

# Occupational type affects the receipt of breast cancer adjuvant chemotherapy in China

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**Abstract.** Adjuvant chemotherapy has been demonstrated to improve the prognosis of patients with early-stage breast cancer; however, the high cost and side effects associated with this treatment may discourage patients from receiving it. The present study assessed the candidate factors that may influence decisions regarding postoperative adjuvant chemotherapy in females with early-stage breast cancer. Patients diagnosed with invasive breast cancer between January 2000 and December 2007 were enrolled in the study. Information about the patients, including socio-demographic factors, clinicopathological characteristics and receipt of adjuvant chemotherapy, was obtained from their medical records. Overall, 434 out of 1,296 (33.5%) patients with breast cancer decided against receiving adjuvant chemotherapy. Receipt of chemotherapy was significantly associated with the age of the patient at the time of diagnosis ( $P=0.029$ ), occupational type ( $P=0.023$ ), and lymph node status ( $P<0.001$ ). Moderate associations were also observed between receipt of adjuvant chemotherapy and the patient's family history of cancer ( $P=0.055$ ) and hormone-receptor status ( $P=0.075$ ). The results of the present study suggest that the occupational type of the patient is associated with receipt of adjuvant chemotherapy in China. This observation may provide a novel strategy for physicians to improve patient's compliance regarding adjuvant chemotherapy. Further studies in additional developing countries are required in order to validate these observations.

## Introduction

Breast cancer is one of the most frequently diagnosed types of cancer among females worldwide. The incidence and mortality rate of breast cancer are decreasing in certain developed countries, but are rising in the majority of developing regions, such as Asia and Africa (1,2). In recent years, breast cancer has become one of the leading causes of cancer-associated mortality among females in China, and is the most frequently diagnosed type of malignant tumor (3,4). With the development of various breast cancer treatments, conventional strategies, including radiotherapy, surgery and chemotherapy, provide patients with multiple therapeutic options.

Adjuvant chemotherapy is usually administered following surgery, and is considered one of the standard treatments for invasive breast cancer (5,6). Previous studies have suggested that adjuvant chemotherapy may improve the prognosis of patients with postoperative breast cancer (7-9). The use of adjuvant chemotherapy significantly prolongs disease-free and overall survival among patients with breast cancer but also can cause long-term side effects, such as suppression of ovarian function with premature menopause. This may result in loss of childbearing potential, menopause symptoms, such as hot flashes and genitourinary dysfunctions, infertility and prolonged exposure to menopausal risks, including osteoporosis and cardiovascular disease, causing physical as well as psychological distress (10,11). For these reasons, certain patients, particularly young women, choose not to receive chemotherapy. Furthermore, the elevated cost of chemotherapy may discourage patients with breast cancer from accepting this effective treatment, particularly in economically developing countries such as China (12-15). Numerous studies have indicated that factors such as ethnicity and marital status may impact the receipt of adjuvant chemotherapy among patients with breast cancer in economically developed countries (16,17). A previous study reported that age, marital status, occupational type and economic level could significantly influence the receipt of chemotherapy (18). However, Lipscomb *et al* (16) reported that the ratio of individuals that completed chemotherapy versus those who did not was not significantly affected by socioeconomic ( $P=0.447$ ) or rural status ( $P=0.165$ ). However, it still remains uncertain

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whether occupational type is be an influencing factor on the receipt of chemotherapy. In addition, similar studies have not been conducted in developing countries thus far. In the present study, possible factors influencing the receipt of adjuvant chemotherapy to target breast cancer in China were explored and evaluated.

## Materials and methods

**Patient selection.** Females diagnosed with invasive breast cancer between January 2000 and December 2007 were enrolled in the present study. Diagnosis of breast cancer was confirmed by surgery and pathological examinations at Qilu Hospital of Shandong University (Jinan, China). Information about the participants was retrieved from their medical records. Previous studies have suggested that receipt of neoadjuvant chemotherapy may disturb the receipt of breast cancer adjuvant chemotherapy (14,16,17). Therefore, patients who had received neoadjuvant chemotherapy prior to surgery, or those who did not meet the clinical criteria for consideration of adjuvant chemotherapy according to the recommended guidelines, were excluded from the study (5).

