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Comorbidities and breast cancer survival: a report from the Shanghai Breast Cancer Survival Study

Sarah Nechuta[1], **Wei Lu**[2], **Ying Zheng**[2], **Hui Cai**[1], **Ping-Ping Bao**[2], **Kai Gu**[2], **Wei Zheng**[1], and **Xiao Ou Shu**[1]

[1]Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, 37203-1738, USA

[2]Shanghai Municipal Center for Disease Control & Prevention, 1380 Zhong Shan Road (W), Shanghai, China 200336

Abstract

BACKGROUND—We investigated the association of major comorbidities with breast cancer outcomes using the Shanghai Breast Cancer Survival Study, a population-based, prospective cohort study of Chinese women diagnosed with breast cancer.

METHODS—Analyses included 4,664 women diagnosed with stage I-III incident breast cancer aged 20–75 years (median age=51) during 2002–2006. Women were interviewed at 3–11 months post-diagnosis (median=6.4) and followed up by in-person interviews and linkage with the vital statistics registry. Multivariable hazard ratios (HRs) and (95% confidence intervals (CIs)) for the associations of comorbidities with breast cancer outcomes were estimated using Cox regression models.

RESULTS—After a median follow-up of 5.3 years (range: 0.64–8.9), 647 women died (516 from breast cancer) and 632 recurrence/metastases were documented. The main comorbidities reported included: hypertension (22.4%), chronic gastritis (14.3%), diabetes mellitus (6.2%), chronic bronchitis/asthma (5.8%), coronary heart disease (5.0%), and stroke (2.2). Diabetes was associated with increased risk of total mortality (adjusted HR: 1.40 (1.06–1.85)) and non-breast cancer mortality (adjusted HR: 2.64 (1.63–4.27)), but not breast cancer-specific mortality (adjusted HR: 0.98 (0.68–1.41)), adjusting for socio-demographics, clinical characteristics, selected lifestyle factors, and other comorbidities. Women with a history of stroke had a non-significant increased risk of total mortality (adjusted HR: 1.42 (0.91–2.22)) and a significant increased risk of non-breast cancer mortality (adjusted HR: 2.52 (1.33–4.78)), but not breast cancer-specific mortality (adjusted HR: 0.78 (0.38–1.62)). Overall, none of the comorbidities investigated were significantly associated with recurrence.

CONCLUSIONS—In this large prospective cohort of breast cancer survivors, diabetes was significantly associated with increased risk of total and non-breast cancer mortality, and history of stroke was associated was associated with increased risk of non-breast cancer mortality.

Keywords

breast cancer; prognosis; survival; comorbidity

Corresponding author: Sarah Nechuta, MPH, PhD, Assistant Professor of Medicine, Vanderbilt Epidemiology Center, Institute for Medicine & Public Health, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 300, Nashville, Tennessee 37203-1738, sarah.nechuta@vanderbilt.edu, Phone: 615.343.0373; Fax: 615.343.5938.

Conflict of Interest
The authors declare that they have no conflicts of interest.

INTRODUCTION

Worldwide there are an estimated 5.2 million breast cancer survivors [1]. Breast cancer incidence increases with age, as does the incidence of many other chronic diseases, such as diabetes, hypertension, and cardiovascular disease (CVD) [2, 3]; hence, many breast cancer patients have one or more comorbid medical conditions at diagnosis [4–7]. Comorbidities have been shown to influence cancer treatment decisions and short- and long-term survival [8–11].

Many studies have reported that comorbidity at/around the time of diagnosis, most often measured by a comorbidity index, such as the Charlson Comorbidity Index (CCI), or simple additive summary scores for number of comorbidities, predicts poorer survival among breast cancer patients [6, 8, 11–19]. However, the influence of individual comorbidities on prognosis may vary, and these summary measures may provide limited information [5, 10, 20, 21]. Few studies to date have investigated the associations of multiple individual comorbid medical conditions at/around diagnosis with breast cancer outcomes [5, 9, 10, 22–24]. Most of these studies have been limited to older populations (i.e., aged >55 years or >66 years) and/or have been registry-based studies with no data on potential confounding factors, such as lifestyle factors (e.g., obesity, exercise participation) [5, 9, 22–24]. In addition, the majority of studies focused on overall mortality, and limited data are available on the association of individual comorbidities with breast cancer-specific mortality or recurrence [10, 11].

