

Accumulation of p53 is prognostic for aromatase inhibitor resistance in early-stage postmenopausal patients with ER-positive breast cancer

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Objective: Studies have indicated that p53 protein accumulation exerts an adverse effect on the survival of breast cancer patients; however, the prognostic value of p53 protein accumulation for aromatase inhibitor (AI) resistance in ER-positive breast cancer is uncertain.

Methods: The expression level of p53 protein was detected by immunohistochemistry in primary early-stage ER-positive breast tumor specimens from 293 postmenopausal breast cancer patients who received first-line AI treatment (letrozole, anastrozole, or exemestane) until relapse, and analysis was performed to determine whether expression of p53 protein affected the response to endocrine therapy.

Results: Of the 293 invasive ductal carcinomas, 65.4% were positive for p53 protein expression. All patients received AI therapy as first-line treatment until relapse. The 5-year disease-free survival rates in p53-positive and p53-negative patients were 78% and 89%, respectively. Patients with primary breast tumors that had p53 protein accumulation showed significantly more resistance to AI treatment (hazard ratio=1.729, 95% confidence interval=1.038–2.880, $P=0.035$).

Conclusion: This study demonstrated that p53 protein accumulation was helpful in choosing patients who may benefit from AI treatment and is a prognostic marker in ER-positive early-stage breast cancer.

Keywords: p53, breast cancer, prognosis, endocrine resistance

Introduction

Aromatase inhibitors (AIs) are the standard therapy for postmenopausal ER-positive breast cancer patients, and it was suggested that AIs were superior to tamoxifen in postmenopausal patients from the ATAC clinical trial.¹ However, a large number of patients unavoidably developed drug resistance after initial use of AIs, which leads to worse survival outcomes. The potential mechanisms behind either intrinsic or acquired endocrine resistance involve ER-coregulatory proteins and cross-talk between the ER pathway and other growth factor-signaling networks.^{2,3} Knowledge of the molecular mechanisms that regulate the activity of the estrogen-signaling network has enabled the appearance of new ways of overcoming endocrine resistance.

Recently, factors such as human epidermal growth factor receptor-2 (HER2) expression have been strongly associated with overall survival prognosis and decreased effectiveness of adjuvant endocrine therapy with tamoxifen.⁴⁻⁶

Identification of more valid prognostic markers such as the expression of the mutant p53 protein encoded by the TP53 tumor suppressor gene – markers that are reproducible, easily assessable, and independent in predicting clinical outcome – would have a useful impact on cancer treatment decisions. Nearly one-third of breast tumors

carry mutations in the p53 gene that are associated with high histological grade and rapid progression.⁷ The p53 protein detected by immunohistochemical (IHC) assays was usually nuclear accumulation of the protein, which is associated with conformational alterations and a prolonged half-life of the encoded protein.^{8,9} Yamashita et al¹⁰ analyzed the expression of factors such as HER2, p53, and Ki67 in 506 invasive ductal carcinoma tissues and found that the coexistence of HER2 overexpression and p53 protein accumulation was a strong prognostic marker in breast cancer.

Studies have reported the predictive value of p53 alterations for response to chemotherapy at either the gene level or protein level. Many of these studies showed that p53 alterations predict resistance to anthracyclines;^{11–17} cyclophosphamide, methotrexate, and fluorouracil; or other agents.^{18–20} Many studies have investigated the relationship between p53 status and response to endocrine therapy.^{21–25} One study²⁵ found a value for p53 in predicting endocrine therapy resistance. Kai et al²⁶ reported that p53 overexpression was a significant factor in predicting resistance to third-generation AIs in hormone-sensitive recurrent or advanced breast cancer. In relation to response to third-generation AIs, the patients with p53-overexpressed tumors had a lower RR (21.4%) than those without (34.6%) ($P=0.06$).²⁶ However, the prognostic significance of p53 in early-stage breast cancer is uncertain. Given the lack of data about p53 overexpression and disease-free survival (DFS) in patients with ER-positive early-stage breast cancer treated with AIs, we conducted this study to evaluate whether p53 overexpression affects breast cancer outcomes among postmenopausal women with ER-positive early-stage breast cancer.

