# Clinical, Biological and Pathological Characteristics of Breast Cancer Patients at the Taleghani University Hospital in Kermanshah, Iran

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## Abstract
*Introduction:* Breast cancer is the most common of all malignant neoplasms in women worldwide. This study aims to demonstrate certain biological, clinical and pathological characteristics of patients treated at the university hospital oncology unit.
*Methods:* A descriptive study was conducted during a period of 2 years, from October 2003 through September of 2005 in Kermanshah, Iran. 555 patients were selected to participate, representing all the cases diagnosed and treated for breast cancer. Data was gathered according to questionnaires and patients' records.
*Results:* The mean age at which breast cancer was first diagnosed was 46.5±11.6 year of age with 89% of tumors being infiltrating intraductal carcinoma. The majority of the patient population had tumors stage II and grade II. Mean tumor size was 2.14±0.57 centimeters. 58% of the tumors were localized to the upper outer quadrant of the affected breast and 89% of the patients received modified radical mastectomies with almost a 92% two year survival.
*Conclusion:* Highest prevalence of breast cancer was recorded in the 40-49 (mean 46) years of age group which compares favorably with studies done under similar circumstances. Tumor size, grade, stage, tumor marker analysis, metastasis and other disease characteristics portray patient population tendencies for breast cancer patients in Kermanshah, Iran.

**Key words:** Breast cancer, Biological Clinical and Pathological Characteristics, Kermanshah

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## Introduction
Breast cancer is the most common malignant neoplasm in women worldwide. Its incidence has been reported to be 105 cases per 100,000 populations per year with a lifetime risk of 1 out of every 8 women. (1)
Prevalence, morbidity and mortality data of breast cancer in Iran is spotty and incomplete at best. One study done by the radiotherapy group at the S. Beheshti Health Sciences University in Tehran, 17,606 cases of malignant neoplasia were recorded during 1972 thru 1996, and breast cancer was identified as the most common of the neoplasms comprising 10.8% of the cases.(2) Cancer Institute of the I. Khomeini Hospital in Teheran had reported 3828 cases of malignant neoplasia during 1995, with 22% having the diagnosis of breast cancer, again being the most common form of cancer.(3) Data from other countries suggests that breast cancer's proportion of total cancer cases is on the rise(1) and Iran is probably no exception to this trend.
Although some cases of breast cancer occur in a familial pattern, the majority of breast cancer cases are sporadic and without any prior family history. Risk factors for the development of breast cancer include family history, increasing age, parity, age at which sexual activity is initiated, nulliparity, environmental factors, previous benign tumors of breast and emotional factors.(4) Fundamental approach to therapy includes surgery, chemotherapy and radiation. Prognosis and 5 year survival rates are dependent on the following factors in decreasing order: 1. Stage of the disease, 2. Axillary lymph node involvement, 3. Tumor size, 4. Tumor grade and differentiation, 5. Lymph node invasion, 6. Vascular and neural invasion, 7. Presence or absence of estrogen and progesterone receptors in tumor cells. Additionally, biological markers such as tumor DNA ploidy, proportion of cells

in S phase of mitosis, presence and concentration of proteases such as Cathepsin-D and oncogenes such as p53 and HER-2/neu contribute to the determination of prognosis of breast cancer patients. It is recommended that biological markers and hormone receptor presence be evaluated before the initiation of chemoradiotheray, which have important therapeutic and prognostic value.

One study performed in Iran of 374 cases of breast mass during 1991-1993, biopsies were positive for primary breast cancer in only 39% of cases with a relative frequency of 31%. Mean age of patients with primary breast cancer is reported to be 48±1 years. Tumor diameter greater than 2.1 cm was seen in 59.4% of the cases and 83.4% were diagnosed with infiltrating intraductal carcinoma.[8] The Breast Cancer Center of Tehran study during the years of 1997-98 was aimed at determining risk factors for breast cancer in 286 patients with a control group of 249. Prior family history and marital status were determined to be important risk factors for the development of breast cancer in women living in Iran.[9] The epidemiology of breast cancer in Iran was evaluated in a retrospective study at the main general district and teaching hospitals of Tehran of 903 patients with primary breast cancer during 1985-95. The mean age at presentation was reported to be 47.1 years and the highest incidence rate was reported in the 40-49 year age group. Tumor pathology of Intraductal carcinoma was diagnosed in 71% of the patients and 70% of patients had stage III disease. In 51% of the patients, the tumor size was reported to be greater than 5 cm.[10]