We investigated the association of individual comorbidities reported at cohort enrollment (3–11 months post-diagnosis) with breast cancer recurrence/metastasis and mortality outcomes in the Shanghai Breast Cancer Survival Study (SBCSS), a population population-based prospective cohort study of Chinese breast cancer patients aged 20–75 years at diagnosis with information collected on clinical characteristics including cancer treatment, socio-demographics, and post-diagnosis lifestyle factors.

METHODS

Shanghai Breast Cancer Survival Study

Details of the study design and methodology of the SBCSS have been previously described [25]. Briefly, women aged 20–75 years who were newly diagnosed with primary breast cancer between March 2002 and April 2006 and were permanent residents of Shanghai were identified from the Shanghai Cancer Registry and approached for study participation. Of 6,299 eligible cases, 5,042 participated (80.0%) and provided written informed consent. Reasons for nonparticipation included refusal (12.0%), visiting other cities (4.1%), unable to contact (1.3%), and other miscellaneous reasons (2.5%).

Data Collection

In-person interviews were conducted by trained interviewers who were mostly retired medical professionals between October 2002 and December 2006, on average 6.5 months (range: 3 to 11) after diagnosis of breast cancer. Information was collected on cancer treatment, tumor characteristics, reproductive history, diet, medical history, selected lifestyle factors, complementary and alternative medicine use, socio-demographics, and quality of life. Anthropometric measurements (height, weight, waist and hip circumference) were taken using a standard protocol. Medical records were reviewed to verify clinical data (e.g., treatment, tumor characteristics) for 98.1% of the cohort.[26]. Information on vital status, recurrence, and disease progression has been collected by in-person follow-up surveys conducted at approximately 18 months, 36 months, and 60 months after diagnosis. The cohort has also been periodically linked to the Shanghai vital statistics registry to ascertain

deaths that occurred between surveys and for women missing one or more in-person follow-up surveys. The latest linkage took place in September 2011. Human subjects Institutional Review Board approval was obtained from all participating institutions.

Comorbidity Assessment

The first post-diagnosis interview, conducted 3–11 months post-diagnosis, included two versions, with 2,230 women interviewed using version one and 2,812 women interviewed using version two. For version one, women could respond either “yes” or “no” regarding diagnoses of specifically assessed comorbidities. For version two, women could respond “known”, “suspected” or “no”. Specific comorbidities assessed for both questionnaire versions included: diabetes mellitus, hypertension, coronary heart disease (CHD), stroke, and chronic gastritis. Chronic bronchitis and asthma were assessed in separate questions for version one, while these conditions were assessed with one question in version two. Women who reported “suspected” (<1% of participants) for any of the comorbidities were included in the “no” group for that specific comorbidity. We combined reported diagnoses of chronic bronchitis and asthma into one variable in the present analysis. Age at diagnosis for each comorbidity was also reported. Information on type of diabetes (insulin-dependent or non-insulin dependent), type of stroke, or severity of conditions was not collected. Women were also asked to report up to three additional medical conditions. For the present analysis, we included five additional major comorbidities or categories of conditions volunteered by women with adequate sample size for analysis (digestive ulcer, rheumatoid arthritis, other digestive disease, other urinary system disease, and other CVD).

Covariates

Potential confounders selected *a priori* included: 1) known clinical factors: TNM stage (I, II, III, missing), estrogen receptor (ER)/progesterone receptor (PR) status (ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−, missing), chemotherapy (yes, no), radiotherapy (yes, no), tamoxifen (yes, no), mastectomy (yes, no)); 2) socio-demographics: education (none/primary school, middle school, high school, ≥college), income in yuan/person/month (<700, 700–999, 1000–1999, >2000); and 3) reproductive and lifestyle factors: menopausal status (premenopausal, postmenopausal), number of live births (0, 1, 2, ≥3), family history of breast cancer (yes, no), ginseng use (yes, no), vitamin supplement use (yes, no), BMI (continuous), regular tea drinker, defined as ≥three times a week for >six months (yes, no), regular alcohol consumption, defined as ≥ three times a week for >six months (yes, no), regular cigarette smoking defined as ≥ one cigarette per day (yes, no), and regular exercise participation, defined as exercise at least twice weekly since diagnosis of breast cancer, in standard metabolic equivalent task [27] hours/week categorized by based on quartiles.

Statistical Analysis

Study events included breast cancer recurrence/metastasis, total mortality, breast cancer-specific mortality, and non-breast cancer mortality. Non-breast cancer deaths included 53 women with unknown cause of death. For the disease-free analysis, women who reported a recurrence/metastasis prior to study enrollment, or with no disease-free follow-up after study enrollment were excluded (n=218).

Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were derived from Cox proportional hazards regression models using age as the time-scale [28].

For survival analyses, entry time was defined as age at diagnosis and exit time was defined age at death, or age at last follow-up (last in-person interview or February 28, 2011 (6 months before the most recent linkage to the vital statistics registry), whichever occurred first). For disease-free analyses, exit time was defined as age at recurrence/metastasis, age at

death, or last in-person contact, whichever occurred first. For 26 women who died of breast cancer, but were missing recurrence information, the date of recurrence was imputed using the disease stage TNM-specific median interval between recurrence and death [25]. Separate Cox models were fitted for breast cancer and non-breast cancer deaths, with the event not of interest in the cause-specific model censored [29]. Initial models included age at diagnosis and each individual comorbid condition. Final multivariable models included additional adjustment for known clinical predictors of survival and factors associated with at least one of the major comorbidities (i.e., education, income, ER status, PR status, TNM stage, chemotherapy, radiotherapy, mastectomy, tamoxifen, menopause, parity, BMI, vitamin supplement use, and ginseng use). We also examined results additionally adjusted for tea consumption, alcohol consumption, cigarette smoking, exercise participation in MET-hours/day, and major dietary factors available in the SBCSS (soy food intake, cruciferous vegetable intake, and meat and fish intake) [25]. Adjustment did not change results; therefore these factors were not included in final models (data not shown).

For the present analysis, we excluded women with non-invasive breast cancer (TNM stage 0, n=156), women with stage IV breast cancer (n=28), women missing comorbidity history (n=2), women who reported age at comorbidity diagnosis (for the specifically assessed comorbidities) after breast cancer diagnosis (n=130), and women with unknown ER status (n=63; these women were excluded because ER status was included in the strata statement in the Cox models (as described below)), for a final sample size of 4,664 women.

The proportional hazards assumption was tested by examining interaction terms for covariates and overall survival time in models with time since diagnosis as the time-scale. The assumption was found to be potentially violated for ER status and radiotherapy, therefore Cox regression models were stratified these covariates. All analyses were performed using SAS version 9.3. Tests of statistical significance were based on two-sided probability and p-values <0.05 were considered statistically significant.

RESULTS

After a median follow-up of 5.3 years (range: 0.64–8.9), 647 women died (516 from breast cancer) and 632 recurrence/metastases were documented. The median age at breast cancer diagnosis was 51.0 years (standard deviation: 10.0). Improved five year survival rates were observed for women with higher education, higher income, earlier TNM stage, ER+/PR+ tumors, premenopausal women, and women who did not receive radiotherapy (Table 1). Tamoxifen use and lower BMI (<25 kg/m^2) were also associated with improved five-year survival (Table 1).

The most common comorbidity reported among breast cancer survivors was hypertension (22.4%), followed by chronic gastritis (14.3%), diabetes mellitus (6.2%), chronic bronchitis/asthma (5.8%), CHD (5.0%), stroke (2.2%), chronic hepatitis (1.8%), and rheumatoid arthritis (1.4%). About half of the women reported none of the comorbidities, 29.2% reported 1 comorbidity, and 19.1% reported ≥2 comorbidities.

As shown in Table 2, hypertension, diabetes, CHD, or stroke were associated with older age, overweight (BMI 25–<30 kg/m^2) or obesity (BMI ≥30 kg/m^2), and non-receipt of chemotherapy and radiotherapy. Diabetes was associated with later stage at diagnosis, while chronic gastritis was associated with earlier stage at diagnosis and lower BMI.

Table 3 displays associations of comorbidities with breast cancer recurrence/metastasis and total mortality. None of the comorbidities were statistically significantly associated with recurrence/metastasis. However, hypertension was non-significantly inversely associated with recurrence/metastasis (adjusted HR: 0.83, 95% CI: 0.67–1.03) and total mortality

(adjusted HR: 0.83. 95% CI: 0.67–1.02), adjusting for socio-demographics, clinical characteristics, selected lifestyle factors, and the other comorbidities. In models adjusted for age (and other comorbidities) only, women who reported a history of chronic gastritis had reduced risk of total mortality (HR: 0.74, 95% CI: 0.58–0.94). However, after further adjustment the association was no longer statistically significant (HR: 0.89, 95% CI: 0.69–1.14). Diabetes, history of stroke, and rheumatoid arthritis were each associated with increased risk of total mortality, although the association for stroke was not statistically significant (adjusted HRs (95% CIs): 1.40 (1.06–1.85), 1.42 (0.91–2.22), and 1.91 (1.13–3.23), respectively).

