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ORIGINAL REPORT

Quality of Life After Breast Cancer Diagnosis and Survival

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ABSTRACT

Purpose
To examine the association of quality of life (QOL) after diagnosis of breast cancer with mortality and recurrence.

Patients and Methods
From 2002 to 2004, a total of 2,230 breast cancer survivors completed the General Quality of Life Inventory-74 6 months after diagnosis as part of the Shanghai Breast Cancer Survivor Study. Also collected at baseline was information on demographic and clinical characteristics. At 36 months postdiagnosis, 1,845 of these women were re-evaluated for QOL. Outcomes were ascertained by in-person interview and record linkage to the vital statistics registry. The association of QOL with total mortality and cancer recurrence was assessed by using Cox regression analysis.

Results
During a median follow-up of 4.8 years after the 6-month postdiagnosis QOL assessment, 284 deaths were identified. Recurrence was documented in 267 patients after 108 patients with stage IV breast cancer or recurrence before study enrollment were excluded. Women with the highest tertile of social well-being QOL score, compared with those with the lowest score, had a 38% decreased risk of mortality (95% CI, 0.46 to 0.85; *P* for trend = .002) and a 48% decreased risk of breast cancer recurrence (95% CI, 0.38 to 0.71; *P* for trend < .001). QOL assessed at 36 months postdiagnosis was not significantly associated with subsequent risk of mortality or recurrence.

Conclusion
Social well-being in the first year after cancer diagnosis is a significant prognostic factor for breast cancer recurrence or mortality, suggesting a possible avenue of intervention by maintaining or enhancing social support for women soon after their breast cancer diagnosis to improve disease outcomes.

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INTRODUCTION

As the most commonly diagnosed cancer among women, breast cancer is also the leading cause of cancer mortality in women worldwide.[1] Because breast cancer is so common and at the same time has a fairly good prognosis, breast cancer is also the most prevalent cancer among women in the world, with an estimated 4.4 million women living with breast cancer within 5 years of diagnosis.[2] If quality of life (QOL) after a diagnosis of cancer is related to survival beyond the currently known disease- and treatment-specific predictors, knowledge of a patient's QOL could enable clinicians to better identify individuals at high-risk for recurrence or mortality. Furthermore, if the aspects of QOL that predict survival are potentially modifiable, there is a potential for interventions to reduce the risk of recurrence or death.

As expected, many studies have found that a diagnosis of breast cancer can negatively affect a woman's QOL,[3,4] but whether the resulting QOL is associated with her probability of survival remains under debate. A breast cancer survivor's physical well-being has most consistently been found to be predictive of survival,[5-9] but several studies have found that even this QOL measure, particularly when taken soon after diagnosis or for women with early-stage breast cancer, is often not associated with prognosis.[6,10,11] Aspects of a breast cancer survivor's social and/or psychosocial well-being have also been examined,[12-14] with several of the studies suggesting that greater social support may be associated with longer survival.[15-18] However, these studies vary in terms of the scope of QOL assessed as well as the ability to adjust for known clinical predictors.

We conducted a large prospective cohort study of female breast cancer survivors, with carefully collected clinical and demographic information along with updated QOL measurements, to evaluate the associations of self-rated QOL at 6 and 36 months after cancer diagnosis with total mortality and recurrence.

PATIENTS AND METHODS

Study Participants

Women included in this study are participants in the Shanghai Breast Cancer Survival Study, a population-based cohort of breast cancer survivors age 20 to 75 years who are permanent residents of Shanghai, China. Detailed information on the study methods has been published previously.[19,20] In short, between March 20, 2002, and February 27, 2004, a total of 2,600 women diagnosed with incident breast cancer were identified and invited to participate in the study; 2,230 women (85.5%) completed baseline interviews at approximately 6 months after their cancer diagnosis. These women were then recontacted at 18 and 36 months postdiagnosis. At 36 months postdiagnosis, 1,845 women (82.7%) completed the in-person interview; 152 (6.8%) died within 36 months postdiagnosis, and the remaining 233 (10.4%) refused to participate or could not be contacted. This study includes analyses of the 2,230 women in the original cohort and of the 1,845 women who completed the 36-month postdiagnosis questionnaire.