In an investigation completed in the United States of America in the year 2003, the relationship between age and biomarkers were evaluated in 4000 patients with primary breast cancer. The results had demonstrated that increasing age correlates with increasing concentrations of biomarkers and changes in breast cancer biology.[6] A separate study, also done in the United States of America during the year 2003, attempted to determine the relationship between biomarkers and advancing age. It has shown that breast cancer biology is directly affected by age. Tumors of older patients had slower growth rates and were more likely to be ER positive. However, older patients tended to have fewer tumors that tested positive for p53, Epidermal Growth Factor Receptor (EGFR) and C-erb B2.[7]

The objectives of our research included the following:

1. Clinical, pathological and biological course and characteristics of patients diagnosed with breast cancer.
2. Determination of the above mentioned criteria based on age of patient at the time of presentation, broken into three categories, under the age of 35, between 35 and 50 years of age and above the age of 50.
3. Ascertaining the differences found in the above mentioned criteria in the 3 age groups and their effect on disease progression. This study was completed at the Taleghani University Hospital, Kermanshah University of Health Sciences.

## Methods

Our study was descriptive-analytical. Patient population was chosen from all the cases of primary breast cancer at the outpatient clinic of the Taleghani hospital as well as the private practice patients. Census sampling was performed and sample size was 555 patients. All patients were thoroughly examined, received treatment and were followed up. The necessary information was gathered and recorded in pre approved questionnaires and forms. All statistical data were analyzed using the windows version SPSS 11.5 software and the results are presented subsequently and in tables and graphs and their significance is discussed.

## Results

Data from 555 patients were recorded from October 2003 through September 2005, and were included in the study. Of these, 184 cases were diagnosed and included in the study after the study had been underway while 371 cases were previously treated cases. Additionally, 529 patients of the study group were followed up for a minimum of 2 months and maximum follow up period of 302 months, and 26 patients did not participate in the follow-up period. 98.4% of the cases were female (546 patients) and 1.6% were male (9 patients). Male patients were excluded from the study.

*Involved Side:* Involvement of the left breast was recorded in 278 patients (51.7%) and the right breast was involved in 268 patients (48.3%).

*Patients' Occupation:* 418 cases or 76.6% of the patients described homemaker as their primary occupation while 15.8% or 86 patients responded to teacher as their occupation. 6.9% or 38 patients said they were regular state employees and 0.7% or 4 patients indicated that they were blue collar workers.

*Education:* 202 patients or 37.1% were illiterate. 104 patients (19%) reported elementary and 70 patients (12.8%), middle school education while 108 patients (19.7%) had a high school diploma and 62 patients (11.3%) had received post secondary education.

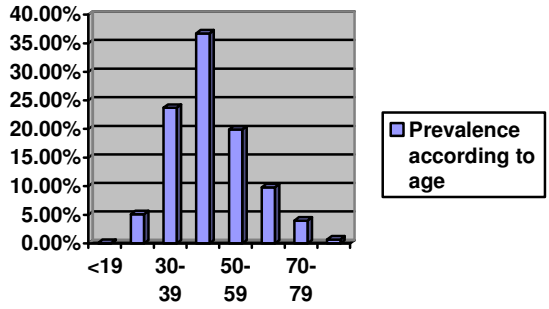
*Marital Status and Parturition:* 22 patients (4%) were single and 524 patients (96%) were married. 19 patients (4%) in the married category reported nulliparity and 464 patients (96%) reported single or multiple parturitions. 71 patients had no recorded parturition history. A mean of 3.51 parturitions with a standard deviation of 2.3, a median of 3, and a maximum of 13 parturitions. 244 patients (44.7%) had a history of oral contraceptive pill use.

*Family History:* 40 patients (7.3%) had a positive family history of breast cancer of whom, 13 patients had an affected mother, 16 patients an affected sister and 2 cases in which both mother and sister were reported as family members inflicted with breast cancer. First degree relatives affected by breast cancer were recorded in 13 cases (grandmothers, aunts, cousins, etc). 2 patients reported past medical histories of ovarian cancer and one patient, cancer of colon. 5 patients (0.9%) had either a history of previous breast cancer or recurrent and persisting disease during follow-up.

*Age:* The youngest patient was 19 years old and the oldest, 83 years of age. Mean age at which breast cancer was first described was 46.5 years with standard deviation of 11.62 years and a variance of 135. Prevalence was highest in the fifth decade of life (Diagram 1). To aid in the analysis of the results, patients were divided into 3 age categories, less than 35 (70 patients, 12.8%), 35 to 50 (305 patients, 55.9%) and older than 50 (171 patients, 31.3%) years of age.