Table 4 displays associations of comorbidities with breast cancer-specific and non-breast cancer mortality. Diabetes and history of stroke were associated with non-breast cancer mortality (adjusted HRs (95% CI): 2.64 (1.63–4.27) and 2.52 (1.33–4.78), respectively), but were not associated with breast cancer-specific mortality (adjusted HRs (95% CIs): 0.98 (0.68–1.41) and 0.78 (0.38–1.62), respectively). Hypertension was suggestively non-significantly inversely associated with breast cancer-specific mortality (adjusted HR (95% CI): 0.82, 95% CI: 0.64–1.04), but not non-breast cancer mortality (adjusted HR (95% CI): 0.92, 95% CI: 0.60–1.41).

We conducted an analysis stratified by age at diagnosis for the specifically assessed comorbidities with adequate sample size (Table S1 in Online Supplemental Data). For chronic gastritis, a positive association with recurrence was found among women <51 years of age (HR: 1.70, 95% CI: 1.22–2.38), and a negative non-significant association was found among women ≥51 years of age (HR: 0.83, 95% CI: 0.60–1.13), *P* for interaction <0.01. A similar pattern was observed for total mortality; however the interaction was not statistically significant (*P* for interaction = 0.07). No evidence for effect modification was found for the other comorbidites, although sample sizes were generally small by strata

DISCUSSION

In this population-based prospective cohort of 4,664 female breast cancer survivors aged 20–75 years, we found that individual comorbidities self-reported at cohort enrollment (3–11 months after breast cancer diagnosis) were differentially associated with breast cancer outcomes, adjusting for socio-demographics, known clinical prognostic factors, lifestyle factors, and each other comorbid condition. Specifically, pre-existing diabetes mellitus was associated with a statistically significant increased risk of total mortality and an over two-fold increased risk of non-breast cancer mortality, but was not associated with recurrence/metastasis or breast cancer-specific mortality. History of stroke was associated with an over two-fold increased risk of non-breast cancer mortality, but was not associated with recurrence/metastasis or breast cancer-specific mortality. Rheumatoid arthritis was associated with increased risk of total mortality, but was not associated with other breast cancer outcomes.

Many studies have reported that various comorbidity indexes, such as the CCI, or simple additive summary scores for number of comorbidities are associated with poorer survival among breast cancer survivors [11, 30]. However, only few relatively recent studies (in breast cancer cases diagnosed after 1990) have investigated the association of multiple individual comorbidities with survival among breast cancer patients [5, 9, 10, 22–24]. A study of older breast cancer patients (≥ 55 years) diagnosed in 1992 (n=1,800) using Surveillance, Epidemiology, and End Results Registry data reported differing effects of comorbidities on overall survival, with stroke, asthma, and diabetes associated with increased risk of death, and hypertension associated with reduced risk of death [22]. Recently, Patnaik and colleagues investigated the role of 13 specific comorbid conditions on

total mortality among older breast cancer patients (age ≥66 years) using linked Surveillance, Epidemiology, and End Results Registry and Medicare data. They reported that each of the individual comorbidities was associated with increased risk of total mortality, including history of myocardial infarction, rheumatoid arthritis, cerebrovascular disease, and diabetes [5]. This study did not investigate hypertension or chronic gastritis. In a second report using the same population, diabetes and CVD were found to be significantly associated with increased risk of both breast cancer-specific mortality and non-breast cancer mortality [24]. Two registry-based studies conducted in the Netherlands with overlapping populations have also reported increased risk of total mortality in association with diabetes, CVD, and cerebrovascular disease among breast cancer patients [9, 23], and a null association for hypertension [23].

