THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

PROGNOSTIC FACTORS IN

CARCINOMA BREAST IN FEMALES –

100 PATIENTS

DISSERTATION SUBMITTED FOR M.S. DEGREE

[BRANCH – I GENERAL SURGERY]

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GOVERNMENT RAJAJI HOSPITAL
MADURAI.

CERTIFICATE

This is to certify that the dissertation entitled **"PROGNOSTIC FACTORS IN CARCINOMA BREAST IN FEMALES -100 PATIENTS"** submitted by **Dr. S. UMADEVI** to the faculty of General Surgery, Government Rajaji Hospital, Madurai Medical College, Madurai, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is in partial fulfillment of requirement in the award of M.S. Degree, branch – I (General Surgery) for the September 2006 examination and is a bonafide research work carried out by her under our direct supervision and guidance.

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ACKNOWLEDGEMENT

DECLARATION

I solemnly declare that this dissertation "**"PROGNOSTIC FACTORS IN CARCINOMA BREAST IN FEMALES -100 PATIENTS"** was prepared by me from the Department of General Surgery, Madurai Medical College and Govt Rajaji Hospital , Madurai , under the guidance and supervision of **Prof. Dr.S. Vijayalakshmi M.S., Professor of Operative Surgery, Madurai Medical College , Madurai.**

This dissertation is submitted to the Tamil Nadu Dr.M.G. R. Medical University, Chennai ,in partial fulfillment of the university regulations for the award of the degree of M.S. Branch I General Surgery examinations to be held in September 2006.

Place :

Date :   **Dr.S. Umadevi**

CONTENTS

INTRODUCTION

Diseases of the breast attracted medical interest as long ago as 3000 B.C. the Edwin Smith surgical papyrus, originating in the advanced civilization of Egypt during the age of Pyramids described several cases of women with tumours of the breast. These included tumours that were hard and cool to touch as well as abscesses and inflammation that were warm.

The most influential physician of Greek antiquity was Hippocrates (460-370 B.C) who is considered the founder of rational medicine and based it upon observation rather than upon supernatural intervention. He recognised the nature of malignant disease which was called Karkinos (or) Karkinoma but he believed it was due to a systemic imbalance of the cardinal humours of the living body. i.e. blood, yellow bile, black bile and phlegm. He believed breast Karkinos to be the result of cessation of menstrual flow, leading to imbalance and engorgement of the breast. Hippocrates was very skeptical of any medical intervention for cancers in the breast saying that "It is better to give no treatment in cases of hidden cancer; treatment causes speedy death, but to omit treatment is to prolong life".

Celsus living in the first century A-D provided a description of stages of malignant growth and considered cancer a disease that occurs mostly in the breast of women.

Leonidus gave a detailed description of operations on the breast which were done by alternating sharp incision with the application of cauteries to stop bleeding.

In the 2nd century and for the next 1000 years medical thinking was dominated by Galen (A.D-130-203) Galen attributed cancer to an excess of black bile and like Hippocrates earlier to a systemic imbalance of the cardinal humours. Galen recommended complete excision of tumours of the breast, "so as not to leave a single root," He likened cancer to the crab with its central body and radiating growth and dilated veins.

In 1543, Andreas Vesalius the father of modern anatomy, published his famous treatise "Dehumani Corpor's Fabrica". Gabriele falloppiu, surgeon and anatomist, extensively discussed the nature of cancerous tumours. A variety of techniques for removal of the breast were introduced during these 2 centuries.

Bernard Peyril advised removal of entire breast, the pectoralis major muscle, and the axillary contents. Then Louis Petit urged wide removal of the breast and axillary nodes and stressed avoidance of partial extirpation of the breast.

In the recent years enormous development in the field of histopathology following the introduction of electron microscopy, development in the field of endocrinology, hormone measurements and radio-immunoassay have been achieved. But clear concept about the breast swelling and breast disease are yet to be attained.

Breast swellings affects both the male and female, no age group is immune. It can affect event he neonates. Hypertrophy of breasts in them supposed to deliver the "Witch Milk", Pubertal or senescent male breast swelling popularly known as gynaecomastia are also not uncommon. Bilateral breast diseases have also variable incidences in both the sexes.

REVIEW OF LITERATURE

DEVELOPMENT OF BREAST

The mammary glands are developed as down growth of the malphigian layer of the epidermis into the cerium. The mammary gland may be looked upon as a collection of greatly modified sweat glands. The epithelial lining of the ducts of the mammary gland and its alveoli are derived from the ectoderm, its supportive connective tissue from the mesenchyme. On each side of the ventral surface of young embryos a thickened band of ectoderm, termed the milk ridge, extends obliquely from the axillas to the inguinal region and in some of the lower animals mammae are developed at intervals along this ridge. In human beings no definite ridge is found and only one mammary gland is developed on each side of the median plane but supernumerary mammae (or) nipples are sometimes found above (or) below the fully developed gland.

