

RESEARCH COMMUNICATION

Variation of Tumor Markers in 277 Breast Cancer Cases

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Abstract

Introduction and purpose: Breast cancer is the most frequently diagnosed cancer in women in the world, Advances in paraclinical methods have resulted in dramatic changes in determining the survival of patients. Serial evaluation of serum levels of tumor markers is one of these methods.

Methods: During 1993-2002, 277 cases with breast cancer after mastectomy were included in this cross sectional study. Data were extracted from the patients records. Characteristics of the patients associated with serum levels of tumor markers like CEA, CA15-3 and receptor markers like ER, PR with P53, Cathepsin-D and HER-2 were evaluated.

Results: The most common involved age was in the 4th decade, accounting for 43.3% of the total. Most of the cases (54.3%) had stage II disease; Ductal carcinoma with frequency of 83.3% was the most common pathology involved and bone metastasis with 59% was prominent. There were elevated serum levels of CEA and CA15-3 in 50.6% and 41.7%, respectively. There was no statistical relation between serum levels of these markers with disease stage (CEA: pearson chi-square = 0.133 CA15-3: Pearson chi-square = 0.064). There was a great increase in serum level of tumor markers during relapse (CEA P = 0.000 CA15-3 P = 0.000).

Discussion and Conclusions: Because diagnosis of breast cancer is generally at advanced stage in our country, serum levels of tumor markers demonstrate great differences from those published for the Western world. It seems, however, that serum levels of tumor markers might be reliable for predicting relapses.

Key Words: Breast cancer - Iran - tumor markers - survival

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Introduction

Breast cancer is the most common malignancy of women throughout the world. According to data from American Cancer Society, there are 183000 new case reports/year indicating 110 new cases in 100,000 population. The risk of breast cancer development in each American woman lifelong is approximately 12.5%, (one in 8). Furthermore, according to the American Cancer Society estimation, there were 43,700 and 400 deaths from breast cancer in American women and men, respectively in 1999 (Haskell, 2001).

In modern medicine, several methods for recognition of breast cancer in early stages, allowing a better outcome, are available. One of them is measurement of tumor markers (Yetes, 1995). Tumor markers are used for prevention, monitoring, treatment, determination of primary success (surgery or radiotherapy), prevention of tumor relapse and assessment of efficacy of treatment modalities (Doben et al., 1996). The present study was performed for comparison of tumor markers levels in various stages of breast cancer as well as to assess their efficacy in early diagnosis, also of relapse, and control of disease progression .

Materials and Methods

All patients with breast cancer presenting after mastectomy, primarily in the oncology clinic of Tabriz Shahid Ghazi hospital from 1993 to 2002, in order to obtain continued treatment and chemotherapy, were evaluated. Data were collected from medical records of patients and then analysed. The variables of this study include serum levels of tumor markers for breast cancer such as CEA and CA15-3; Moreover, the tumor receptors such as estrogen receptor (ER), progesteron receptor (PR), and other prognostic markers including cathepsin D (Intracellular Proteinase), P53 and HER-2 were evaluated if possible.

Results

Of all 277 cases, 273 were female and 4 were male. The patients were classified in various age groups but there were none patient younger than 20 years old. Those in the 40-49 year group (120 patients) were most frequent, accounting for 43.5%.

Of the blood groups, A⁺ and O⁺ were the most common

at 30% and 29.2%, respectively. Of 272 patients 141 had right breast involvement (51.8%), and 131 had left breast involvement (47.8%), lesions being bilateral in one.

