December 31, 2004 at the Fudan University Shanghai Cancer Center. Prior to surgery, the patients received a complete physical examination, chest radioscopy, bilateral mammography, ECG, ultrasonography of the breasts, axillary fossa, cervical parts, abdomen and pelvis, complete blood count and routine biochemical tests for disease evaluation. After exact staging, each patient underwent surgery followed by adjuvant therapy according to the standards in place at the time of diagnosis. Follow-up information concerning tumor recurrences and survival status was obtained from follow-up medical records kept by the outpatient department, personal contact with the patient, as well as the assistance of the Shanghai Center for Disease Control and Prevention (CDC). Personal contact with the patients referred to routine correspondence or telephone contact, carried out at the Fudan University Shanghai Cancer Center every 3 months during the first 2 years, every 6 months during the next 2 years, and once a year thereafter. Recurrence or its absence was identified by querying patient, by biopsy, or by bone, chest, abdomen, pelvis or skull scans. In cases of tumor recurrence, additional information, including sites of recurrence and therapy, was obtained. Data were entered into a computerized database and verified to minimize errors in data entry.

Similar to other relevant reports (18,19), a total of 3,317 patients were included in our study. The patients met the following criteria: female gender, an initial diagnosis of unilateral primary invasive breast cancer without distant metastases, a single initial symptom at diagnosis and the availability of at least 1 month of follow-up data regarding disease recurrence and death. The mean age at diagnosis was 51 years (range 23-90). Median follow-up was 3.01 years, ranging from 1 month to 12 years. Among the patients, 2,790 (88.52%) were administered adjuvant chemotherapy under different regimens for 4-6 cycles. Out of 1,961 patients with positive ER and/or PR (ER/PR), 1,007 (51.35%) received adjuvant endocrine therapy. Of these, 987 were administered tamoxifen and 20 aromatase inhibitors. None of the patients received trastuzumab.

Immunohistochemistry and scoring. For each patient in our database, ER, PR, ERBB2 and Cathepsin-D status were determined by immunohistochemical staining, carried out as a standard operating procedure in the pathology department of Fudan University Shanghai Cancer Center. All primary monoclonal antibodies were from Dako. The percentage and the intensity of stained tumor cells were assessed by at least two pathologists and were denoted respectively as a proportion score and an intensity score. The former was interpreted as follows: a score of 0, no staining; 1, ≤25% of cells; 2, 25-50% of cells; 3, 50-75% of cells; and 4, >75% of cells stained. For the intensity score, a negative result was defined as a score of 0, weakly positive as 1, moderately positive as 2 and strongly positive as 3. The final score was calculated as the product of the proportion score and the intensity score. Staining results ranged from a score of 0 to 12. According to this semiquantitative scoring system, nuclear ER, PR and plasma Cathepsin-D were defined as negative with a score of 0 and as positive with a score of 1-12 with staining of carcinoma cells, whereas ERBB2 status was defined as negative for scores of 0-8 (namely, 0, 1+ and 2+ according to the DAKO scoring system) and as positive for strong membranous staining with a score of 9-12 (namely, a DAKO score of 3+).

Statistical analysis. Recurrence-free survival (RFS) was defined as the time from surgery to the earliest occurrence of relapse (locoregional or distant) or death from any cause. Those without any evidence of relapse were censored at the last date they were known to be alive.

Clinicopathological parameters were compared between different subgroups using the Student's t-test for continuous variables, the χ^2 test for unordered categorical variables and the non-parametric Wilcoxon rank-sum test for ordinal categorical variables.

Multivariate logistic regression was used to identify the association between ND and the following factors: age (≤50 and >50 years), tumor size (≤2, 2-5 and >5 cm), ALN status (0, 1-3 and ≥4), hormone receptor (HR) status (negative and positive), ERBB2 status (negative and positive) and Cathepsin-D expression (negative and positive).

Survival distributions were estimated by the Kaplan-Meier product-limit method and were compared using the log-rank test. The proportional hazards assumption was tested by the global test. Cox non-proportional hazards regression was

Table I. Summary of subgroup characteristics.