**Data collection.** Socio-demographic factors and clinico-pathological characteristics of the candidates, including age at the time of diagnosis, menstrual status, occupational type, comorbidities, history of benign breast disease, family history of cancer, tumor size, lymph node metastasis, hormone receptor status, and tumor stage, were retrieved and coded anonymously for analysis in the present study. Data collection was performed independently by 2 individuals. All of the participants provided their informed consent prior to inclusion in the study. The present study was approved by the ethical committees of the Qilu Hospital of Shandong University and Bengbu Medical College (Bengbu, China).

**Variables.** Clinicopathological characteristics, such as estrogen (ER) and progesterone receptor (PR) status, were assessed by immunohistochemical staining, and tumors were classified according to the pathological tumor-node-metastasis (pTNM) staging system (18). Comorbidities included cardiovascular disease, tuberculosis, rheumatism and other chronic conditions excluding tumors. Patients without menses for >6 months were classified as postmenopausal individuals. The variables were measured at the initial time of treatment.

**Immunohistochemical staining.** Briefly, the tissue sections (4- $\mu$ m) were deparaffinized and rehydrated, followed by antigen retrieval with pH 6.0 citrate buffer (ZSGB-BIO, Beijing, China). Endogenous peroxidase activity was inhibited with 3% H<sub>2</sub>O<sub>2</sub> for 15 min and the sections were incubated with 10% normal goat serum (ZSGB-BIO) to block non-specific binding. After incubation with monoclonal rabbit anti-human ER (cat. no. ZA-0102)/PR (cat. no. ZA-0255) antibodies (ZSGB-BIO) at 4°C overnight, the sections were washed, treated with biotinylated polyclonal goat anti-rabbit anti-immunoglobulin antibody (cat. no. SP-9001; ZSGB-BIO) for 20 min and reacted with horseradish peroxidase-conjugated streptavidin. Subsequently, a the liquid DAB

Table I. Characteristics of the patients<sup>a</sup>.

Variable	No. cases (%)
Age	
Mean $\pm$ SD (years)	50.01 $\pm$ 11.22
Ethnicity	
Asian	1,296 (100%)
Menopausal status	
Premenopausal	620 (47.8%)
Postmenopausal	676 (52.2%)
Occupational types	
Peasant	341 (26.3%)
Laborer	472 (36.4%)
Civil servant and cadre	174 (13.4%)
School teacher	76 (5.9%)
Medical staff	37 (2.9%)
Housewife	126 (9.7%)
Other/unknown	70 (5.4%)
Comorbid conditions	
0	914 (70.5%)
$\geq 1$	382 (29.5%)
History of breast disease	
0	1,178 (90.9%)
$\geq 1$	118 (9.1%)
Family history of cancer	
0	1,193 (92.1%)
$\geq 1$	103 (7.9%)
Tumor size (cm)	
$\leq 2$	1,084 (83.6%)
$> 2$	201 (15.5%)
Lymph node metastasis	
Negative	737 (56.9%)
Positive	558 (43.1%)
Hormone receptor status	
ER <sup>-</sup> and PR <sup>-</sup>	187 (14.4%)
ER <sup>+</sup> and/or PR <sup>+</sup>	660 (50.9%)
Stage	
I	171 (13.2%)
II	927 (71.5%)
III	198 (15.3%)
Receipt of adjuvant chemotherapy	
No	434 (33.5%)
Yes	862 (66.5%)

<sup>a</sup>Data regarding tumor size, lymph node metastasis and hormone receptor status could not be obtained from all patients. SD, standard deviation; ER, estrogen receptor; PR, progesterone receptor.

substrate/chromogen system (Maixin Bio, Fuzhou, China) was used to stain the sections, prior to counterstaining with hematoxylin (Beijing Solarbio Science & Technology Co., Ltd., Beijing, China).

Table II. Univariate analysis of factors associated with the receipt of adjuvant chemotherapy<sup>a</sup>.