In 273 patients, primary mass size could be determined; it was less than 2 cm (T₁) in 9.9% (27 cases), 2-5 cm (T₂) in 65.2% (177 cases), and greater than 5cm (T₃) in 22.7% (62 cases). In 6 cases (2.2%) the tumor had adhesion with chest wall or skin, with no obvious link to size. At mastectomy, there was no involvement of lymph nodes in 28% of cases. Axillary lymph nodes were involved in 69.1%. Also, there was involvement of lymph nodes in other sites of the body (supraclavicular and internal mammary). The number of involved lymph nodes in all of 196 cases was determined. From this, 69.4% of cases were in the N1 stage, 27.6% in N2, and 13.1% in N3, according to the TNM system. After mastectomy, there were no confirmed metastases in 85.9% (238 cases) and metastases in 14.1% (39 cases). The most frequent sites for metastasis were bone (59%), lung (23.4%), and liver (20.3%).

Pathologically, types of breast cancers included ductal carcinoma (83.3%), lobular (8%), and other types (8.7%). From results obtained from the pathology report sheets as well as considering staging criteria for patients according to the TNM system, 2.5% of patients (7 cases) were in stage I, 54.3% (150 cases) in stage II, 29% (80 cases) in stage III, and 14.1 (39 cases)% in stage IV.

The CEA levels were available in records of 276 cases and CA 15-3 levels in 223. The CEA levels were in the normal range in 49.4% and elevated in 50.6%. Of these, the tumor sizes were less than 2cm in 10.5% (14 cases), 2-5cm in 65.4% (87 cases), and greater than 5cm in 24.1% (32 cases). Elevated serum levels of CEA, therefore, were observed in 52% of T₁ patients, 49% of T₂ and 51% of T₃ when diagnosis was established.

The CA15-3 levels were normal in 58.3% of patients, and increased in 41.7%. The sizes of tumors in these patients (93 cases) were less than 2cm in 9.7% (9 cases), 2-5cm in 61.3% (57 cases), and greater than 5cm in 29% (27 cases). Elevated CA15-3 levels were observed in 33% of T₁ patients, 32.2% of T₂, and 43.5% of T₃ when diagnosis was established.

In patients with ductal carcinoma malignancy, elevated serum levels of CEA and CA13-5 were observed in 53.2% and 44.9%, respectively. In the lobular type, the respective figures were 52.4% and 35.3%, and in non-ductal/tubular types were 25% and 17.6%. Elevated serum levels of CEA and CA15-3 in relation to disease stage were observed respectively as follows: 57.1% and 50% in stage I, 46.6% and 34.1% in stage II, 50% and 49.5% of stage III, and 68.6% and 56.7% in stage IV.

Estrogen receptors were evaluated in 108 patients and 67.6% of them were receptor - positive. Of 101 patients evaluated for progesteron receptors, 56.4% were positive. In the progesteron receptor - positive patients, the CEA and CA 15-3 levels were elevated in 46.6% and 34.5%, respectively. Cathespin D levels evaluated in 74 patients were high in 83.8%. P53 was evaluated in 39 cases and found

Table 1. The Relation Ship between Tumor Markers and Tumor Size

Tumor marker	Size Total Number	< 2cm		2-5 cm		> 5cm	
		Number	%	Number	%	Number	%
Normal CEA	130	12	9.2	85	65.4	33	25.4
Elevated CEA	133	14	10.5	87	65.4	32	24.1
Normal CA 15-3	127	10	7.9	88	69.3	29	22.9
Elevated CA 15-3	93	9	9.7	57	61.3	27	29

positive in 60.5% and negative in 39.5%. In cases with increased cathepsin D levels, the serum levels of CEA and CA 15-3 had been elevated in 45.2% and 50%, respectively.

In evaluation of HER-2 tumor receptors in HER-2-positive patients, elevation of CEA and CA15-3 levels was evident in 39.1% and 21.7%, respectively. Also, in P53 – positive cases, elevated CEA and CA15-3 levels were observed only in 30.8% and 46.2%.

Data for tumor markers relative to lesion size are summarized in Table 1. There was no significant linkage. In evaluation of records for metastasis and comparison of serum levels of tumor markers during treatment period for presence or absence of serum levels elevation, 261 patients were evaluated for CEA and 218 patients for CA15-3. The results are presented in Figure 1.