Patients and methods

Patients and specimens

An informed consent form was signed by each participant, and appropriate ethical committee approval was obtained. A total of 293 stage I–II primary breast cancer samples from postmenopausal ER-positive patients with invasive ductal carcinoma were collected at the Department of Breast Surgery at the Fudan University Shanghai Cancer Center (Shanghai, People's Republic of China) between January 2000 and December 2006. The patients in this cohort study underwent either a mastectomy and axillary lymph node dissection or breast conservation surgery. All the patients received first-line AI treatment (letrozole, anastrozole, or exemestane) until relapse. Therapeutic regimen decisions were based on the Chinese Anti-Cancer Association

guidelines for the diagnosis and treatment of breast cancer. Each case was given a unique identifier and linked to a database containing clinicopathological data. Patient information and tumor pathology are summarized in Table 1. In this study, the patients were regularly followed, and the clinical outcome of 293 cases was obtained, with the last update occurring in September 2014. The median follow-up time was 72 months (range, 6–140 months).

IHC staining for p53 protein

To identify whether p53 accumulation influenced response to AI treatment, we performed IHC assay. Anti-p53 (Clone

Table 1 Summary of the association between patients' baseline characteristics and disease-free survival for all patients

Characteristics	No of patients	Log-rank test, <i>P</i>
All patients	293	
Age (years)	59 (51–84)	$P \leq 0.01$
50–65	231 (78.8%)	
66–69	27 (9.2%)	
≥ 70	35 (9.2%)	
Diabetes mellitus	23 (7.8%)	$P=0.002$
TNM stage		$P=0.001$
I	57 (19.5%)	
II	206 (70.3%)	
III	30 (10.2%)	
Histological grade		$P=0.004$
I	6 (2.0%)	
2	248 (84.6%)	
3	39 (13.3%)	
Vascular invasion		$P=0.427$
Yes	43 (14.7%)	
No	250 (85.3%)	
Lymph node status		$P \leq 0.01$
0	162 (55.3%)	
1–3	74 (25.3%)	
4–6	36 (12.3%)	
≥ 10	21 (7.2%)	
p53 status		$P=0.025$
Negative	101 (34.5%)	
Positive	192 (65.5%)	
PR status		$P=0.238$
Negative	61 (20.8%)	
Positive	232 (79.2%)	
HER2/neu status		$P=0.442$
Negative or positive	260 (88.7%)	
2+ or 3+	33 (8.7%)	
Chemotherapy		$P=0.582$
Undo	97 (33.1%)	
Do	196 (66.9%)	
Radiation therapy		$P=0.027$
Yes	13 (3.4%)	
No	280 (95.6%)	

Abbreviations: PR, progesterone receptor; HER2/neu, human epidermal growth factor-2.

DO-7, DAKO, Carpinteria, CA, USA) antibodies were used at 1:100 dilution with a 10-minute high-temperature antigen retrieval in citrate buffer (pH=6.0). Detection was by EnVision+ (DAKO) with diaminobenzidine chromogen as per routine protocol. Known positive and negative controls were used to ensure the quality control of staining.

Evaluation of IHC variables

The score used for all subsequent analyses was the average across the available cores. All IHC slides were examined by light microscopy by two independent pathologists who were blinded to patient outcome. The staining was graded by percentage of cells stained (0, no staining; 1, 0% to <25%; 2, 25%–50%; 3, 50%–75%; 4, 75%–100%) and the intensity of staining (0, negative; 1, weak; 2, moderate; 3, strong). Those two scores were combined and produced a final score that ranged from 0 to 12. A score of 0 was defined as negative and 1–12 as positive, while scores of 9–12 for strong membranous staining (DAKO score 3+) were defined as strong positive.

Statistical analysis

The follow-up period was defined as the time from surgery to the last observation for censored cases or relapse/death for complete observations. DFS was defined as the time from the date of primary surgery to the date of relapse, diagnosis of contralateral breast cancer, and breast cancer-specific death. The categories listed were all considered as DFS events. Patients with study end date and loss of follow-up were all regarded as censored cases. The DFS probability was performed by Kaplan–Meier log-rank test. Univariate and multivariate analyses were performed using the Cox risk proportion model. Statistics were analyzed

using SPSS 16.0 (SPSS Inc, Chicago, IL, USA). All *P*-values are two-sided, and *P*-values less than 0.05 were considered significant.