This study was approved by the institutional review boards of all institutions involved in the Shanghai Breast Cancer Survival Study. Written informed consent was obtained from all participants before interviews were conducted.

Data Collection

Trained interviewers, all of whom were retired health care professionals, conducted in-person interviews using a structured questionnaire. At the 6-month postdiagnosis baseline visit, information on demographic characteristics, lifestyle factors, diet, medication use, complementary and alternative medicine use, reproductive history, disease history, and QOL was collected. A standard protocol was used to measure anthropometrics, including height, weight, waist circumference, and hip circumference. Clinical information, including TNM stage at diagnosis, estrogen receptor (ER) and progesterone receptor (PgR) status, and primary treatment (type of surgery, chemotherapy, radiotherapy, immunotherapy, and tamoxifen use), was collected by the interviewer and then verified through review of inpatient medical charts. To assess the level of comorbidity for each woman, the Charlson comorbidity index, based on a validated comorbidity scoring system, was created.[21] The 36-month follow-up interview collected information on current health condition, medication use, recent diet, tea and alcohol consumption, physical activity, recurrence, and updated QOL.

Ascertainment of recurrence and/or death took place through in-person interviews at 18, 36, and 60 months after cancer diagnosis and was supplemented by linkage to the Shanghai Vital Statistics Registry. For women lost to follow-up, outcome information was obtained by annual linkage to the registry database. Survival status was censored at the date of the last in-person contact or on May 31, 2008 (5 months before the most recent linkage to the registry), whichever was most recent.

QOL Assessment

At 6 months (median, 6.8 months; range, 4.1 to 11.8 months) and 36 months (median, 3.1 years; range, 2.8 to 3.8 years) after cancer diagnosis, the QOL of breast cancer survivors was assessed by using the General Quality of Life Inventory-74. This inventory was created specifically for use in the Chinese population and was based on the WHO Quality of Life Assessment Instrument. The QOL assessment provided by this instrument has been shown to have satisfactory levels of reliability and validity,[22,23] and its utility among breast cancer patients has been previously described.[24,25]

The inventory comprises 74 items that can be classified into 20 facets that are then categorized into a global health status/QOL assessment and the following four domains: (1) physical well-being (sleep and energy, pain and physical discomfort, eating functioning, sexual functioning, sensory functioning, and capability of daily living), (2) psychological well-being (psychological distress, negative feelings, positive feelings, cognitive functioning, and body/self-image), (3) social well-being (social support, interpersonal relationships, work and study capacity, recreational and leisure activities, and marriage and family), and (4) material well-being (housing situation, community services, living environment, and financial situation). Patients' responses were converted to a score of 0 to 100 on each domain and facet, with higher scores reflecting higher QOL. For the analyses in this study, the sexual functioning score was excluded from the calculation of physical well-being and total QOL because 93% of breast cancer survivors at baseline and 89% of survivors at 36 months postdiagnosis selected the lowest category, "none or little" sexual activity in the previous week, at time of survey.

Statistical Analysis

Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95% CIs to evaluate the associations between QOL and total mortality and recurrence separately. Age was used as the time scale, with entry time defined as age at interview, for the analyses of QOL at 6 months and 36 months postdiagnosis, respectively, and exit time was defined as age at event or censoring. For the analyses of baseline QOL and mortality, all 2,230 women who completed the baseline QOL questionnaire were included. For the analyses of baseline QOL and recurrence, all women except for those who were diagnosed at stage IV or who reported a prior relapse or recurrence (n = 108) were included. For the analyses of QOL at 36 months postdiagnosis and total mortality, only those 1,845 women who completed both surveys were included. For the analyses of QOL at 36 months postdiagnosis and recurrence, all women except for those who were diagnosed at stage IV, reported a relapse or recurrence before the 36-month survey, or for whom we did not have follow-up information past the date of the 36-month survey (n = 262) were included. QOL scores for each domain and overall at baseline and at 36 months postdiagnosis were categorized into tertiles on the basis of the cohort distribution. In the multivariate analyses, in addition to age at diagnosis, menopausal status, and comorbidity (as well as whether a relapse had occurred, for the total mortality analyses), known clinical prognosis factors collected at baseline and a priori believed to be confounders were adjusted for. These included TNM stage, ER status, PgR status, and types of primary treatment (chemotherapy, radiotherapy, and tamoxifen use). Models additionally including marital status, education, income, body mass index, exercise, tea consumption, and soy protein consumption had little to no effect on the HRs for the main QOL variables, and results are not presented.