Discussion

Breast cancer has been reported to be very uncommon in people younger than 20 and most common in perimenopause women before 50 years old (Pike et al., 1991). In this study, also, there was no patient younger than 20 and the most common age group was 40-49. Blood group assessment demonstrated no significant difference from the distribution in normal individuals. Metastasis to the bone, lung, and liver has been reported in 60%, 15-25% and 10-20%, respectively (Bennett, 2000), and our results are thus

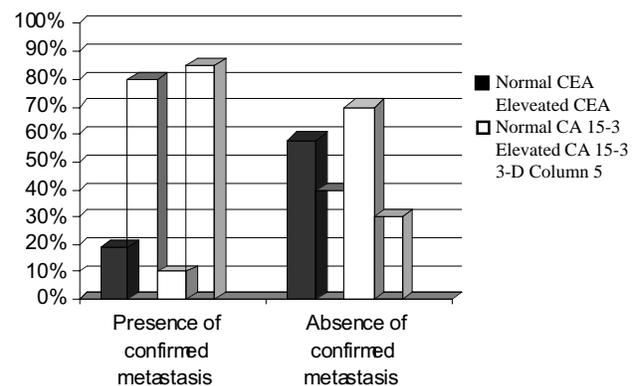


Figure 1. Assessment of Correlation between Serum Levels of Tumor Markers and Relapse Rate in Patients

in line with the literature. The types of cancers observed here demonstrated differences for those described earlier (Haskell, 2001) in that there were more invasive ductal type breast cancers, related to late diagnosis. The tumor size during diagnosis and mastectomy was 2-5cm in 65.2% of cases and only 9.9% were less than 2cm in diameter.

Of all cases, breast cancer resulted in death in 18.8 % and 81.2% of all cases were alive during the study. Despite the high metastasis rate in this study, the less than one year and 1-2 years survival were quantitatively greater than reported earlier (Citron, 2003), but 10 years overall survival showed no difference.

Possible related to this, CEA and CA15-3 tumor markers serum levels were elevated in 50.6% and 41.7%, respectively, much higher than the average of 22.8% described for another series (Molina et al., 2003). In an American study, estrogen and progesteron receptors were positive in 75% and 65% of patients, respectively, with little variation from the 67.6% and 56.4% observed here.

Because there is no significant difference in serum levels of CEA and CA15-3 and stage of disease or size, it seems that tumor markers depend on other factors for their production. It seems that the serum levels of tumor markers were more often normal in PR, ER, and also in HER-2-positive patients. Also, serum levels of the tumor markers were elevated in patients with normal cathepsin D, and often normal in P53 - negative patients. There was evidence of CEA and CA15-3 serum elevation in the medical records of majority of clinically relapsed patients, indicating a significant relationship (CEA : $P = 0.000$; CA15-3 : $P=0.000$).

Conclusions

The present study of 277 patients with breast cancer presenting after mastectomy at the oncology clinic of Tabriz Shahid Ghazi hospital 10 years ago, revealed an incidence peak in the 4th decade of life in the Azarbaijan region, all patients being locals.

Early onset of metastasis and clinical relapse after surgical therapy of patients with breast cancer are considerable in this region and there is short time interval between recognition of tumor markers elevation in serum and appearance of symptoms of clinical relapse which both are probably due to of inadequate local and systemic treatment, lack of routine screening in society, and delayed diagnosis of breast cancer patients. Possible differences in natural history of disease in relation to race or chromosomal differences are subjects which require complementary prospective assessment.

It appears that, therefore, general policies of country for health and treatment must be programmed on the basis of promotion of screening tests and early diagnosis of diseases when there is low peripheral tissue involvement and small tumor size. Development of specialized surgery centers and closer coordination of doctors responsible for treatment of such patients must be included in programming priorities of

university centers which are primarily responsible for cancer control in Iran.

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