All of the above-mentioned studies were registry-based, with limited data on potential confounding factors, such as lifestyle-related factors. Further, most were limited to older women, and none investigated the association of comorbidities with breast cancer recurrence. Recently, a report from the Women's Healthy Eating & Living (WHEL) study, a prospective follow-up of participants of a dietary intervention trial, investigated the association between individual comorbidities and breast cancer prognosis among breast cancer survivors aged 26–70 years. In the WHEL study (n=2,542), diabetes was associated with increased risk of additional breast cancer events and total mortality, osteoporosis was inversely associated with total mortality, and other comorbidities (including hypertension) were not associated with breast cancer outcomes [10]. Lifestyle-related factors were considered (e.g., BMI, physical activity, smoking), although these factors were not adjusted for in final models. It is worth mentioning that this study excluded women with a history of stroke or CHD prior to enrollment, and comorbidities were assessed at a mean of two years after diagnosis, and therefore may be more likely to include both pre-existing (before diagnosis) and new medical conditions. A second report, using data from the Life after Cancer Epidemiology (LACE) study (n=2,272), a prospective cohort of breast cancer survivors, evaluated hypertension alone and the CCI in association with mortality outcomes, adjusting for treatment, tumor characteristics, and lifestyle factors. This study reported increased risk of all-cause and non-breast cancer death in association with both the CCI index and hypertension, and null associations for breast cancer-specific mortality [30]. A second report from the LACE cohort, for which the main objective was to investigate beta-blockers and angiotensin-converting enzyme inhibitors in association with breast cancer outcomes, also reported associations for diabetes and breast cancer outcomes [31]. Similar to our study, diabetes was not associated with recurrence or breast cancer-specific mortality, but was associated with increased risk of total mortality. Most reports of diabetes have only investigated total mortality and generally found increased risk of mortality in association with diabetes [5, 9, 22, 32].

We observed that rheumatoid arthritis, a pro-inflammatory condition [33], was associated with increased risk of total mortality among breast cancer survivors, which is consistent with at least one previous report [5]. Rheumatoid arthritis was not associated with specific type of deaths (e.g., breast cancer death or non-breast cancer death); however, sample sizes were small (only 15 total events among women with rheumatoid arthritis). With additional follow-up of the SBCSS cohort we will be able to investigate this association with a larger sample size.

In the SBCSS, hypertension was suggestively inversely associated with recurrence/metastasis, breast cancer-specific mortality, and total mortality, although associations did not reach statistical significance. Although the epidemiological data is sparse, a few studies have suggested that medications used to treat hypertension may be associated with improved breast cancer survival, and this could be one potential mechanism for the observed

suggested inverse associations [34]. Specifically, four studies to date suggest beta-blockers may be associated with reduced risk of breast cancer recurrence and/or breast cancer-specific mortality [31, 35–37]. In addition, two cohort studies have reported some evidence to suggest angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be associated with improved prognosis, with one study observing a non-significant inverse association [37] and the other a statistically significant inverse association for relapse-free survival [38]. In contrast, a third study among the LACE cohort reported that angiotensin-converting enzyme inhibitor use was associated with increased risk of recurrence [31]. We did not collect information on treatment for comorbidities in the SBCSS, and future studies with data on medication use and detailed comorbidity history are warranted.

The strengths of the SBCSS include the large sample size, high baseline response and follow-up rates, population-based prospective design, and detailed data collection on clinical characteristics, medical history, standard medical treatments, and lifestyle-related factors. Despite these strengths, several limitations should be considered. First, information on comorbidities was collected via in-person interviews and data from medical records or clinical databases was not available to verify the diagnoses. However, use of patient questionnaires to assess comorbidity has been shown to be reliable [39]. In addition, we have previously shown in our study population that breast cancer patients recall medical procedures and cancer treatment use reliably [26]. Further, we compared the prevalence of hypertension (22.4%), diabetes (6.2%), and CHD (5.0%) reported in the SBCSS, to those reported at baseline in the Shanghai Women's Health Study, a population-based cohort of 74,941 women residing in Shanghai, China and observed similar prevalences for these conditions (hypertension (23.8%), diabetes (4.4%), and CHD (7.4%)). Second, detailed information on the reported comorbidities, including severity of disease and type of stroke or diabetes (e.g., insulin-dependent or non-insulin dependent) was not available. Third, although adjustment for additional lifestyle factors reported at study enrollment, including physical activity, tea intake, smoking, drinking, and dietary factors (soy food intake, meat intake, cruciferous vegetable intake) did not alter results (data not shown), we cannot completely rule out the possibility of residual confounding from unmeasured or inadequately measured lifestyle factors. Fourth, we did not investigate the role of newly diagnosed comorbidities in long-term prognosis, as the objective of the present study was to investigate comorbidities at diagnosis and breast outcomes, and current median follow-up in the SBCSS is 5.3 years. However, a detailed comorbidity assessment was conducted at the 5-year follow-up survey among survivors; therefore, with continued long-term follow-up we can investigate this question in the future.

