Original Article

Value of pre-treatment biomarkers in prediction of response to neoadjuvant endocrine therapy for hormone receptor-positive postmenopausal breast cancer

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Objective: To determine the predictive ability of biomarkers for responses to neoadjuvant endocrine therapy (NET) in postmenopausal breast cancer.

Methods: Consecutive 160 postmenopausal women with $T_{1-3}N_{0-1}M_0$ hormone receptor (HR)-positive invasive breast cancer were treated with anastrozole for 16 weeks before surgery. New slides of tumor specimens taken before and after treatment were conducted centrally for biomarker analysis and classified using the Applied Imaging Ariol MB-8 system. The pathological response was evaluated using the Miller & Payne classification. The cell cycle response was classified according to the change in the Ki67 index after treatment. Multivariable logistic regression analysis was used to calculate the combined index of the biomarkers. Receiver operating characteristic (ROC) curves were used to determine whether parameters may predict response.

Results: The correlation between the pathological and cell cycle responses was low (Spearman correlation coefficient =0.241, P<0.001; Kappa value =0.119, P=0.032). The cell cycle response was significantly associated with pre-treatment estrogen receptor (ER) status (P=0.001), progesterone receptor (PgR) status (P<0.001), human epidermal growth factor receptor 2 (Her-2) status (P=0.050) and the Ki67 index (P<0.001), but the pathological response was not correlated with these factors. Pre-treatment ER levels [area under the curve (AUC) =0.634, 95% confidence interval (95% CI), 0.534-0.735, P=0.008] and combined index of pre-treatment ER and PgR levels (AUC =0.684, 95% CI, 0.591-0.776, P<0.001) could not predict the cell cycle response, but combined index including per-treatment ER/PR/Her-2/Ki67 expression levels could (AUC =0.830, 95% CI, 0.759-0.902, P<0.001).

Conclusions: The combined use of pre-treatment ER/PgR/Her-2/Ki67 expression levels, instead of HR expression levels, may predict the cell cycle response to NET.

Key Words: Breast cancer; neoadjuvant endocrine therapy (NET); responsiveness; predictive value

Submitted Mar 03, 2011. Accepted for publication May 10, 2011

doi: 10.3978/j.issn.1000-9604.2013.08.01

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Introduction

Endocrine therapy is a standard adjuvant treatment for endocrine-responsive breast cancer. Estrogen receptor (ER) positivity and/or progesterone receptor (PgR) positivity are indications for endocrine therapy (1,2). However, there are factors other than receptor status that can influence endocrine responsiveness. In the P024 trial, the clinical response rate was less than 70% in strongly hormone

receptor (HR)-positive breast cancers with 4 months of neoadjuvant letrozole treatment (3); the IMPACT trial had similar results (4). Recent studies have demonstrated that a four-marker immunohistochemical (IHC) panel [ER, PR, human epidermal growth factor receptor 2 (Her-2), and Ki67], may have the ability to guide adjuvant therapy and predict long-term outcomes for HR-positive breast cancers (5). And the four markers were used to surrogate definitions of intrinsic subtypes of breast cancer in recent guidelines (2). However, the correlations between the four markers and responses to neoadjuvant endocrine therapy (NET) were still controversial.

NET provides a unique opportunity to assess tumor responses to treatment and to select molecular biomarkers that may be able to predict responses. However, there remains uncertainty regarding the standard classification of responses to NET.

The aim of this study was to determine the predictive ability of ER, PgR, Her-2 and Ki67 for responses to NET for HR-positive postmenopausal breast cancer. Furthermore, the associations between ER, PgR, Her-2 and Ki67 expression levels and responses to NET as well as the correlation between the responses classified in different systems were investigated.

Patients and methods

Patients

Eligible cases were retrospectively screened from the Breast Cancer Center of the Peking University Cancer Hospital & Institute, database using the following criteria: postmenopausal $T_{1-3}N_{0-1}M_0$ invasive breast cancer, strongly HR-positive cancer (more than 50% of tumor cells positive for ER or PgR), and intention to receive endocrine therapy alone as the adjuvant treatment (Arimidex 1 mg/d for 16 weeks) followed by surgery.