Variable	No. cases (N=1,296)	Received adjuvant chemotherapy (%, N=862)	$\chi^2$ (P-value)
Age (years)			
<50	691	68.6	0.018
50-70	529	65.8	
>70	76	52.6	
Occupational types			
Peasant	341	61.9	0.053
Laborer	472	67.6	
Civil servants and cadre	174	64.9	
School teacher and medical staff	113	76.1	
Housewife	126	70.6	
Menopausal status			
Premenopausal	620	67.9	0.310
Postmenopausal	676	65.2	
Comorbidities			
0	914	66.7	0.789
≥1	382	66.0	
History of breast disease			
No	1178	66.7	0.611
Yes	118	64.4	
Family history of cancer			
No	1193	65.6	0.022
Yes	103	76.7	
Tumor size (cm)			
≤2	1084	67.2	0.337
>2	201	63.7	
Lymph node metastasis			
Negative	737	62.4	<0.001
Positive	558	72.0	
Tumor stage			
I	171	63.7	0.396
II	927	67.6	
III	198	63.6	
Hormone receptor status			
ER <sup>-</sup> and PR <sup>-</sup>	187	61.5	0.095
ER <sup>+</sup> and/or PR <sup>+</sup>	660	68.0	

<sup>a</sup>Data regarding tumor size, lymph node metastasis and hormone receptor status could not be obtained from all patients. ER, estrogen receptor; PR, progesterone receptor.

**Statistical analysis.** Univariate analyses were conducted for each of the variables and the receipt of adjuvant chemotherapy using  $\chi^2$  tests, accompanied by 2-sided P-values. Multivariate logistic regression analyses, performed using the Hosmer-Lemeshow model, evaluated the associations between these parameters, which were expressed as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). P>0.5 was considered as high goodness-of-fit. Statistical analyses were performed using the IBM SPSS Statistics software, version 20.0.0 (IBM SPSS, Armonk, NY, USA), and based

on 2-tailed probability. P<0.05 was considered to indicate a statistically significant difference.

## Results

A total of 1,296 females diagnosed with invasive breast cancer (pTNM stage I-III) were enrolled in the present study (Table I). All of the patients were of Asian descent, and their age ranged from 23 to 85 years. Among the participants, 434 (33.5%) decided against receiving adjuvant chemotherapy.

Table III. Multivariate analysis of candidate factors associated with the receipt of adjuvant chemotherapy.

Variable	OR <sup>a</sup>	95% CI <sup>a</sup>	Adjusted P-value <sup>a</sup>
Age (years)	0.988	0.978-0.999	0.029
Occupational types			0.023
Peasant	1.000		
Laborer	1.377	1.022-1.857	0.036
Civil servants and cadre	1.273	0.862-1.881	0.226
School teacher and medical staff	2.215	1.349-3.635	0.002
Housewife	1.669	1.061-2.627	0.027
Family history of cancer			
No	1.000		
Yes	1.598	0.990-2.578	0.055
Lymph node metastasis			
Negative	1.000		
Positive	1.633	1.276-2.089	<0.001
Hormone receptor status			
ER <sup>-</sup> and PR <sup>-</sup>	1.000		
ER <sup>+</sup> and/or PR <sup>+</sup>	1.366	0.970-1.925	0.075

<sup>a</sup>Adjusted using multivariate logistic regression model. OR, odds ratios; CI, confidence interval; ER, estrogen receptor, PR, progesterone receptor.

In order to assess the factors influencing the receipt of breast cancer adjuvant chemotherapy, all the possible factors were included in the univariate analyses. As indicated in Table II, certain factors, including the patient's menopausal status ( $P=0.310$ ), comorbidities ( $P=0.789$ ), history of breast disease ( $P=0.611$ ), tumor size ( $P=0.337$ ) or tumor stage ( $P=0.396$ ), were not significantly associated with the receipt of adjuvant chemotherapy ( $P>0.1$ ). Therefore, these parameters were temporarily excluded from the multivariate analysis.