In conclusion, in this large prospective cohort of Chinese breast cancer survivors with a median follow-up of five years, diabetes was associated with increased risk of total and non-breast cancer mortality and stroke was associated with increased risk of non-breast cancer mortality. These conditions were not associated with recurrence/metastasis or breast cancer-specific mortality. Rheumatoid arthritis was associated with increased risk of total mortality, but not other breast cancer outcomes. Our findings suggest that to improve understanding of the role of comorbidities in breast cancer outcomes, and provide individualized prognostic information to breast cancer patients and health care professionals on the survival impact of comorbidities, it is important to examine the influence of individual comorbidities on breast cancer outcomes. Future studies with detailed assessments of individual comorbidities and associated treatment are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
CCI	Charlson comorbidity index
CIs	Confidence intervals
CHD	Coronary heart disease
ER	Estrogen receptor
LACE	Life After Cancer Epidemiology
HRs	Hazard ratios
PR	Progesterone receptor
SBCSS	Shanghai Breast Cancer Survival Study
WHEL	Women's Healthy Eating & Living

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Table 1

Prevalence and 5-year overall survival rates by socio-demographics and clinical characteristics, Shanghai Breast Cancer Survival Study (n=4,664)

				5-year Overall Survival	
Characteristic	**N**	**%**	**No. of Deaths**	**Percent**	***P*[a]**
Age at diagnosis, y					
<50 (median= 45.8)	2,093	44.9	240	90.8	
50–59 (median= 53.7)	1,372	29.4	184	89.2	
≥60 (median= 67.9)	1,199	25.7	223	85.7	<0.01
Education					
None/Elementary	537	11.5	131	81.7	
Middle school	1,621	34.8	238	88.2	
High School	1,763	37.8	208	90.2	
≥College	743	15.9	70	93.3	<0.01
Income (Yuan/person/month)					
<700	1,311	28.1	208	87.4	
700–999	1,382	29.6	215	87.8	
1000–1999	1,411	30.3	169	90.3	
≥2000	560	12.0	55	92.9	<0.01
Menopausal status					
Premenopausal	2,304	49.4	272	90.6	
Postmenopausal	2,360	50.6	375	87.6	<0.01
TNM stage					
I	1,622	34.8	99	95.1	
II	2,394	51.3	340	89.0	
III	445	9.5	188	66.0	
Unknown	203	4.4	20	92.1	<0.01
ER/PR status					
ER+/PR+	2,379	51.2	264	91.9	
ER+/PR−	616	13.3	87	89.2	
ER−/PR+	351	7.6	50	89.4	
ER−/PR−	1,304	28.0	244	83.6	<0.01

				5-year Overall Survival	
Characteristic	**N**	**%**	**No. of Deaths**	**Percent**	***P*[a]**
Chemotherapy					
No	355	7.6	53	87.7	
Yes	4,309	92.4	594	89.2	0.43
Radiotherapy					
No	3,127	67.1	354	92.1	
Yes	1,537	33.0	293	84.8	<0.01
Mastectomy[b]					
No	305	6.5	24	92.6	
Yes	4,359	93.5	623	88.9	<0.01
Tamoxifen use					
No	2,244	48.1	363	86.5	
Yes	2,420	51.9	284	91.4	< 0.01
BMI (kg/m^2)					
<25	3,047	65.3	385	90.1	
25–30	1,362	29.2	208	87.8	
≥30	255	5.5	54	83.1	<0.01

Abbreviations: estrogen receptor (ER), progesterone receptor (PR), body mass index (BMI).

[a]P-values are from the log-rank test.

[b]Excludes ten women who did not have surgery (n=10).

Table 2

Major comorbidities assessed at study enrollment (3–11 months post-diagnosis) by clinical characteristics, Shanghai Breast Cancer Survival Study (n=4,664)