IHC analysis of ER, PR, Her-2 and Ki67

IHC analyses of pre- and post-treatment biomarkers were centrally repeated. Four- percent-formalin-fixed, paraffin-embedded pre-treatment needle biopsy and post-treatment surgical specimens were collected and used to prepare 4 μm sections. Whole tumor sections were incubated with the specific primary mouse monoclonal antibodies to ER (clone SP1), PgR (clone 1E2) or Her-2 (clone 4B5) (all from Ventana, Arizona, USA), while Ki67 labeling index was assessed using mouse monoclonal antibody MIB-1 (Dako, Glostrup, Denmark). Avidin-biotin complex was also purchased from Ventana Medical Systems (Arizona, USA). A Benchmark XT Staining Instrument (Ventana Medical Systems, Inc., Arizona, USA) was used for automated immunostaining.

Stained slides were digitized with an Ariol MB-8 automatic image analysis system (Applied Imaging Inc., San-Jose, California, USA). All slides were scanned at 5× objective magnification, and representative areas of invasive tumors were selected by an experienced pathologist. Then, all selected areas were scanned once more at 20× objective magnification, and the intensity of positively stained nuclei and membranes, the completeness of the positively stained membranes and the percentage of positive cells of all stained sections were obtained automatically.

ER and PgR were scored as percentages of stained tumor cells (6,7). The cutoff for ER or PgR positivity was ≥10% positive cells. Her-2 IHC was scored by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) criteria, which assess the intensity and completeness of membrane staining (7).

A score of 0/+ was considered negative, and +++ was considered over-expression. The Ki67 index was the percentage of Ki67-positive cancer nuclei. Low proliferation was defined as Ki67 staining of <15% tumor cells (8).

Evaluation of response

The pathological responses of primary tumors were intensively evaluated by two dedicated pathologists according the Miller and Payne grading system (9). The grades were defined as follows: Grade 1 (G1): no change or some alteration to individual malignant cells, but no reduction in overall cellularity; Grade 2 (G2): a minor loss of tumor cells, but the overall cellularity is still high, up to 30% loss; Grade 3 (G3): an estimated reduction in tumor cells between 30% and 90%; Grade 4 (G4): a marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; greater than 90% loss of tumor cells; Grade 5 (G5): no malignant cells identifiable in sections from the site of the tumor, only vascular fibroelastotic stroma remains, often containing macrophages. Ductal carcinoma *in situ* (DCIS) may be present. In this study, G5 was defined as pathological complete response (pCR), G3/4 were defined as pathological partial response, and G1/2 were defined as no response. A post-treatment Ki67 index value of ≤1% was

Table 1 Patients' characteristics

Parameters		n	%
Age (years)			
Median		66	
Range		48-90	
Histology			
IDC		138	86.3
ILC		10	6.2
Others		12	7.5
Tumor size (Ultrasound)			
≤2 cm		95	59.4
2-5 cm		64	40.0
>5 cm		1	0.6
Pre-treatment node status (pathology)			
Negative		90	56.3
Positive		53	33.1
Unknown		17	10.6
Hormone receptors			
ER + and PgR +		111	69.4
ER + and PgR -		26	16.2
ER - and PgR +		10	6.3
ER - and PgR -		13	8.1
ER	<10%	23	14.4
	10-50%	4	2.5
	≥50%	133	83.1
PgR	<10%	39	24.4
	10-50%	34	21.2
	≥50%	87	45.4
Her-2 status			
0, +		115	71.9
++		36	22.5
+++		9	5.6
Pre-treatment Ki67			
≤15%		82	51.3
>15%		78	48.7
Surgery			
Breast-conserving surgery		68	42.5
Mastectomy		92	57.5

defined as cell cycle complete response (cell cycle CR), a decrease in the Ki67 index with an index value of >1% after therapy was defined as cell cycle partial response, and no decrease was defined as no response (10).

