Biomarker Profiling (Erbb2, P53, and PR) for Stage I of Breast Cancer

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ABSTRACT

Breast cancer (BC) accounts for one of the major health problems around the world. Since the diagnosis process can have great effect on therapy outcomes, we studied the biomarkers specific to breast tumors stage I based on examining different Iranian patients. Cases from different stages were examined to discover their highly expressed proteins. In addition, pathologic evaluations were performed as the diagnosis procedure. Considering positive percentage of over-expressed protein in different stages in the population, it is guessed that over-expression of ErBb2 and PR are positively correlated, while P53 is in negative correlation with them. Therefore, these molecules can probably account for stage I biological marker. This study suggests that alterations in over-expression of specific biomarkers in different stages may be associated to the stage classification, and can help achieve more effective therapies of this malignancy.

Keywords: Breast cancer; Biomarker; Detection; Staging; Treatment.

INTRODUCTION

Breast cancer as the most frequent malignancy in women in the East is a primary cause of death in women, with 1.15 million new cases and 410,000 deaths in 2002 [1], which is about 18% of women cancers [2]. Furthermore, it is the most common cancer among Iranian women with a considerable proportion in stage II or III at diagnosis [3]. Breast cancer occurs with an unregulated developing of abnormal cells in different parts of breast tissue which probably grows in milk ducts and glands of its tissue. The two main kinds of breast cancer are: ductal carcinoma and lobular carcinoma [4, 5]. In this malignant disease, about one-third of those with primary breast cancer have reappearance of micro metastasis after about 10 years. Consequently, it is essential to discover a reliable biomarker for examining this disease [6]. Despite new advances in the resolution of imaging techniques such as commonplace mammography, they still lack adequate sensitivity and specificity [6-8]. On the other hand, diagnosis based on molecular approaches has been shown promising in this field of study [9, 10]. Marker panels have the potential to detect cancer biomarker evaluations [11]. In fact, biological markers have been incrementally used for improving population screening, diagnosis, prognosis, therapeutic decisions, and staging [12], which have considerably decreased the mortality rates [4]. There are lots of established biomarkers as an indicator for breast cancer such as Human Epidermal Growth Factor Receptor 2 (HER2) (ErBbr2), which has been reported positive in breast cancer previously [13, 14], and estrogen receptor (ER), which is certainly the most prominent biomarker in breast cancer, in that it provides the index for sensitivity to endocrine treatment [15]. In addition, P53 is another comparatively reliable source for cancer analysis [16], and also PR as highly expressed protein in low stage tumors. Staging is one of the essential prognostic factors for patients with BC [17]. Indeed, amplification or over-expression of these genes have been revealed to play a key role in the pathogenesis and progression of definite aggressive forms of breast cancer and it has developed to become a significant biomarker and target of therapy for the disorder recently [18]. It is divided into loco

regional and distant or systemic based on the level of disease progress [19]. This research underlies the breast cancer staging diagnostic based on clinical markers examinations.

MATERIALS AND METHODS

A total number of 191 Iranian women patients were visited in Shohada Hospital between the years 1991 and 2001 that in average most of them were followed up for five years and validated for breast cancer tumors with different grades based on their pathological diagnosis. A standard medical history of all cases was obtained examining stages, recording of race, and dates of birth, diagnosis of breast cancer and last menstrual period, the date and type of therapy comprising: radiotherapy, chemotherapy, hormone therapy and surgery of the tumor, the time of first recurrence, and dates, agents and the recorded result of previous treatment of recurrent breast cancer. Based on these records, the average age among patients when were diagnosed with these stages was 45 years. Five stages of breast cancer in these patients were evaluated in this study; from low grade to invasive breast cancer, of which 21 were in stage 0, and 29, 61, 30, and 50 of them were in stage I, II, III and IV, respectively. Among them the percentage of highly amplified proteins were investigated by plotting methods.

RESULTS

Number of patients with three over-expressed markers in different grades is given in Table 1.

Table 1. Collection of population-based cancer staging with their markers presence

Markers / Stages	ErBb2	P53	PR	Total number of cases
0	8	16	8	21
I	19	11	23	29
II	31	32	40	61
III	18	20	19	30
IV	38	32	30	50

In order to determine biomarker specific to stage I, three over-expressed proteins among a series of 191 patients with discrete grades of breast tumor were evaluated. (See figures 1, 2, and 3)

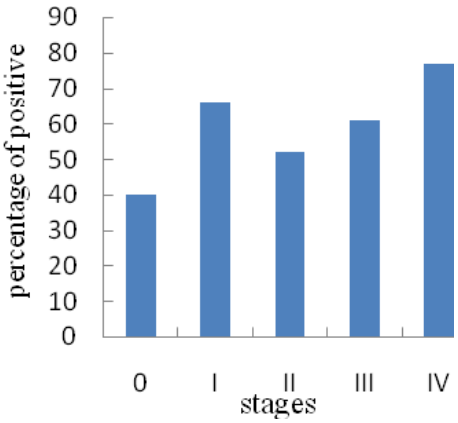

Figure 1. Erbb2^{+} displayed different positive percentages in the population of study with different stages of BC.

