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The importance of EGFR as a biomarker in molecular apocrine breast cancer☆,☆☆

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Summary Molecular apocrine breast cancer (MABC) is a molecular subtype with a poor prognosis, and there is urgent need to find new therapeutic targets. Epidermal growth factor receptor (EGFR) plays an important part in regulating the biological behavior of tumor cells, and EGFR-targeted drugs have already been used in therapy for lung and colorectal cancers. The purpose of this study was to analyze the significance of EGFR expression in MABC. A total of 400 patients with invasive breast cancer were analyzed, including 200 MABC and 200 non-MABC cases. Immunohistochemistry and immunofluorescence were carried out to evaluate the expression of estrogen receptor, progesterone receptor, androgen receptor (AR), EGFR, epidermal growth factor receptor 2 (HER2), and other biomarkers. Two hundred twelve (53%) cases were positive for EGFR expression, including 173 MABC and 39 non-MABC cases. EGFR expression was positively associated with AR expression in MABC, as well as with more advanced tumor stage and high Ki67 expression. Patients with EGFR expression had worse outcomes than those without. As a prognosis biomarker, EGFR was significantly associated with poorer clinical outcomes, and the co-expression of EGFR and HER2 often predicted worse outcomes in MABC. This study suggests that the identification of new targets such as HER2 and EGFR may help with assessing the prognosis of patients with MABC. Using both AR and EGFR as therapeutic targets may be especially important in MABC and may help to guide the choice of suitable treatments for individual breast cancer patients.

1. Introduction

Breast cancer is the major reason of cancer-related deaths in female patients worldwide, and it is regarded as a heterogeneous disease, with subtypes manifesting substantial differences in their biological behaviors and requiring particular therapeutic methods. Although expression of the androgen receptor (AR) is correlated with that of the estrogen receptor (ER) and progesterone receptor (PR), it retains independent prognostic significance in breast cancer, which suggests that AR expression may define a specific breast cancer subtype [1]. Molecular apocrine breast cancer (MABC), which was first identified by Farmer et al [2], is characterized by increased androgen signaling and does not manifest all the histopathological traits

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which are characteristic of classical carcinomas with apocrine differentiation. The defining characteristics of MABC are ER and PR negative expression, together with AR positive expression; it therefore includes the triple-negative breast cancer (TNBC) and epidermal growth factor receptor 2 (HER2)–overexpression subtypes. Studies have shown that patients with TNBC and HER2-overexpression breast cancer have the shortest survival times [3,4], and MABC has also been reported as a molecular subtype with poor prognosis [5]. Therefore, new therapeutic targets for MABC are urgently needed.

Epidermal growth factor receptor (EGFR, ErbB1, or HER1) is 1 of the 4 members of the transmembrane ErbB family. EGFR plays an important part in the signal transduction pathways that regulate cellular function, including proliferation, differentiation, and regulation of anabolism in tumor cells [6,7]. EGFR-targeted treatments have been used as a standard of care in lung cancer and colorectal cancer for selected patient populations. Thus, many reports have focused on the role of EGFR in breast cancer [8,9]. However, although EGFR-targeted drugs have been evaluated in clinical trials in breast cancer, the response to therapy has not been optimal [10-12]. Recently, the antiproliferative effects of EGFR inhibitors in combination with antiandrogen therapy to decrease the amount of AR were reported [13]. Although MABC is characterized by AR positive expression, the correlation between AR and EGFR expression in MABC remained unknown. Additionally, until now, the expression and prognosis of EGFR in MABC have not been clear.

We hypothesized that combining EGFR with other receptors, such as AR and HER2, might provide useful diagnostic and prognostic biomarkers for MABC. Furthermore, this study aimed to analyze whether combining EGFR and AR or HER2 would be potential therapeutic targets for MABC, which might improve the life quality of patients with MABC during the process of this disease.

2. Materials and methods

2.1. Patients and groups

A total of 1000 patients with invasive breast cancer diagnosed between January 2007 and December 2011 were randomly selected. The participants were registered in the archives of the Department of Breast Cancer Pathology and Research Laboratory, Tianjin Medical University Cancer Institute and Hospital. This study was reviewed and approved by the Institutional Ethic Committee of Tianjin Medical University Cancer Institute and Hospital. Patients who had received preoperative treatments were excluded, as were those with bilateral primary breast cancers or a preceding carcinoma during the past 10 years. The clinicopathological date of those who were included in the study was available.

First, participants were classified into 2 subgroups based on the immunohistochemical analysis of ER, PR, and AR, including MABC (defined as ER−PR−AR+) and non-MABC (defined as ER±PR±AR−, ER±PR+AR+, and ER+PR−AR+; that is, except for MABC, the rest is non-MABC). Then, the same number of cases in the verified MABC and non-MABC subgroups, respectively, was randomly selected. Subsequently, all of the selected samples were detected using immunohistochemical analysis for EGFR, HER2, Ki67, and p53.

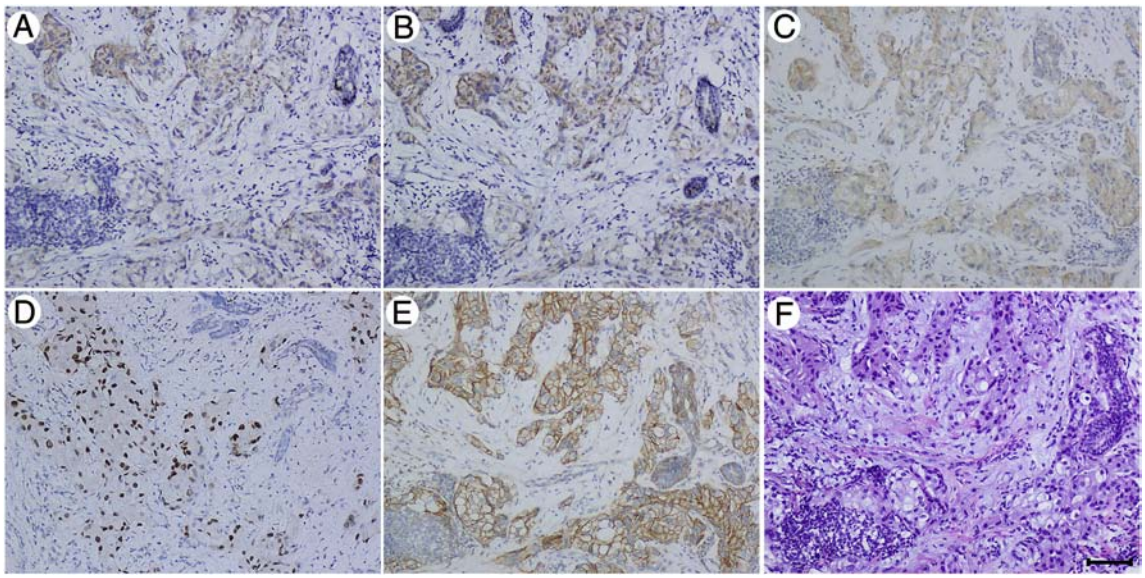

Fig. 1 An invasive breast cancer classified as MABC with EGFR-positive expression. Immunohistochemical staining of ER (negative) (A), PR (negative) (B), HER2 (negative) (C), AR (positive) (D), and EGFR (positive) (E). F, HE staining. Original magnification ×200 (bar = 40 μm).