Statistical analysis

Pearson's chi-square test was used to test the associations between pre-treatment ER/PgR/Her-2/Ki67 status and response. Spearman correlations and Kappa tests were used to analyze the correlation between the responses classified using different systems. Spearman correlation coefficient <0.4 was considered a low correlation, ≥0.4 and <0.7 was considered a moderate correlation, and ≥0.7 was considered a high correlation. Kappa value <0.4 was considered a low consistency, ≥0.4 and <0.7 was considered a moderate consistency, and ≥0.7 was considered a high consistency. Multivariate logistic regression analysis was used to calculate the combined index including ER, PR, Ki67 (as continuous variables) and Her-2 expression (0, +, ++ *vs.* +++). Receiver operating characteristic (ROC) curves were used to determine whether parameters can predict responses, and the area under curves (AUC) >0.75 was considered as the parameter capable of predicting the response.

Results

Patients characteristics

From October 2004 to March 2010, a consecutive cohort of 174 $T_{1-3}N_{0-1}M_0$ primary breast cancer cases met the selection criteria. Fourteen cases were excluded from analysis because the specimens were not large enough to prepare new slides. Finally, data for 160 patients were analyzed retrospectively. The characteristics of the patients are summarized in *Table 1*.

Evaluation of response

The pCR rate was 5.6% (9/160), the pathological partial response rate was 50.0% (80/160), and the pathological no response rate was 44.4% (71/180). The cell cycle complete response rate was 24.4% (39/160), the cell cycle partial response rate was 46.9% (75/160), and the cell cycle no response rate was 28.7% (46/160, *Table 2*).

The correlation between the pathological response and cell cycle response was low (Spearman correlation coefficient = 0.241, P<0.001; Kappa value =0.119, P=0.032; *Table 2*).

Associations between pre-treatment ER/PgR/Her-2/Ki67 status and responses

The pathological response was not significantly associated with pre-treatment ER status, PgR status, Her-2 status,

Table 2 Correlation between the pathological response and the cell cycle response

Pathological response	Total	Cell cycle response					
		No response		Partial response		Complete response	
		n	%	n	%	n	%
No response	71	24	33.8	36	50.7	11	15.5
Partial response	80	22	27.5	39	48.8	19	23.8
Complete response	9	0	0	0	0	9	100

Table 3 Association between pre-treatment biomarkers and the pathological response

Biomarkers		Total	No response		Response		P
			n	%	n	%	
ER	Negative	23	9	39.1	14	60.9	0.584
	Positive	137	62	45.3	75	54.7	
PgR	Negative	39	17	43.6	22	56.4	0.910
	Positive	121	54	44.6	67	55.4	
Her-2	0, +, ++	151	67	44.4	84	55.6	0.997
	+++	9	4	44.4	5	55.6	
Ki67	≤15%	82	32	39.0	50	61.0	0.162
	>15%	78	39	50.0	39	50.0	

Table 4 Association between pre-treatment biomarkers and the cell cycle response

Biomarkers		Total	No response		Response		P
			n	%	n	%	
ER	Negative	23	13	56.5	10	43.5	0.001
	Positive	137	33	24.1	104	75.9	
PgR	Negative	39	20	51.3	19	48.7	<0.001
	Positive	121	26	21.5	95	78.5	
Her-2	Negative	151	46	30.5	105	69.5	0.050
	Positive	9	0	0	9	100	
Ki67	≤15%	82	37	45.1	45	54.9	<0.001
	>15%	78	9	11.5	69	88.5	

and Ki67 index (*Table 3*). The cell cycle response was significantly associated with pre-treatment ER status, PgR status, Her-2 status, and the Ki67 index (*Table 4*).

The PgR status was significantly associated with the cell cycle response in ER-positive patients (P=0.016). There were more cases with decreases in the Ki67 index among PgR-positive tumors than among PgR-negative tumors. Among ER-negative patients, there were more cases with decreases in the Ki67 index than among ER-positive patients, but this difference was not statistically significant (57.1% *vs.* 30.8%, P=0.251, *Table 5*).