To test for a linear trend across levels of QOL scores for each domain, a variable was created and assigned the median score for each tertile of QOL domain. Additionally, scores for each QOL domain were evaluated as continuous variables. Schoenfeld residuals were assessed to test the proportional hazards assumption. All analyses were conducted by using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

During a median follow-up of 4.8 years (range, 0.1 to 5.6 years) from the 6-month QOL survey, 284 deaths occurred among the 2,230 women enrolled at baseline in this study. From the 6-month survey, the median survival time was 4.9 years for those who lived and 2.3 years for those who died, whereas from the 36-month follow-up, it was 2.4 years for those who lived and 1.2 years for those who died. Among the 1,845 women who also completed the 36-month QOL questionnaire, there were 101 deaths and 76 recurrences after completion of the follow-up survey. Baseline characteristics of all women and those who survived to 36-months postdiagnosis and completed the QOL questionnaire are generally comparable except that the subcohort of women interviewed at 36 months was slightly less likely to have been treated originally with radiotherapy, more likely to be ER-positive/PgR-positive than ER-negative/PgR-negative, and more likely to have been diagnosed at an early stage rather than at a late stage. Most of the differences were due to their association with breast cancer prognosis. The 233 women who survived to 36 months postdiagnosis but did not participate in the follow-up survey were generally similar to the 1,845 women who agreed to participate at 36 months but were on average 1.5 years younger at diagnosis (49.8 v 51.3 years), better-educated, of a

			Participation in Follow-Up Survey for Women Who Survived to 36 Months Postdiagnosis			
	All Women (N = 2,230)		Agreed to Participate (n = 1,845)		Refused to Participate (n = 233)	
Characteristic	No.	%	No.	%	No.	%
Age at diagnosis, years						
< 40	125	5.6	103	5.6	14	6.0
40-49	893	40.0	733	39.7	104	44.6
50-59	597	26.8	490	26.6	63	27.0
≥ 60	615	27.6	519	28.1	52	22.3
Marital status						
Married/living together	1,946	87.3	1,608	87.2	207	88.8
Other	284	12.7	237	12.9	26	11.2
Education*						
< High school	1,095	49.1	922	50.0	88	37.8
High school	801	35.9	655	35.5	92	39.5
> High school	334	15.0	268	14.5	53	22.8
Body mass index, kg/m^2*						
< 25	1,445	64.9	1,177	63.8	168	72.1
25-29.9	646	29.0	555	30.1	55	23.6
≥ 30	136	6.1	112	6.1	10	4.3
Regular exercise, MET h/wk						
None	716	32.1	570	30.9	77	33.1
< 8.3	666	29.9	570	30.9	60	25.8
≥ 8.3	848	38.0	705	38.2	95	41.2
Soy consumption, g/d						
< 126	1,131	50.7	926	50.2	126	54.1
≥ 126	1,099	49.3	919	49.8	107	45.9
Menopausal status*						
Premenopausal	1,105	49.6	899	48.7	133	57.1
Postmenopausal	1,125	50.5	946	51.3	100	42.9
Charlson comorbidity score*						
0	1,796	80.5	1,474	80.0	204	87.6
≥ 1	434	19.5	371	20.0	29	12.5
Type of surgery						
Mastectomy	2,097	94.3	1,733	94.0	222	95.7
Conservation	126	5.7	110	6.0	10	4.3
Chemotherapy						
Yes	2,049	91.9	1,695	91.9	212	91.0
No	181	8.1	150	8.1	21	9.0
Radiotherapy						
Yes	681	30.5	525	28.5	75	32.2
No	1,549	69.5	1,320	71.5	75	67.8
Tamoxifen use						
Yes	1,278	57.3	1,087	58.9	124	53.2
No	952	42.7	758	41.1	109	46.8
ER/PgR status*						
ER-positive/PgR-positive	1,129	50.6	969	52.5	121	51.9
ER-negative/PgR-negative	615	27.6	480	26.0	55	23.6
ER-positive/PgR-negative, ER-negative/PgR-positive	436	19.6	365	19.8	46	19.7
Unknown	50	2.2	31	1.7	11	4.7
TNM stage						
0-I	771	34.6	670	36.3	87	37.3
IIA	740	33.2	627	34.0	75	32.2
IIB	439	19.7	345	18.7	46	19.7
III-IV	182	8.2	127	6.9	14	6.0
Unknown	98	4.4	76	4.1	11	4.7