Results

Patient characteristics

Initially, a total of 293 ER-positive early-stage invasive ductal breast cancer cases were included in this study. The clinicopathological characteristics of the cohort study are summarized in Table 1. All patients were postmenopausal with a median age of 59 years at the time of diagnosis. After a mean follow-up time of 72 months, 83 of the 293 patients experienced disease recurrence. Risk factors that could potentially influence DFS were evaluated in univariate analyses for each of the 13 baseline quartile-based categorical and dichotomous variables. Among these variables, five were found to be associated with a significant increase in the risk of locoregional recurrence and distant metastasis, including advanced age, diabetes mellitus, high pathological stage, high histological grade, lymph node metastasis, and prior radiotherapy (Table 1). However, only four covariates were significantly associated with increased risk of locoregional recurrence and distant metastasis after adjustment for all other variables in the full multivariate model. These included advanced age (hazard ratio [HR]=1.988, 95% confidence interval [CI]=1.511–2.617, *P*<0.01), high pathological stage (HR=2.270, 95% CI=1.399–3.681, *P*=0.001), and high histological grade (HR=2.328, 95% CI=1.312–4.133, *P*=0.004). The four variables that were associated with a statistically significant increase in risk of locoregional recurrence and distant metastasis remained significant covariates after applying stepwise backward elimination of all nonsignificant variables in the multivariate model (Table 2).

Table 2 Summary of the association between patients' baseline characteristics and disease-free survival: Cox univariate and multivariate regression analysis

Factors	Univariate analysis			Multivariate analysis		
	<i>P</i> -value	HR	95% CI	<i>P</i> -value	HR	95% CI
Age	≤0.01	1.861	1.451–2.388	≤0.01	1.988	1.511–2.617
Diabetes mellitus	0.002	2.567	1.419–4.644			
Lymph node status	<0.009	1.785	1.459–2.183			
Histological grade	0.002	2.211	1.335–3.660	0.004	2.328	1.312–4.133
TNM stage	0.001	1.983	1.323–2.972	0.001	2.27	1.399–3.681
Vascular invasion	0.414	1.271	0.715–2.260			
p53 expression	0.027	1.749	1.066–2.871	0.035	1.729	1.038–2.880
PR status	0.226	0.737	0.449–1.208			
HER2/neu status	0.442	1.283	0.680–2.423			
Chemotherapy	0.582	0.88	0.557–1.389	0.306	0.62	0.249–1.548
Radiation therapy	0.01	2.642	1.266–5.513			

Abbreviations: HR, hazard ratio; CI, confidence interval; PR, progesterone receptor; HER2/neu, human epidermal growth factor-2.