		Hypertension		Diabetes		CHD		Stroke		Chronic Gastritis	
	N	n	%	n	%	n	%	n	%	n	%
Age at diagnosis, y											
<50	2,093	172	8.2	39	1.9	3	0.14	3	0.14	226	10.8
50–59	1,372	306	22.3	62	4.5	43	3.1	16	1.2	226	16.5
≥60	1,199	567	47.3[a]	187	15.6[a]	186	15.5[a]	82	6.8[a]	217	18.1[a]
TNM stage[b]											
I	1,622	360	22.2	87	5.4	84	5.2	34	2.1	282	17.4
II	2,394	530	22.1	147	6.1	113	4.7	48	2.0	305	12.7
III	445	110	24.7	37	8.3[a]	23	5.2	13	2.9	49	11.0[a]
ER/PR status[b]											
ER+/PR+	2,379	537	22.6	147	6.2	115	4.8	56	2.4	344	14.5
ER+/PR−	616	168	27.3	43	7.0	38	6.2	16	2.6	86	14.0
ER−/PR+	351	62	17.7	13	3.7	11	3.1	5	1.4	50	14.3
ER−/PR−	1,304	269	20.6[a]	83	6.4	67	5.1	22	1.7	189	14.5
Mastectomy[c]											
No	305	56	18.4	17	5.6	15	4.9	10	3.3	44	14.4
Yes	4,359	989	22.7	271	6.2	217	5.0	91	2.1	625	14.3
Chemotherapy											
No	355	166	46.8	62	17.5	61	17.2	24	6.8	61	17.2
Yes	4,309	879	20.4[a]	226	5.2[a]	171	4.0[a]	77	1.8[a]	608	14.1
Radiotherapy											
No	3,127	782	25.0	209	6.7	189	6.0	77	2.5	476	15.2
Yes	1,537	263	17.1[a]	79	5.1[a]	43	2.8[a]	24	1.6	193	12.6[a]
Tamoxifen use											
No	2,244	500	22.3	142	6.3	106	4.7	46	2.1	325	14.5

		Hypertension		Diabetes		CHD		Stroke		Chronic Gastritis	
	N	n	%	n	%	n	%	n	%	n	%
Yes	2,420	545	22.5	146	6.0	126	5.2	55	2.3	344	14.2
BMI (kg/m^2)											
<25.0	3,047	486	16.0	155	5.1	110	3.6	52	1.7	460	15.1
25.0–29.99	1,362	426	31.3	113	8.3	92	6.8	42	3.2	184	13.5
≥30	255	133	52.2[a]	20	7.8[a]	30	11.8[a]	7	2.7[a]	25	9.7[a]

Abbreviations: estrogen receptor (ER), progesterone receptor (PR), body mass index (BMI). P values were derived from the chi-square test for general association.

[a]P value <0.05 based on chi-square test.

[b]Excludes unknown (for TNM, n= 203; for ER/PR n =14).

[c]Excludes ten women who did not have surgery (n=10).

Table 3

HRs for the association of individual comorbidities reported at study enrollment (3–11 months post-diagnosis) and breast cancer recurrence/metastasis and total mortality, Shanghai Breast Cancer Survival Study (n=4,664)

		Recurrence/Metastasis			Total Mortality		
			Model A[a]	Model B[b]		Model A[a]	Model B[b]
Comorbidities	**Cohort**	**Events**	**HR (95% CI)**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**HR (95% CI)**
Specifically assessed[c]							
Diabetes	288	44	1.10 (0.80–1.52)	0.98 (0.71–1.36)	67	1.55 (1.18–2.03)*	1.40 (1.06–1.85)*
Hypertension	1045	139	0.91 (0.74–1.12)	0.83 (0.67–1.03)	157	0.88 (0.72–1.07)	0.83 (0.67–1.02)
CHD	232	29	0.81 (0.55–1.21)	0.85 (0.57–1.27)	36	0.80 (0.56–1.15)	0.80 (0.56–1.15)
Stroke	101	10	0.60 (0.31–1.15)	0.63 (0.33–1.20)	23	1.29 (0.83–2.02)	1.42 (0.91–2.22)
Chronic bronchitis/asthma	268	44	1.13 (0.83–1.54)	1.00 (0.73–1.38)	47	1.09 (0.81–1.47)	0.96 (0.70–1.30)
Chronic gastritis	669	91	0.97 (0.77–1.21)	1.14 (0.91–1.43)	74	0.74 (0.58–0.94)*	0.89 (0.69–1.14)
Chronic hepatitis	82	12	1.11 (0.62–1.97)	1.16 (0.65–2.06)	7	0.60 (0.28–1.26)	0.64 (0.30–1.35)
Volunteered[d]							
Digestive ulcer	74	9	0.88 (0.46–1.71)	0.93 (0.48–1.82)	7	0.58 (0.28–1.24)	0.59 (0.28–1.26)
Rheumatoid arthritis	65	10	1.12 (0.60–2.11)	1.24 (0.66–2.34)	15	1.68 (1.00–2.81)	1.91 (1.13–3.23)*
Other digestive disease	492	66	0.97 (0.75–1.25)	0.98 (0.76–1.28)	71	1.03 (0.80–1.32)	1.07 (0.83–1.38)
Other urinary system disease	81	9	0.72 (0.37–1.39)	0.77 (0.40–1.49)	7	0.53 (0.25–1.13)	0.59 (0.28–1.24)
Other cardiovascular disease	160	21	0.96 (0.62–1.48)	0.94 (0.61–1.46)	22	1.09 (0.71–1.67)	1.02 (0.67–1.58)