Predictive value of pre-treatment ER/PgR/Her-2/Ki67 expression levels for the cell cycle response

Pre-treatment ER expression was not able to predict the cell cycle response after 16 weeks of neoadjuvant treatment with anastrozole for postmenopausal breast cancer [AUC =0.634, 95% confidence interval (95% CI), 0.534-0.735, P=0.008, *Figure 1*] or the combined index of pre-treatment ER and PgR (AUC =0.684, 95% CI, 0.591-0.776, P<0.001, *Figure 2*). However, the combined index including pre-treatment ER/PgR/Her-2/Ki67 expression levels may predict cell cycle

Table 5 Association between PgR status and cell cycle response among cases with different ER statuses

ER	PgR	Total	No response		Response		P
			n	%	n	%	
Negative	Negative	13	9	69.2	4	30.8	0.251
	Positive	7	3	42.9	4	57.1	
Positive	Negative	26	11	42.3	15	57.7	0.016
	Positive	111	22	19.8	89	80.2	

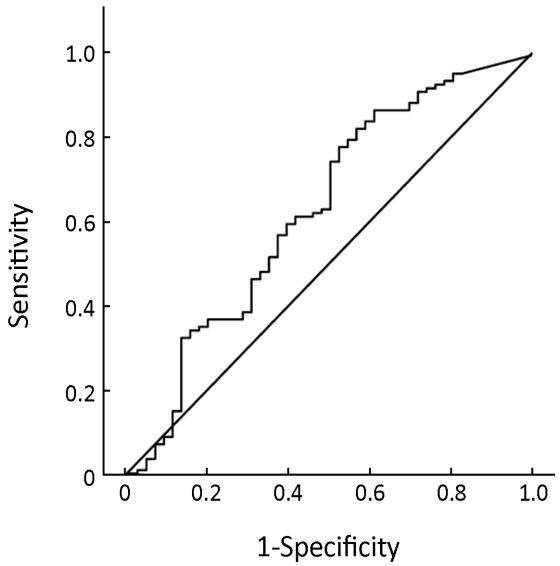

Figure 1 Predictive ability of ER with respect to the cell cycle response

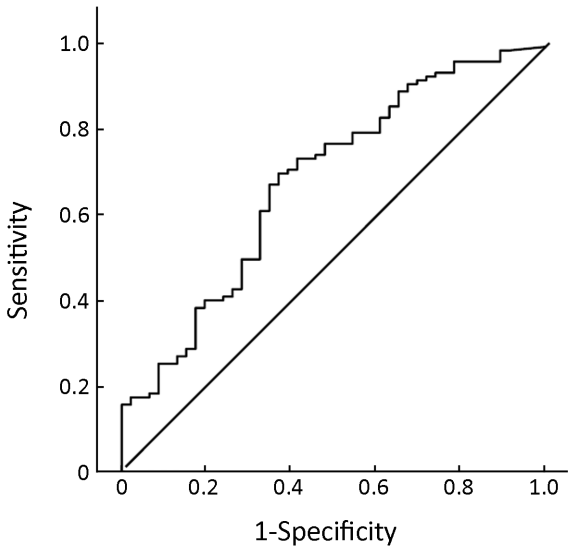

Figure 2 Predictive ability of the combined index including ER and PgR with respect to the cell cycle response

responses (AUC =0.830, 95% CI, 0.759-0.902, P<0.001, *Figure 3*). In Her-2-negative tumors (0 or +, n=115), the combined index including pre-treatment ER/PgR/Ki67 levels may predict the cell cycle response (AUC =0.850, 95% CI, 0.786-0.932, P<0.001, *Figure 4*) but was unable to predict the cell cycle CR (AUC =0.628, 95% CI, 0.515-0.743, P=0.036, *Figure 5*).

Discussion

NET is an excellent platform for predictive factor study, but a standard classification of responses has not been established. In previous studies, the clinical response has been most commonly used. However, the clinical response has the potential for factitious bias and is not reproducible. In addition, the clinical response is difficult to assess accurately, especially in small cancers (11). Finally, the clinical response might not be related to survival (12).

Recent studies suggested that the pathological response may be a predictive factor for the long-term outcome following NET (13). And pathological response was generally used as an evaluation of response to primary endocrine therapy (14,15). Because pCR, a validated surrogate endpoint for neoadjuvant chemotherapy study, was uncommon after NET (3,4,16), we choose the Miller and Payne system to grade the residual invasive tumor and classify the pathological response to NET in this study.