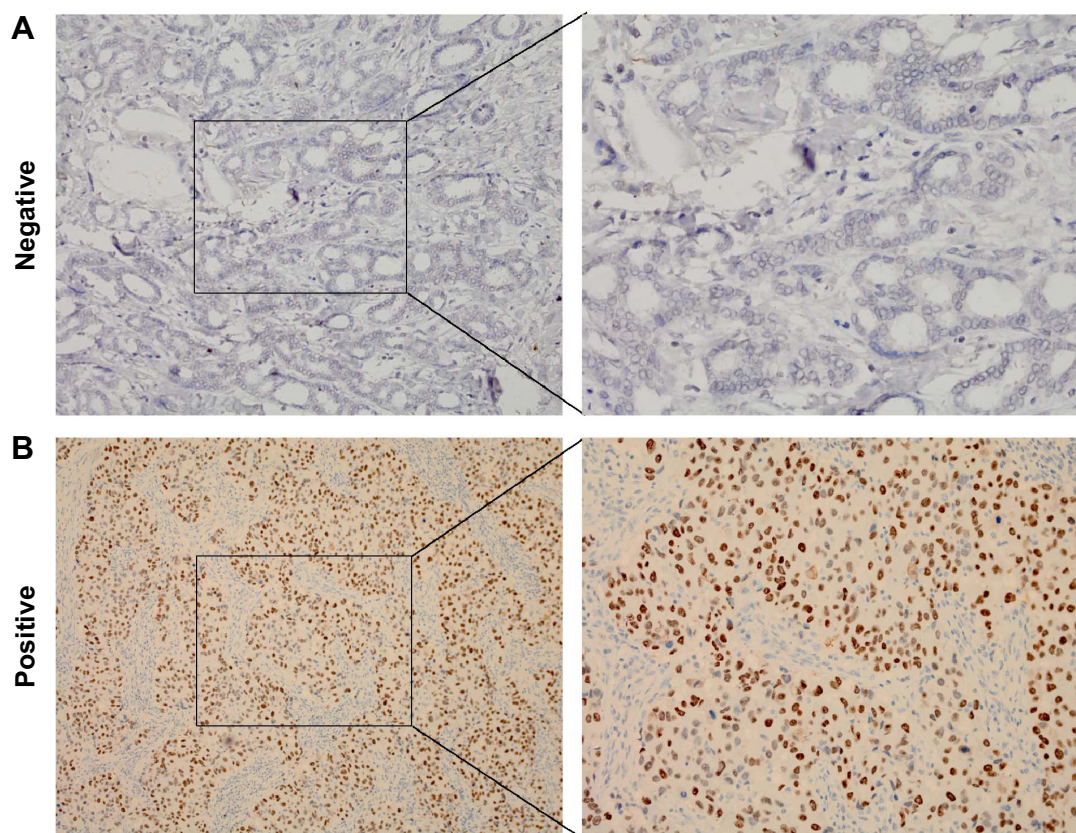


Figure 1 Representative p53 immunohistochemical staining is presented in the large (400× magnification) and small images (100× magnification) in breast-invasive ductal carcinoma. **Notes:** (A) Negative staining for p53. (B) Positive staining for p53.

p53 protein expression in breast cancer patients

In the cohort of 293 patients, IHC was used for p53 protein detection (Figure 1). Positive p53 staining was detected in 65.4% (N=191; Table 1) of tumors according to the scoring criterion described previously.

p53 protein accumulation is associated with decreased DFS in postmenopausal ER-positive breast cancer patients

To evaluate the clinical value of p53 protein accumulation in ER-positive breast cancer, we analyzed the relationship between p53 expression and DFS. Both univariate and adjusted multivariate survival analyses revealed a significant difference between the p53-positive and p53-negative groups. In this cohort, positive p53 staining cases exhibited a higher likelihood for disease events (HR=1.749, 95% CI=1.066–2.871, $P=0.027$; Table 2) in univariate analysis and exhibited a similar trend upon multivariate analysis (HR=1.729, 95% CI=1.038–2.880, $P=0.035$; Table 2). Additionally, p53-positive patients generally exhibited poor DFS upon the Kaplan–Meier analysis ($P=0.025$; Figure 2).

Thus, these results strongly indicate that p53 protein accumulation is directly associated with recurrent disease for patients with breast cancer.

p53 protein accumulation is predictive of AI resistance in postmenopausal ER-positive breast cancer patients who received AI treatment

All patients received AI therapy as first-line treatment until relapse. To evaluate the predictive significance of p53 protein accumulation for responsiveness to single AI treatment, we performed a stratification analysis of 94 patients who received only AI treatment (since chemotherapy and radiotherapy would interfere with the result). Primary breast tumors with p53 protein accumulation were significantly more likely to exhibit resistance to endocrine therapy ($P=0.026$; Figure 3).

Discussion

This study demonstrates the new finding that a shorter disease-free interval in breast cancer for the ER-positive early-stage breast cancer patients treated with AIs is associated with p53 overexpression. All patients in this study

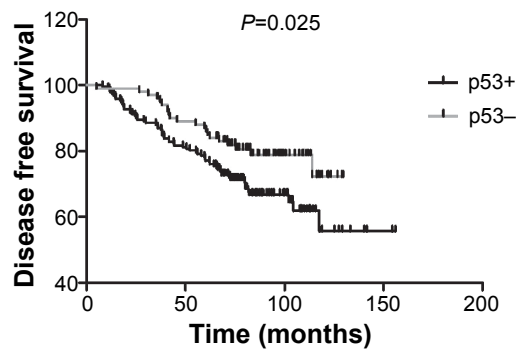


Figure 2 Effect of p53 protein accumulation on disease-free survival among 293 postmenopausal patients with ER-positive early-stage breast carcinoma. Disease-free survival was significantly worse in patients with p53 protein accumulation tumors than in patients without p53 protein accumulation tumors ($P=0.025$).

received AI treatment, which remains standard therapy for ER-positive postmenopausal patients.¹ However, most breast cancer patients failed to respond to AIs after initial use. A key finding from these analyses is the emergence of p53 overexpression as a significant and powerful prognostic variable for risk of locoregional recurrence and distant metastasis in ER-positive early-stage breast cancer patients treated with AIs.