Abbreviations: MET, maximum exercise test; ER, estrogen receptor; PgR, progesterone receptor.
*$P < .05$ (among women who survived 36 months postdiagnosis, those who agreed to participate in the follow-up survey v those who refused).

lower body mass index, premenopausal, more likely to have no co-morbidities, less likely to be ER-negative/PgR-negative, and more likely to have an unknown TNM stage (Table 1).

At baseline, of the four QOL domains of physical, psychological, social, and material well-being, only greater social well-being was significantly associated with a decreased risk of total mortality or recurrence (highest tertile compared with lowest tertile: HR, 0.62; 95% CI, 0.46 to 0.85; P for trend = .002 and HR, 0.52; 95% CI, 0.38 to 0.71; P for trend < .001, respectively; Table 2). Although having a psychological well-being score in the middle tertile was significantly associated with risk of mortality (HR, 0.66; 95% CI, 0.49 to 0.88), a psychological well-being score in the highest tertile was not statistically associated with either mortality or recurrence. Suggestion of a trend in decreased risk of recurrence with increased psychological well-being was detected when modeling the score as a continuous predictor (P = .04). Overall, having a total QOL score in the third (highest) tertile at 6 months postdiagnosis was associated with a 27% reduced risk of recurrence compared with having a QOL score in the lowest or first tertile (HR, 0.73; 95% CI, 0.54 to 0.98).

Assessed at 36 months after cancer diagnosis, none of the domains of QOL nor total QOL score was associated with risk of mortality or recurrence (Table 3). There was a suggestion that women in the second or third tertiles of social well-being had a 40% decreased risk of mortality (HR, 0.61; 95% CI, 0.36 to 1.03 and HR, 0.62; 95% CI 0.35 to 1.11, respectively), but these associations were not statistically significant and neither was the trend of increasing social well-being with decreasing risk of mortality (P = .07).

Among the five facets that make up the domain of social well-being, there were suggestions that all were inversely associated with mortality and/or recurrence at 6 months postdiagnosis, but the facets most strongly inversely related with risk were those related to emotional support. Specifically, women in the highest tertiles of the facets of marriage and family, social support, and interpersonal relationships had reduced risks of recurrence of 43% (95% CI, 0.41 to 0.78), 40% (95% CI, 0.44 to 0.83), and 35% (95% CI, 0.47 to 0.89).

DISCUSSION

This study found that of measures of QOL among breast cancer survivors at 6 months after diagnosis, greater social well-being was significantly associated with a decreased risk of mortality or recurrence. At 36 months postdiagnosis, however, no measures of QOL were associated with mortality or recurrence, although these analyses were based on a smaller sample size. The facets of social well-being at 6 months postdiagnosis that were most strongly inversely related with mortality or recurrence were those of marriage and family, social support, and interpersonal relationships.

Studies of QOL as a predictor of survival in cancer patients have generally found greater physical well-being to be associated with longer survival,[5,26-28] although some of the more recent studies have found this association to be strongest or only among those in later stages of disease.[6,11,13] These results suggest that the association may be

Table 2. Association of Baseline Measures of QOL With Total Mortality and Recurrence in the Shanghai Breast Cancer Survival Study (N = 2,230)