*Tumor Size and Location:* Of the 408 patients whose pathology reports were available, 51 patients (10.2%) had a tumor diameter equal to or less than 2 cm corresponding to stage T1 in the TNM staging system. 236 patients (65.5%) were placed in TNM stage T2, with tumor diameters greater than 2 cm but less than or equal to 5 cm. Finally, 121 patients (24.3%) had TNM stage T3 with a tumor diameter greater than 5 cm. Smallest tumor size (diameter) recorded was 1 cm and the largest 13 cm. Mean tumor size was 2.14 centimeters with a standard deviation of 0.571 centimeters. Tumor location was categorized based on following descriptions of the anatomical locations of the involved breast and the description of tumor morphology: Upper Outer Quadrant (UOQ), Upper Inner Quadrant (UIQ), Lower Outer Quadrant (LOQ), Lower Inner Quadrant (LIQ), Central (below nipple), multifocal and diffuse. Of the 494 patients whom were included here, 58.1% had tumors localized to the UOQ (Diagram 2).

**Diagram 1: Age category distribution of subjects in the study.**




*Tumor Histopathology:* Of the 532 patients whose data was analyzed, 89.7% had intraductal adenocarcinoma, 4.5% of the tumors were reported as lobular adenocarcinoma, 3% medullary adenocarcinoma and 1.3% other types of adenocarcinoma. 0.8% of tumors were sarcomas and 0.8% were lymphomas (Table 1). 460 patients were evaluated for lymph node involvement, and 287 cases (62.4%) had positive lymph node invasion. 437 patients were checked for nerve involvement and 33 cases (7.5%) had nerve fiber invasion. Of the 440 patients evaluated for vascular involvement, 61 cases (13.8%) of vascular invasion and obstruc-

tion were reported. Tumor grade one (I) was reported in 41 cases, grade two (II) in 332 cases (70.3%) and grade three (III) in 99 cases (21%). Tumor Grading was evaluated in 472 patients.

Of the 502 patients evaluated for tumor TNM staging, analyzed criteria included tumor size, the number and the manner of axillary lymph node involvement, metastasis to the lung (evaluated by chest x-rays), liver metastasis (evaluated by ultrasonography and liver radioisotope scan) and bone metastasis (evaluated through bone scans) as recorded in Table 2. The majority of subjects had stage II disease. Of the 460 cases whom were evaluated for axillary lymph node involvement, 62.4% had positive axillary lymph node invasion at the time of diagnosis. Metastasis was evaluated in 507 patients. Presence of a primary metastatic lesion to the bone was seen in 33 cases (6.5%), to the liver in 17 cases (3.3%) and to the lung in 9 cases (1.7%) at the time of diagnosis. 20 patients (4%) had multiple metastasis at the time of diagnosis.

*Tumor Markers:* Tumor markers CEA and CA15-3 were measured in 436 patients before treatment was initiated. Elevated CEA was seen in 50 patients (11.5%) while an elevated CA15-3 was recorded in 59 patients (13.5%).

***Surgery:*** Surgical procedure was determined for 546 patients. The vast majority of patients (486 cases or 87.4%) received Modified Radical Mastectomies (MRM). 31 patients or 5.6%, received lumpectomies while 33 patients or 4.1%, received quadrantectomies. Finally, only 6 patients or 1.1%, received radical mastectomies.

*Biologic and Immunohistologic Markers:* Estrogen Receptor (ER) and Progesterone Receptor (PR) analysis of tumor cells, activity of p53 and HER2/neu oncogenes in tumor cells, as well as the immunohistochemistry analysis of the Cathepsin-D enzyme were performed. Of the 356 tumors checked for the presence of the ER, 234 tumors (65.7%) were positive (1+ to 8+) as seen in Table 3. Presence of PR was checked in 361 tumors and 240 tumors (66.4%) were positive. Oncogene HER-2/neu activity was measured in 248 tumors and 161 (64.9%) tumors were shown to be positive while 56 of these tumors (22.6%) showed HER2/neu over expression (3+) as seen in Table 4. The p53 oncogene activity was evaluated in 243 tumors and 124 tumors (51%) were positive. Finally, activity of the enzyme Cathepsin-D was investigated in 243 tumors and 80 tumors (32.9%) tested positive.

**Table 1: Tumor histopathology data.**

| Histopathology | Number of cases | Percent |
|---|---|---|
| Intraductal adenocarcinoma | 477 | 89.7 |
| Lobular adenocarcinoma | 24 | 4.5 |
| Medullary adenocarcinoma | 16 | 3 |
| Adenocarcinoma, other types | 7 | 1.3 |
| Sarcoma | 4 | 0.8 |
| Lymphoma | 4 | 0.8 |
| Total | 532 | 100 |

**Table 2: Tumor staging.**

| Disease Stage | Number of cases | Percent |
|---|---|---|
| I | 24 | 4.8 |
| IIa | 146 | 29.1 |
| IIb | 184 | 36.7 |
| IIIa | 85 | 16.9 |
| IIIb | 24 | 4.8 |
| IV | 39 | 7.8 |
| Total | 502 | 100 |