Previous studies have suggested that changes in the Ki67 index after a period of endocrine therapy may be associated with treatment benefit and long-term outcomes (10,17,18). These data suggested that decrease of in the Ki67 index after a period of anti-hormone treatment could, at least to some extent, reflect the anti-proliferative effects of endocrine therapy and might be a candidate indicator of benefit from endocrine therapy. Furthermore, cell cycle CR, which represents a superior suppression of proliferation,

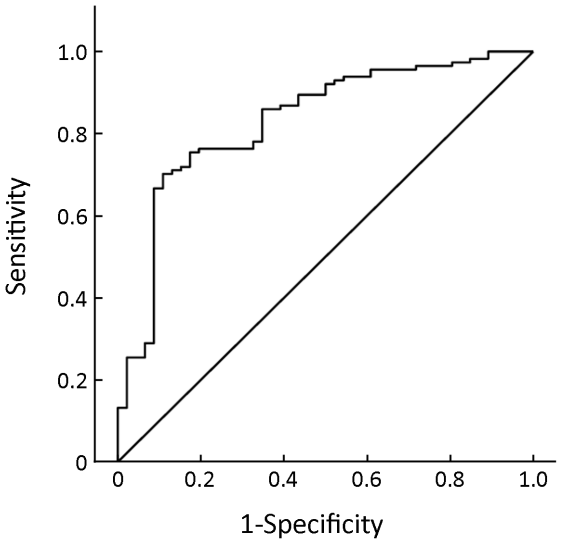

Figure 3 Predictive ability of the combined index including pre-treatment ER/PgR/Her-2/Ki67 expression levels with respect to the cell cycle response

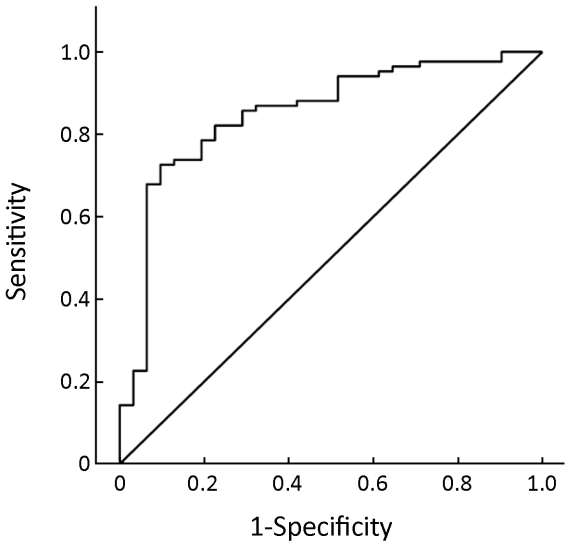

Figure 4 Predictive ability of the combined index including pre-treatment ER/PgR/Ki67 expression levels with respect to the cell cycle response in Her-2-negative cases

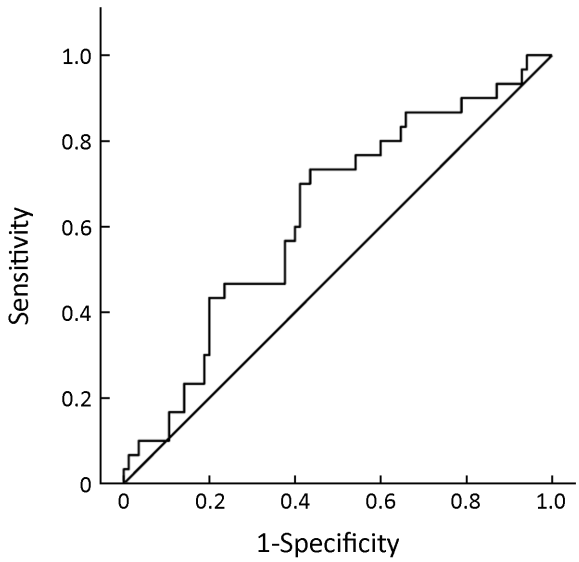

Figure 5 Predictive ability of the combined index including pre-treatment ER/PgR/Ki67 expression levels with respect to cell cycle CR in Her-2-negative cases

may be able to determine if a tumor is highly sensitive to endocrine therapy and to select eligible patients to safely avoid the use of adjuvant chemotherapy (10,12).