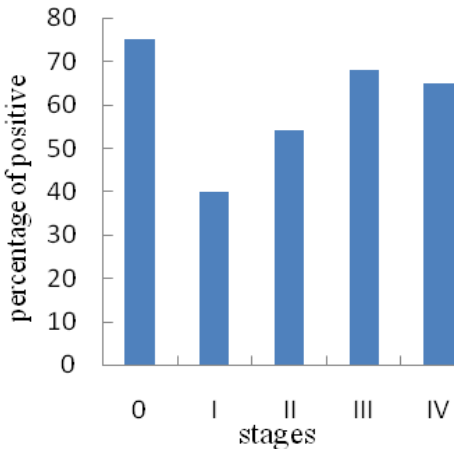

Figure 2. It shows the rate of P53 positive percentage in population of different stages from low grade to severe types.

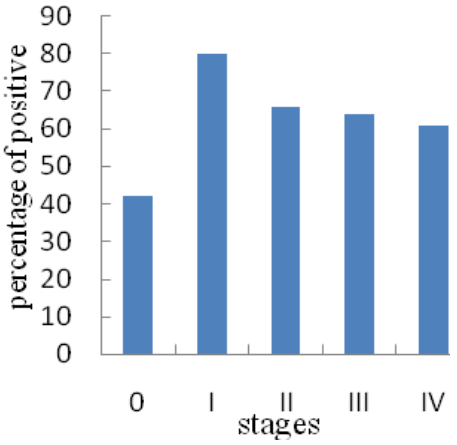

Figure 3. It shows the rate of PR positive percentage in population of grades from 0 to 4.

DISCUSSION

Protein biomarkers have lately been seriously researched in their key roles in the recognition, quantification, and follow up of different kinds of breast cancer [20]. In other words, owing to these evaluations such as the ability to prospectively identify stages, this malignancy has underwent several changes recently which enable the application of more individualized treatment optimizing to different molecular subgroups, as under treatment or incorrect therapy has to be avoided [15]. Inasmuch as detection in late stages may not lead to appropriate therapy, cancer detection in low grades such as stage 0 and I is vital for acceptable treatment outcomes [21]. Some breast cancer biological indicators have been evaluated in this study, which there was a significant correlation between three of them. From table 1 it can be inferred that 8 out of 21 cases in stage 0, 19 out of 29 in stage I, 31 out of 61 in stage II, 18 out of 30 in stage III, and 38 out of 50 in stage IV were reported with ErBb2 positive over-expression; 16 out of 21 patients in stage 0, 11 out of 29 in stage I, 32 out of 61 in stage II, 20 out of 30 in stage III, and 32 out of 50 in stage IV were reported with high expression in P53. In addition, 8 out of 21 of them in stage 0, 23 out of 29 in stage I, 40 out of 61 in stage II, 19 out of 30 in stage III, and 30 out of 50 in stage IV were diagnosed with PR positive amplifications.

As it is depicted in Figure 1, Erbb2 has different expressions in different stages of these patients. Now that its percentage is significantly great among different grades, it can possibly account for the biomarker of stage two. Here observed in Figure 2, the percentage of protein expression level of P53 is noticeably high in different stages, while in stage two it significantly decreases in the population. Furthermore, in Figure 3, the percentage of PR is examined, and the degree of this biological marker has raised in the population of stage I, which is in positive correlation with Erbb2 and negative correlation with P53. In other words, ErBb2, P53, and PR can account for potential biomarkers profile in stage I examination. Statistical analysis (Binomial Test) was investigated in this study for more resolution. The finding indicated that ErBb2 can differentiate stage 0 versus Stage I (P value is about 0.05) and also stage I compared to the higher stages (P value less than 0.001). P53 cannot differentiate the stages 0 and I but it differentiates I from the higher stages (P value less than 0.001). PR, like ErBb2, differentiates stage I from stage 0 and the other higher stages with P value less than 0.01 and 0.001, respectively. However, ER is a significant biomarker for breast cancer diagnostic aspects; here it could not differentiated stage 0 from the other stages. Finally based on these findings, ErBb2, P53 and PR can be considered as suitable criteria for diagnostic probes for stage I of breath cancer.

CONCLUSION

In brief, these markers with significant changes probably have high sensitivity and specificity. Hence, they can be possibly useful in characteristic stage I of breast cancer, and finally may lessen the therapeutic failures of breast cancer patients.

ACKNOWLEGMENT

This research has been supported by Cancer Research Center and Proteomics Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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