Variable	Subgroups, n (%)		P-value
	ND	NND	
Mean age at diagnosis (years)	53.6	51.2	0.059[a]
Recurrence			0.017
Yes	5 (5.49)	461 (14.29)	
No	86 (94.51)	2,765 (85.71)	
Duration of initial symptoms			0.061
≤3 months	64 (71.11)	1,974 (61.36)	
>3 months	26 (28.89)	1,243 (38.64)	
Unknown	1	9	
Tumor size			0.013[a]
≤2 cm	35 (50.00)	1,026 (36.29)	
2-5 cm	32 (45.71)	1,553 (54.94)	
>5 cm	3 (4.29)	248 (8.77)	
Unknown	21	399	
No. of ALN involved			<0.001[a]
0	56 (77.78)	1,385 (48.94)	
1-3	12 (16.67)	751 (26.54)	
≥4	4 (5.55)	694 (24.52)	
Unknown	19	396	
Hormone receptor status			0.196
Positive	50 (65.79)	1,911 (72.52)	
Negative	26 (34.21)	724 (27.48)	
Unknown	15	591	
ERBB2 status			0.408
Positive	26 (35.14)	775 (30.63)	
Negative	48 (64.86)	1,755 (69.37)	
Unknown	17	696	
Cathepsin-D status			0.062
Positive	44 (63.77)	1,749 (73.83)	
Negative	25 (36.23)	620 (26.17)	
Unknown	22	857	
Surgery			0.035
Breast-conserving	0 (0.00)	151 (4.68)	
Mastectomy	91 (100.00)	3,075 (95.32)	
Radiotherapy			0.021
Yes	7 (7.95)	542 (17.38)	
No	81 (92.05)	2,577 (82.62)	
Unknown	3	107	
Chemotherapy			0.036
Yes	70 (81.40)	2,720 (88.71)	
No	16 (18.60)	346 (11.29)	
Unknown	5	160	
Endocrine therapy			0.408
Yes	34 (37.78)	1,344 (42.14)	
No	56 (62.22)	1,845 (57.86)	
Unknown	1	37	

[a]Calculated using the non-parametric Wilcoxon rank-sum test; all others using the χ^2 test.

applied to model the time-dependent relationship between the subgroups and RFS, adjusted for known prognostic variables including age (≤50 and >50 years), tumor size (≤2, 2-5 and >5 cm), ALN status (0, 1-3 and ≥4), HR status

Table II. Logistic regression analysis of risk factors for ND.

Variable	Odds ratio	95% CI	P-value
Tumor size	0.903	0.530-1.537	0.707
Axillary lymph node status	0.471	0.287-0.772	0.003
Age at diagnosis	1.592	0.857-2.956	0.141
Hormone receptor status	0.625	0.338-1.158	0.135
ERBB2 status	1.599	0.835-3.065	0.157
Cathepsin-D status	0.491	0.263-0.916	0.025

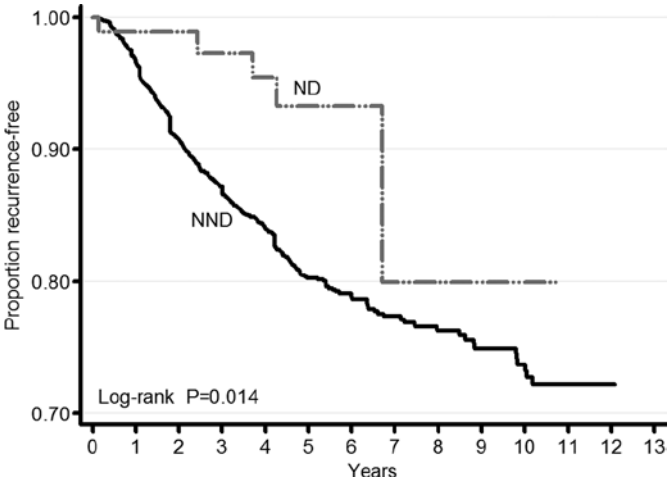

Figure 1. Kaplan-Meier curves for RFS in 3,317 breast cancer patients by ND status.

(negative and positive), ERBB2 status (negative and positive) and Cathepsin-D expression (negative and positive), as well as the use of adjuvant chemotherapy (yes and no). For graphical display of RFS, annual hazard rates were estimated using a Kernel method of smoothing.

All statistical tests were two sided and P<0.05 was considered significant. Statistical analysis was performed with the Stata statistical software package (version 10.0; Stata Corp., College Station, TX, USA). The odds ratios (OR) and relative risk (RR) are presented with their 95% confidence intervals (95% CI).