QOL Measure	Total Mortality (n = 284)				Recurrence (n = 282)			
	No. of Events	HR	95% CI	P Trend	No. of Events	HR	95% CI	P Trend
Physical well-being				.65				.12
≤ 57.6	113	1.00	Reference		104	1.00	Reference	
> 57.6 to ≤ 67.2	89	0.99	0.74 to 1.32		101	0.96	0.73 to 1.27	
> 67.2	82	0.93	0.69 to 1.26		77	0.78	0.58 to 1.06	
Psychological well-being				.17				.16
≤ 65.0	122	1.00	Reference		106	1.00	Reference	
> 65.0 to ≤ 73.8	75	0.66*	0.49 to 0.88		89	0.78	0.59 to 1.04	
> 73.8	87	0.84	0.63 to 1.11		87	0.82	0.62 to 1.09	
Social well-being				.002*				< .001*
≤ 59.6	129	1.00	Reference		126	1.00	Reference	
> 59.6 to ≤ 67.9	92	0.79	0.60 to 1.03		95	0.79	0.60 to 1.03	
> 67.9	63	0.62*	0.46 to 0.85		61	0.52*	0.38 to 0.71	
Material well-being				.68				.39
≤ 48.8	95	1.00	Reference		94	1.00	Reference	
> 48.8 to ≤ 59.2	100	1.08	0.81 to 1.43		103	1.16	0.87 to 1.54	
> 59.2	90	0.94	0.70 to 1.26		85	0.88	0.65 to 1.18	
Perceived QOL				.67				.39
≤ 50.0	143	1.00	Reference		135	1.00	Reference	
> 50.0 to ≤ 62.5	79	0.90	0.68 to 1.19		84	0.91	0.69 to 1.20	
> 62.5	62	0.96	0.70 to 1.30		63	0.89	0.65 to 1.20	
Total QOL score				.28				.03*
≤ 58.7	123	1.00	Reference		114	1.00	Reference	
> 58.7 to ≤ 65.7	77	0.73*	0.54 to 0.97		90	0.77	0.58 to 1.02	
> 65.7	84	0.87	0.65 to 1.16		78	0.73*	0.54 to 0.98	

NOTE. HRs adjusted for age at diagnosis, menopausal status, comorbidity, chemotherapy, radiotherapy, tamoxifen use, estrogen receptor status, progesterone receptor status, and TNM stage. For total mortality analyses, also adjusted for whether a relapse occurred prior to interview.
Abbreviations: QOL, quality of life; HR, hazard ratio.
*P < .05.

Table 3. Association of Measures of QOL Assessed At 36 Months After Diagnosis With Subsequent Risk of Total Mortality in the Shanghai Breast Cancer Survival Study

QOL Measure After 36 Months	Total Mortality (n = 101)				Recurrence (n = 76)			
	No. of Events	HR	95% CI	P Trend	No. of Events	HR	95% CI	P Trend
Physical well-being				.17				.75
≤ 60.4	60	1.00	Reference		28	1.00	Reference	
> 60.4 to ≤ 70.3	25	0.67	0.39 to 1.13		21	0.84	0.47 to 1.51	
> 70.3	20	0.71	0.40 to 1.28		28	1.09	0.63 to 1.89	
Psychological well-being				.82				.05
≤ 65.0	44	1.00	Reference		19	1.00	Reference	
> 65.0 to ≤ 74.4	35	1.11	0.67 to 1.83		27	1.46	0.80 to 2.68	
> 74.4	26	1.06	0.60 to 1.85		31	1.79	0.99 to 3.23	
Social well-being				.07				.71
≤ 59.8	59	1.00	Reference		26	1.00	Reference	
> 59.8 to ≤ 69.2	26	0.61	0.36 to 1.03		29	1.22	0.70 to 2.12	
> 69.2	20	0.62	0.35 to 1.11		22	1.11	0.61 to 2.04	
Material well-being				.57				.17
≤ 42.0	36	1.00	Reference		21	1.00	Reference	
> 42.0 to ≤ 52.4	36	1.15	0.69 to 1.92		26	1.18	0.65 to 2.14	
> 52.4	33	0.86	0.50 to 1.47		30	1.49	0.83 to 2.65	
Perceived QOL				.50				.31
≤ 50.0	62	1.00	Reference		27	1.00	Reference	
> 50.0 to ≤ 62.5	27	0.95	0.58 to 1.56		23	1.26	0.71 to 2.24	
> 62.5	16	0.81	0.44 to 1.47		27	1.33	0.77 to 2.31	
Total QOL score				.35				.39
≤ 58.1	54	1.00	Reference		21	1.00	Reference	
> 58.1 to ≤ 65.4	31	0.70	0.43 to 1.17		30	1.45	0.81 to 2.59	
> 65.4	20	0.82	0.46 to 1.47		26	1.32	0.72 to 2.41	