Notably, p53 gene codes for a nuclear phosphoprotein that is normally expressed at low levels in all human cells and is able to regulate cell growth and division.²⁷ The potential role of p53 as a prognostic biomarker in oncology has long been recognized. Nearly one-third of breast tumors carry mutations in the p53 gene, which are correlated with high histological grade and rapid progression.⁷ Silvestrini et al²⁷ found that p53 was an independent prognostic marker in lymph node-negative breast cancer patients. In the 2005 ASCO Annual Meeting, Kai et al²⁶ reported that p53 overexpression was a significant factor in predicting resistance to third-generation AIs in hormone-sensitive recurrent or advanced breast

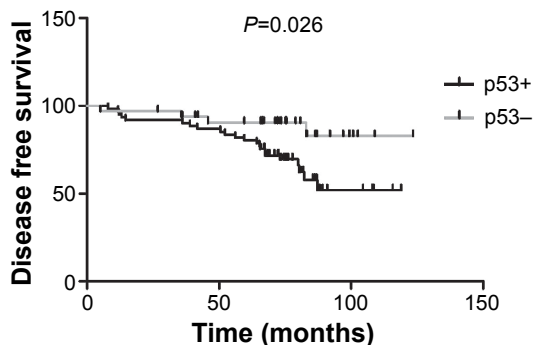


Figure 3 Effect of p53 protein accumulation on disease-free survival among 94 postmenopausal patients with ER-positive early-stage breast carcinoma who received only aromatase inhibitor treatment. Primary breast tumors with p53 protein accumulation were significantly more likely to exhibit resistance to aromatase inhibitor treatment ($P=0.026$).

cancer. Recently, studies in whole-genome analysis indicated that p53 mutations were significantly correlated with AI resistance.²⁸ Taken together, these various analyses support the potential prognostic value of p53 overexpression across several studies.

In this current study, we found that p53 accumulation was a significant prognostic factor in patients who received no chemotherapy and radiotherapy. It is well known that chemotherapy could improve DFS in several cancer types; thus, we chose a group that only received AI treatment, which eliminated the confounding factors. The result showed that in a single AI-treated group, p53 protein accumulation was predictive for drug resistance.

Studies found that patients with higher p53 had a worse survival; however, p53 expression was not correlated with response to tamoxifen in patients with metastatic breast cancer.²³ To the contrary, Berns et al²⁵ found that in patients with metastatic breast cancer, p53 expression detected by enzyme immunoassay of cytoplasmic extracts from primary tumors was a predictor of tamoxifen resistance. Further studies to investigate the association between effectiveness of endocrine therapy drug and p53 status are essential to clarify the role of p53 in endocrine therapy resistance. In addition, the conflicting results may be due to different evaluation methods of p53 status. Geisler et al¹³ reported that nearly 30% of all mutations in primary breast cancer (particularly those of the nonsense type) are not detected. Studies assessing p53 status by deoxyribonucleic acid sequencing have found mutations that predict resistance to endocrine therapy.¹³

Different mutations of p53 result in different biological effects.^{29–31} The effect of TP53 status on endocrine therapy has been reported by two retrospective studies. These studies indicated that TP53 status may influence response to tamoxifen.^{32,33} Studies in mouse xenograft models have also suggested that response to tamoxifen is reduced in the absence of p53. p53 mutation plays a significant role in the molecular pathogenesis of breast cancer and could influence its hormone sensitivity. Different regions of the molecule perform distinct functions, and mutations in these areas may result in the loss of specific functions, depending on where they occur.³⁴ Elledge et al²³ found that in the presence of wild-type p53, mutant 179 p53 protein does not result in tamoxifen resistance. However, the results do not exclude the possibility that other p53 mutational types could result in tamoxifen resistance.

p53 mutation and/or deletion cause amino acid substitutions and may change the conformation of the p53 molecule, which leads to increased expression of the protein and

a higher steady-state protein level.³⁵ Therefore, overexpression of p53 protein and mutation of the p53 gene are closed related events. The half-life of the wildtype p53 was very short. The p53 protein detected by IHC assays was usually nuclear accumulation of the protein.^{8,9} The current study indicated that p53 protein accumulation, which generally has been considered indicative of p53 gene mutation,³⁶ was associated with AI resistance in early-stage postmenopausal patients with ER-positive breast cancer.

There are potential limitations in this study worthy of note. IHC was a major method used to identify p53 protein status in tumor sections, however, it has more or less bias. If p53 is to be used in the future as a prognostic factor for survival for breast cancer patients, it is desirable to agree on a common approach to p53 measurements across centers. This study had a limited sample size, which may weaken the reliability of all the results.

Based on the current study, the combination of p53 with other prognostic factors into a weighted prognostic score for DFS in ER-positive postmenopausal patients treated with AIs would be a valuable next step. Such a score would then require confirmation and validation in a future prospective study before adoption into new management guidelines. Assessment of p53 status should therefore be incorporated into future large breast cancer studies, and p53 may also be an important stratification factor in the design of future randomized trials.

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Disclosure

The authors declare that they have no competing interests.

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