Results

General characteristics. According to the initial symptoms at diagnosis, 3,317 patients were categorized into the ND (2.74%) and non-ND (NND; 97.26%) subgroups. There was a relatively lower proportion of delayed presentation for more than 3 months in patients with ND as compared to the NND subgroup (28.89 and 38.64%, P=0.061; Table I). Women who presented with ND tended to be older at diagnosis than those without ND (53.6±12.6 vs. 51.2±11.2 years, P=0.059; Table I). The proportion of larger tumors (>2 cm in diameter) was higher in the ND subgroup than in the NND subgroup (50.00 and 63.71%, P=0.019). In addition, 22.22% of patients with ND had positive lymph nodes in the axilla as compared to 51.06% in the patients without ND (P<0.001). In terms of HR and ERBB2 status, the distributions were comparable between the subgroups (P=0.196 and 0.408, respectively; Table I). In terms of Cathepsin-D status, a lower percentage of patients exhibited overexpression in the ND subgroup as compared to the NND subgroup, with marginal significance (73.83 and 63.77%, P=0.062; Table I).

Treatment options varied from one subgroup to another. Regarding local treatment, the ND subgroup was more likely to receive mastectomy than the NND subgroup (100.00 and 95.32%, P=0.035; Table I), while in the case of radiotherapy this was just the opposite, with a rate of 7.95% for the ND subgroup and of 17.38% for the NND subgroup (P=0.021; Table I). With regard to adjuvant systemic treatments, patients with ND were less likely to receive chemotherapy than those without ND (81.40 and 88.71%, P=0.036; Table I), whereas a significant difference was not observed for endocrine therapy (P=0.408; Table I). As compared to the NND subgroup, fewer events of recurrence were observed in patients with ND (P=0.017; Table I).

Multivariate logistic regression analysis showed that ALN status (OR=0.471, 95% CI 0.287-0.772, P=0.003) and Cathepsin-D status (OR=0.491, 95% CI 0.263-0.916, P=0.025) were independent predicting factors for ND, excluding tumor size (OR=0.903, 95% CI 0.530-1.537, P=0.707), age at diagnosis (OR=1.592, 95% CI 0.857-2.956, P=0.141), HR status (OR=0.625, 95% CI 0.338-1.158, P=0.135) and ERBB2 status (OR=1.599, 95% CI 0.835-3.065, P=0.157; Table II).

Survival analysis. In the univariate analysis, a significantly different RFS was found between patients with and without ND (P=0.014), with a rate of 79.94% for women with ND and 72.11% for the NND group at the 11th year, respectively (Fig. 1).

In order to evaluate whether the prognostic effect of ND status remained unabated over time, the test for lack of proportionality was performed. However, both ND and ERBB2 status were statistically significant (global test, P=0.0190 and 0.0489, respectively), which clarified a violation of proportional hazards for these two factors and suggested the need for the employment of Cox non-proportional hazards regression in this analysis. In a time-dependent Cox model, ND status (P=0.028; RR=2.174, 95% CI 1.086-4.351), as well as tumor size (P<0.001; RR=1.779, 95% CI 1.406-2.250), ALN status (P<0.001; RR=2.257, 95% CI 1.886-2.702), ERBB2 status (P=0.011; RR=0.759, 95% CI 0.613-0.940) and use of adjuvant chemotherapy (P=0.048; RR=0.642, 95% CI 0.414-0.995; Table III) were independent prognosticators for RFS.

Table III. Survival analysis of RFS in 3,234 breast cancer patients.

Variable	Univariate analysis	Time-dependent Cox non-proportional hazards regression		
	P-value	Relative risk	95% CI of relative risk	P-value
Tumor size	<0.001	1.779	1.406-2.250	<0.001
Axillary lymph node status	<0.001	2.257	1.886-2.702	<0.001
Hormone receptor status	0.805	0.796	0.597-1.063	0.122
ERBB2 status	0.049	0.759	0.613-0.940	0.011
Cathepsin-D status	0.460	0.816	0.605-1.101	0.184
Chemotherapy	0.281	0.642	0.414-0.995	0.048
Age at diagnosis	0.192	0.785	0.595-1.036	0.087
Nipple discharge status	0.014	2.174	1.086-4.351	0.028

Recurrence hazard analysis. Regarding hazard peaks, discrepancies existed between the two subgroups. Patients with ND showed a wide initial plateau-like wave peaking at 3.5 years after surgery, whereas the hazard plot for the NND subgroup exhibited a sharp early tapering at 1.5 years. Furthermore, the risk of early recurrence was lower for women with ND than for the NND subgroup (Fig. 2).