Abbreviations: hazard ratio (HR), coronary heart disease (CHD), not applicable (NA).

*P value <0.05.

[a]HRs were from Cox proportional hazards regression models and adjusted for age and each other comorbid condition in the table (as applicable).

[b]Additionally adjusted for education, income, estrogen receptor and progesterone receptor status, TNM stage, chemotherapy, radiotherapy, breast cancer surgery, tamoxifen, menopause, parity, BMI, vitamin supplement use, and ginseng use.

[c]Women were specifically asked if they had this condition.

[d]Women volunteered these medical conditions when queried regarding “other” type of chronic disease.

Table 4

HRs for the association of individual comorbidities reported at study enrollment (3–11 months post-diagnosis) and breast cancer-specific and non-breast cancer mortality, Shanghai Breast Cancer Survival Study (n=4,664)

		Breast Cancer-Specific Mortality			Non-Breast Cancer Specific Mortality			
			Model A[a]	Model B[b]		Model A[a]	Model B[b]	
Comorbidities	**Cohort**	**Events**	**HR (95% CI)**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**HR (95% CI)**	
Specifically assessed[c]								
Diabetes	288	36	1.14 (0.80–1.62)	0.98 (0.68–1.41)	31	3.00 (1.90–4.73)*	2.64 (1.63–4.27)*	
Hypertension	1045	110	0.87 (0.69–1.09)	0.82 (0.64–1.04)	47	0.95 (0.62–1.43)	0.92 (0.60–1.41)	
CHD	232	20	0.66 (0.41–1.06)	0.64 (0.40–1.03)	16	1.15 (0.64–2.06)	1.29 (0.70–2.36)	
Stroke	101	8	0.68 (0.33–1.40)	0.78 (0.38–1.62)	15	2.55 (1.38–4.71)*	2.52 (1.33–4.78)*	
Chronic bronchitis/asthma	268	35	1.07 (0.75–1.51)	0.93 (0.65–1.33)	12	1.17 (0.64–2.13)	1.03 (0.55–1.91)	
Chronic gastritis	669	62	0.80 (0.61–1.05)	0.99 (0.76–1.31)	12	0.53 (0.29–0.96)*	0.55 (0.30–1.01)	
Chronic hepatitis	82	6	0.64 (0.29–1.44)	0.70 (0.31–1.59)	NA[e]		NA[e]	
Volunteered[d]								
Digestive ulcer	74	6	0.67 (0.30–1.51)	0.69 (0.31–1.58)	NA[e]		NA[e]	
Rheumatoid arthritis	65	10	1.45 (0.77–2.73)	1.67 (0.88–3.18)	5	2.27 (0.92–5.62)	2.47 (0.97–6.28)	
Other digestive disease	492	55	1.01 (0.76–1.34)	1.04 (0.78–1.39)	16	1.07 (0.63–1.81)	1.13 (0.66–1.94)	
Other urinary system disease	81	6	0.57 (0.26–1.29)	0.66 (0.29–1.48)	NA[e]		NA[e]	
Other cardiovascular disease	160	15	0.90 (0.54–1.51)	0.82 (0.49–1.39)	7	1.90 (0.88–4.10)	1.96 (0.90–4.28)	

Abbreviations: hazard ratio (HR), coronary heart disease (CHD), not applicable (NA).

*P value <0.05.

[a]HRs were from Cox proportional hazards regression models and adjusted for age and each other comorbid condition in the table (as applicable).

[b]Additionally adjusted for education, income, estrogen receptor and progesterone receptor status, TNM stage, chemotherapy, radiotherapy, breast cancer surgery, tamoxifen, menopause, parity, BMI, vitamin supplement use, and ginseng use.

[c]Women were specifically asked if they had this condition.

[d]Women volunteered these medical conditions when queried regarding “other” type of chronic disease.

[e] Inadequate number of events for analysis (<5 events).