Adjusted values were estimated by controlling covariates in a multivariate logistic regression model, including the patient's age at the time of diagnosis, occupational type, family history of cancer, lymph node metastasis and hormone receptor status. The results suggest that the patient's age at the time of diagnosis (OR=0.988, 95% CI=0.978-0.999, adjusted  $P=0.029$ ), occupational type (adjusted  $P=0.023$ ) and lymph node status (OR=1.633, 95% CI=1.276-2.089, adjusted  $P<0.001$ ) were statistically associated with the receipt of adjuvant chemotherapy ( $P<0.05$ ; Table III). Covariates, including patient's family history of cancer and hormone-receptor status were observed to be moderately associated with the receipt of adjuvant chemotherapy ( $0.05<P<0.10$ ). Subsequently, the multivariate models were re-estimated using all of the variables, including patient's age, occupational type, menopausal status, comorbidities, history of benign breast disease, family history of cancer, tumor size, lymph node status, tumor stage and hormone receptor status. The results suggest that the statistical pattern was not altered (data not shown).

The logistic regression models adopted in the present study exhibited high goodness-of-fit (Hosmer-Lemeshow,  $P>0.5$ ).

## Discussion

Adjuvant chemotherapy is vital for patients with invasive breast cancer, and has been associated with improved prognosis, as demonstrated by previous experimental data and clinical trials (19-21). Furthermore, consensus guidelines have identified subsets of female patients with invasive breast cancer that benefit from appropriate adjuvant chemotherapy (5,22,23). Previous studies have suggested that numerous factors, including age, comorbidities, and variability in provider recommendation, were associated with the receipt of adjuvant chemotherapy by females in Western countries (24-28). Since adjuvant chemotherapy is generally recommended to patients with invasive breast cancer, cases of carcinoma *in situ* were not included in the present study. Records of those patients who were recommended chemotherapy but refused it were used to identify and recruit suitable candidates for the present study.

In the present study it was observed that a large number of peasants decided against receiving adjuvant chemotherapy, as compared with laborers, housewives, and, particularly, teachers and health professionals. This may be due to rural-urban disparities in education levels, lifestyles and cultural values of females in China (15,29,30). In economically developing countries such as China, urban females are usually exposed to cultural globalization and better education, as compared with those in rural areas. Therefore, urban females tend to believe in modern medicine and are more familiar with the benefits of adjuvant chemotherapy (14,15). The present study also demonstrated that the patient's age at the time of diagnosis was associated with the rate of receipt of adjuvant chemotherapy (8,31-33). The results suggested that a reduced number of elderly females accepted adjuvant chemotherapy, as compared with young females (OR=0.988/year). In practice,



the tolerance of elderly patients to chemotherapy is reduced, as compared with in young females, which may explain the apparently stronger will for the elderly to adopt a more conservative type of treatment (22,34,35). The fact that a large number of patients with positive lymph node metastasis were willing to receive adjuvant chemotherapy may be due to the importance of lymph node status on patient survival. Consequently, doctors may have encouraged these patients to receive the treatment (5,6,22).

The present study possesses several limitations. Patients who did not receive adjuvant chemotherapy were regarded as in-compliant patients, because they were recommended to receive the treatment but refused to do so. However, in certain cases, doctors did not offer chemotherapy to the patients, despite being indicated in the recommended guidelines. In those cases, the patients should not be considered in-compliant, despite not receiving adjuvant chemotherapy. The patients who were not recommended to receive chemotherapy by their doctors due to their old age or other reasons, were excluded from the present study. In addition, the level of education of the patients was not included as a confounding variable in the analyses, since the patient registration system and medical records did not contain information regarding the patients' education, and the majority of patients would not provide their certificates of education, since it was considered troublesome, private and usually unnecessary. However, the education levels of the patients may be a relevant factor in the present study.

In conclusion, the results of the present study suggest that the occupational type of patients is independently associated with the receipt of adjuvant chemotherapy in China. This observation may provide a novel strategy for physicians to improve patient's compliance with adjuvant chemotherapy. Further studies in other developing countries are required in order to validate these observations.

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