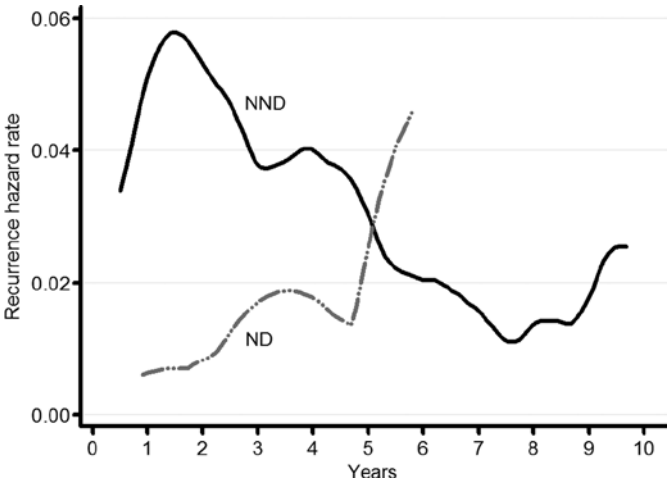

Figure 2. Annual recurrence hazard rate for 3,317 breast cancer patients by ND status.

Discussion

To the best of our knowledge, the present study is the largest retrospective analysis of the demographic features and prognostic profiles of women with ND among Chinese breast cancer patients. This has yet to be well studied in Western populations. Despite being a frightening symptom, ND is manifested in only 1-5% of all breast cancers (20). This was partly congruent with our findings (2.74%). It is worth noting that women with invasive carcinomas were exclusively recruited in this study to avoid the confounding effect of *in situ* carcinomas on prognosis. In the great majority of series, ND is the presenting symptom in 7-8% of patients with ductal carcinoma *in situ* (21), whereas an invasive cancer rarely causes ND in the absence of a clinical mass (22-24).

In this study, patients with ND were less prone to delayed presentation of their breast symptoms than the NND subgroup. This was in disagreement with other relevant reports (10,11,25). A series of analyses determined that patient delay in seeking treatment was associated with a failure to recognize the seriousness of the initial symptom, negative attitudes towards consulting a doctor, negative beliefs about cancer treatment and perceptions of other priorities over personal health (25). Accordingly, conflicting results on symptom duration between various populations are not merely a matter of disparities in education and economics, but are attributed to a complex combination of personal, social and economic factors (26).

Unexpectedly, our analysis demonstrated that a lower rate of Cathepsin-D positivity was observed in the ND-related breast cancers, which had not been noted in previous research. Cathepsin-D, secreted by breast cancer cells, is the precursor of a lysosomal protease, which degrades extracellular matrices and proteoglycans (27). Despite inadequate evidence for routine use in clinical practice, Cathepsin-D is somewhat indicative of prognosis (28). Recent studies substantiated that Cathepsin-D is critically involved in the regulation of a multitude of biological functions in different stages of mammary tissue development and remodeling (29,30). These findings suggest that the etiology and biology may differ between patients with and without ND. This prompted us to investigate the molecular mechanisms intrinsic to both disease entities. Our results provide new data with therapeutic implications.

The data also revealed that recurrence hazards in both the ND and NND subgroups were not proportional from the beginning to the end of follow-up. It has been reported that some prognostic factors appear to be strongly related to survival in early studies with short follow-up, while the relationships seem to weaken as follow-up continues (31). Our analysis adds to the growing body of evidence that indicates that failure to recognize the patterns of time-variation may result in overlooking the effects of clinically important or biologically interesting factors (31,32).

To our knowledge, there have been no reports on the time distribution of recurrence hazards for patients with varying ND status. In our series, we observed that the NND subgroup experienced recurrence earlier than women with ND. As far

as heterogeneity is concerned, these investigations suggest that the growth pattern of micrometastatic foci may differ between women with and without ND on account of their distinct molecular biology, including Cathepsin-D status as identified in this study, in addition to other unknown variables, which remain to be explored.

As this study is retrospective in nature, some latent limitations are inevitable. Recurrences are probably somewhat underreported or incorrect for a substantial portion of the patients in this database; nonetheless, underreporting or misinformation of recurrences would not have varied according to clinicopathological parameters (33). Additionally, we did not evaluate the effect of treatment on survival in the present study, but all the RRs were adjusted for the treatment administered (34).

In conclusion, the ND and NND subgroups may be two distinct entities due to their contrasting biological behavior and prognostic profiles. This warrants further investigation of the two subgroups.

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