**Table 3: Estrogen Receptor (ER) presence.**

| ER quantification | Number of cases | Percent |
|---|---|---|
| 1+ | 9 | 2.5 |
| 2+ | 9 | 2.5 |
| 3+ | 20 | 5.6 |
| 4+ | 37 | 10.4 |
| 5+ | 33 | 9.2 |
| 6+ | 66 | 18.5 |
| 7+ | 55 | 15.4 |
| 8+ | 6 | 1.7 |
| Negative for ER | 122 | 34.2 |
| Total | 356 | 100 |

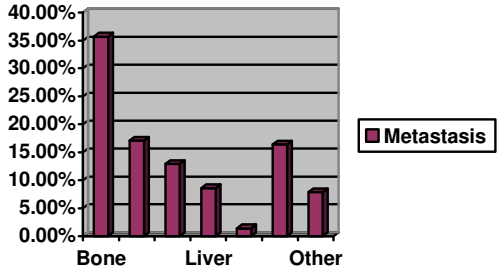
**Table 4: HER2/neu activity.**

| HER-2 quantification | Number of cases | Percent |
|---|---|---|
| 1+ | 6 | 2.4 |
| 2+ | 97 | 39.1 |
| 3+ | 58 | 23.4 |
| HER-2 negative | 87 | 35.1 |
| Total | 248 | 100 |

*Morbidity and Mortality:* Of the 529 patients who were followed up, 22 patients (4%) had

died less than one year after the initial diagnosis while 44 patients (8.1%) died less than 2 years after the initial diagnosis. Total mortality of 111 patients (21%) was recorded, of which 91 patients (82%) died of complications of distant metastasis. 16 patients (14.4%) died due to advancing primary disease, and 3.6% died of other causes. In total, 39 cases of primary metastasis were recorded and 36 cases of secondary metastasis and recurrence were noted. The most common site of metastasis was bone (35.7%) and the data is collected and presented in Diagram 2.

**Diagram 2: Site of metastasis distribution in the studied subjects.**




## Discussion

This observational study initially had 9 cases of males diagnosed with breast cancer but were excluded from the present analysis.

In regards to the socioeconomic status of the patients, no discernable differences were noted. However, left breast was slightly more affected than the right (51.7%). The majority of the patients were homemakers (76.6%) and illiterates (37.1%). Previous history of oral contraceptive pill use was recorded in 43.9% of the participants, and past family history of breast cancer noted in only 7.3% of the patients.

Most utilized surgery was the MRM, with 89% of the participants receiving the procedure. It compared favorably with the Iranian Cancer Institute study in which 76% of the subjects had received MRM.[10] 55.4% of the patients fell into the 35-50 age category with the prevalence being the highest in the 40-49 age group. Mean age at diagnosis was calculated to be 46.5 ± 11.62 years. In the study conducted by the oncology group at the Tehran University in 2002, the highest prevalence was seen in the 40-49 age group with mean age at diagnosis of 48.8 years [9]. S. Beheshti Medical University study of 2003, the mean age at diagnosis was reported to be 51 years in the city of Yazd and 41.5 years in the city of Babel [8]. In Hong Kong, the mean age was reported to be 56.6 years[11], in Pakistan 47.7 years[12], in Saudi Arabia 42 years [13], and in Nigeria 42.7 years of age [14].

Most patients were staged T2 in the TNM system (65.5%) with mean tumor size of 2.14 centimeters. In the Hong Kong study of 1997, 51.8% of the participants were staged T2[11] while the Pakistan study of 2002 reported mean tumor size of 5.7 centimeters.[12]

58.1% of tumors were localized to the UOQ of the involved breast with 89.7% being compatible with intraductal adenocarcinoma. The S. Beheshti study of 2003 had shown that up to 83.5% of the subjects were diagnosed with intraductal adenocarcinoma.[8]

In regards to the tumor grade and stage, 91.3% of the subjects were given grades II and III while 36.7% had tumors in stage IIb. 65.8% of the tumors were stage II, 21.7% were stage III, 7.8% were stage IV and 4.8% of the tumors studied were stage I. In the Iranian Cancer Institute study of 2000, stage I tumors were of the lowest prevalence (4.8%)[10] while the Hong Kong study of 1997 showed stage II tumors to have the most prevalence (59.6%).[11] Similar study performed in Saudi Arabia reported the prevalence of stage II tumors to be 44%, stage III at 30% and stage IV tumors at 16% of all subjects.[13] In the present study, most common primary metastatic site was the bone (6.5%) followed by the liver (3.3%) and the lungs (1.7%).

With regards to tumor marker analysis, 69.4% of subjects had tested positive for CEA, 67.8% positive for CA 15-3 and 66.5% positive for the PR. Cathepsin D tumor marker was found in 33.9% of the subjects while p53 activity was detected in 50.8% and 34.2% of the tumors were ER positive.

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