In this study, the correlation between the pathological response and the cell cycle response was low. In addition, the pre-treatment ER status, PgR status, Her-2 status, and Ki67 index were significantly associated with the cell cycle response but not the pathological response. This difference may be the result of the different mechanisms of these two evaluations. The pathological response was graded according to the changes in tumor cellularity after treatment, but the cell cycle response was assessed according to the inhibition of tumor proliferation. The main mechanism of breast cancer chemotherapy is cytotoxic action on tumor cells, and its key feature is a reduction of tumor cellularity (10). This fact may be the reason why the pathological response was validated to reflect the efficacy of neoadjuvant chemotherapy. However, the mechanism of endocrine therapy for breast cancer is primarily the inhibition of tumor cell proliferation without a cytotoxic effect. It is reasonable to hypothesize that the cell cycle response may be the better way to evaluate the efficacy of NET than the pathological response is.

The cutoff point for ER positivity has long been considered 10% positive cells (1). Recently, a 1% cutoff for ER positivity was set by the ASCO/CAP guidelines (6,19). In this study, the ER status was significantly associated with the cell cycle response, and a greater number of ER-positive (≥10% cells positive) cases showed cell cycle responses than ER-negative cases. However, 30.8% (4/13) of ER-negative tumors showed a cell cycle response after 16 weeks of NET

in PgR-negative cases. This result implies that the 10% cutoff might not be suitable for ER positivity. Our cohort was not large enough to address in this issue.

In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis, PgR played no role in ER-positive tumors in predicting the benefit of adjuvant tamoxifen therapy (20). In the ATAC trial, PgR may not be a predictive factor of the efficacy of endocrine therapy but was a prognostic factor for breast cancer (21,22). In the IMPACT study, Ki67 expression was reduced to a greater extent in PgR-positive tumors than in PgR-negative tumors after 2 weeks and 12 weeks of anastrozole neoadjuvant treatment (23). Our data demonstrate that the pre-treatment PgR status was significantly associated with the cell cycle response in our study group. There were more PgR-positive cases than PgR-negative cases that showed decreases in the Ki67 index after treatment, regardless of ER status, but our cohort was too small to observe a significant difference in ER-negative cases.

Although HR positivity (ER and/or PgR-positive) is indications for endocrine therapy (1,2,24), factors other than receptor status can influence endocrine responsiveness. Maggie *et al.* demonstrated that a four-marker surrogate IHC panel (ER, PR, HER2, and Ki67) can independently predict long-team outcomes for HR-positive breast cancers (5). Cuzick J *et al*. also suggested that an amount of prognostic information contained in the four IHC assays (25). In this study, neither pre-treatment ER expression nor the combined index of pre-treatment ER and PgR were able to predict the cell cycle response to NET, but the combined index of pre-treatment ER, PgR, Her-2 and Ki67 expression levels could predict this response. This result implies that the combined use of the pre-treatment four biomarker expression levels, instead of pre-treatment HR expression levels alone, may predict which patients could benefit from endocrine therapy.

Currently, it is difficult in clinical practice to distinguish which HR-positive, Her-2-negative breast cancers can be treated successfully with endocrine therapy, obviating the need for adjuvant chemotherapy (26). In this study, although the combined index of pre-treatment ER, PgR and Ki67 could predict the cell cycle response in HR-positive, Her-2-negative tumors, it was difficult to predict cell cycle CR, which identified tumors as highly sensitive to endocrine therapy in this sub-group. This result suggested that combined IHC analysis of ER, PgR, Her-2 and Ki67 may identify breast cancer patients who would benefit from endocrine therapy as mentioned above, but it is difficult to identify patients who could benefit sufficiently from endocrine therapy to obviate the need for chemotherapy.

In summary, our study demonstrated that the correlation between the pathological response and the cell cycle response to NET was low; the combined use of pre-treatment ER, PgR, Her-2 and Ki67 expression levels, instead of pre-treatment HR expression levels alone, may predict the cell cycle response after 16 weeks of neoadjuvant anastrozole treatment. In contrast, it was difficult to predict cell cycle CR in HR-positive, Her-2-negative tumors.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Ying M, He Y, Qi M, Dong B, Lu A, Li J, Xie Y, Wang T, Lin B, Ouyang T. Value of pre-treatment biomarkers in prediction of response to neoadjuvant endocrine therapy for hormone receptor-positive postmenopausal breast cancer. Chin J Cancer Res 2013;25(4):397-404. doi: 10.3978/j.issn.1000-9604.2013.08.01