NOTE. HRs adjusted for age at diagnosis, menopausal status, comorbidity, chemotherapy, radiotherapy, tamoxifen use, estrogen receptor status, progesterone receptor status, TNM stage, and whether a relapse occurred prior to interview.
Abbreviations: QOL, quality of life; HR, hazard ratio.

a result of physical well-being serving as a proxy for physical health and/or the possibility of reverse causation. In our study, we found no association between physical well-being at 6 or 36 months postdiagnosis and survival when adjusting for clinical predictors, which supports this notion.

A recent review of studies of psychosocial factors and breast cancer outcomes[14] found that the majority of studies (81%) observed a significant association between at least one psychosocial variable and disease outcome. Although the factors associated with survival were not consistent across many studies and the studies used different measurement techniques and had different follow-up times, factors associated with social support and marriage were most consistently associated with better prognosis. The association between social support and cancer progression was further analyzed in a 2009 review,[18] which found that five of the seven methodologically sound papers that investigated the relationship with breast cancer observed strong evidence for an association with social support, interestingly, more for structural support (eg, the quantitative properties of the social network) than for functional support (eg, the qualitative aspects of the components of the structural support). A recent meta-analysis of studies of social networks and cancer mortality found that perceived social support, larger social network, and being married were associated with reductions in risk of 12% to 25%.[16] This meta-analysis includes the report from the Nurses' Health Study,[15] which found significant increases in risk for socially isolated women. Additionally, a recent study of

breast cancer survivors in Washington, DC, found that, at 14 months postdiagnosis, both a confiding marriage or partnership and increasing numbers of nonhousehold supports were associated with a 59% to 69% decrease in risk of mortality.[17] Contradicting those findings are the results of a larger study among young women with nonmetastatic breast cancer in Australia,[12] which found no association between confidant or affective support at 11 months postdiagnosis and risk of recurrence or survival. The mechanism by which social support is associated with survival is not completely understood, but one possibility is provided by a recent study[29] which found that mice in chronic social isolation compared with group-housed mice developed significantly larger mammary gland tumors and had heightened corticosterone stress responses.

Of course, we cannot rule out that these associations of social well-being and survival among breast cancer survivors are due to reverse causality. It is certainly possible that healthier individuals are more likely to have greater social well-being. However, we did adjust for all known clinical predictors, including stage, ER and PgR status, primary treatment, comorbidity at study enrollment, and whether a recurrence had taken place for the outcome of total mortality. Additionally, no associations were observed with psychological well-being, which one might assume would also be subject to the reverse causality problem. Another potential limitation of this study is the generalizability of the findings. The women who completed the follow-up questionnaire were older and of

lower socioeconomic status than the breast cancer survivors who did not. Although we did not find an association with social well-being at 36 months postdiagnosis and survival, the impact of strong social well-being at 6 months postdiagnosis was not limited to immediate outcomes. When we excluded all follow-up and events happening within the first year after the QOL assessment (63 deaths and 30 recurrences), we found no change in the association between greater social well-being and lower risk of both mortality and recurrence.

Thus, the association between social well-being in the first year following diagnosis and breast cancer survival raises some interesting questions, because one's social well-being is potentially modifiable. Unfortunately, interventions to improve social well-being in breast cancer survivors have not generally been successful in prolonging survival,[14,30] with two exceptions.[31,32] More recently, a few interventions using online support groups have been successful in increasing breast cancer survivors' QOL[33,34]; perhaps this is a potential avenue for future studies on social well-being intervention and breast cancer survival.

The findings of this study, which included a large number of women and had a high response rate, indicate that social well-being in the first year after diagnosis of breast cancer is significantly associated with mortality and recurrence, above and beyond known clinical predictors and self-assessed physical well-being. Should this association be replicated in future studies, the testing of a social well-being intervention for breast cancer survivors is warranted.

AUTHOR CONTRIBUTIONS

Conception and design: Wei Zheng, Wei Lu, Xiao-Ou Shu
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