The rudiment of the mammary gland appears as a thickening and subsequent in growth of the ectoderm and from this in growth fifteen to twenty solid cords branch off each cord representing the deep ends of the cords. The subdivide in the mesenchyme and form alveoli, the alveoli of the gland. In the later weeks of foetal life the tubules and alveoli become canalized and the lactiferous tubules then open into the floor of an epidermal pit. Just before (or) soon after birth, the mesenchyme underlying this depression proliferates and the pit becomes everted to form the nipple.

ANATOMY

The mammary glands exist in the male as well as in the female but in the former only in the rudimentary state. In the female they are two large hemispherical eminences lying within the superficial fascia on the front vertically from the second rib to sixth rib, costal cartilage and from the side of the sternum to near the mid axillary line. The deep surface of each is flattened (or) slightly concave and irregularly circular in outline, its longest diameter being directly upwards and laterally towards the axilla where the gland extends along the lower border of the pectoral muscles as the 'Axillary Tail'. It is separated from the fascia covering the pectoralis major serratus anterior and external oblique by loose areolar tissue. The subcutaneous surface of the mammary gland is convex. The nipple is a cylindrical (or) conical eminence situated about the level of the fourth intercostals space. The base of the nipple encircled by a coloured area of skin called the aerola. Near the base of the nipple and upon the surface of the aerola there are numerous seabaceous glands which becomes much enlarged during lactation and present the appearance of small tubercles beneath the skin. The ligaments of Cooper are conical projections of fibrous tissue which extend from the deep layer of superficial fascia to the dermis of the skin.

VESSELS AND NERVES

Blood supply

The principle blood supply is from the perforating branches of the internal mammary artery. The deeper aspect is supplied by the pectoral branches of the acromiothoracic artery. The lateral portion is supplied by the lateral thoracic artery and the lateral branches of the posterior intercostal arteries.

Venous drainage

Most of the venous drainage is via the perforating branches of the internal mammary veins. The deepest portion of the breast drains by tributaries which empty into the axillary vein and by the intercostals veins into azygos vein. These form the pathway for pulmonary secondaries. **Batsons's** plexus is a network of veins extending from the base of the skull to the sacrum and these communicate with the thoracic, abdominal and pelvic veins. These form the pathway for vertebral body secondaries.

Nerve Supply

The nerves are derived from the anterior and lateral cutaneous branches of the fourth fifth and sixth thoracic nerves. Nerve fibres both medulated and non-medulated are found in profusion and beneath the skin and especially in relation to opening of lactiferous ducts.

LYMPHATIC DRAINAGE

The lymph vessels make a richly anastomosing network continuous with the lymph capillaries of neighbouring structures in this case those of the opposite breast and of the abdominal wall. Most of the lymph of the breast drains, in fact to the axilla. The superficial parts of the breast drain to a sub-aerola plexus, the deep part drain to a submammary plexus, both communicate freely through the breast. The submammary plexus lies in the deep fascia over pectoralis major and serratus anterior.

Axillary lymph node groups

1. **Lateral group** – These are 4 to 6 nodes which are medial or posterior to the axillary vein. These drain the upper and lateral quadrant of the breast.
2. **Anterior (pectoral) group** – There are 5 to 6 nodes along the lower border of pectoralis minor and the lateral thoracic vessels which drain the lateral aspect of the breast.
3. **Posterior (Subscapular) group –** These are 5 to 7 nodes in the posterior wall of the axilla lying along the Subscapular vessels.
4. **Central group –** There are 3 to 4 nodes behind the pectoralis minor and receive efferents from above three groups (Level I Nodes).
5. **Interpectoral (Rotter's) group** - These include 1 to 4 nodes lying between the pectoralis major and the pectoralis minor. They drain into apical via central nodes.
6. **Subclavian (apical) group –** This includes 6 to 12 nodes lying posterosuperior to the upper border of the pectoralis minor. They receive efferents from all nodes and drain into subclavian trunk via supraclavicular nodes.

HISTOLOGY

The mammary glands are large compound recemose glands serving for the secretion of milk. Each mammary gland actually represents a group of glands which open by numerous ducts upon the apex of the nipple. Each duct is dilated into a small reservoir - the sinus lactiferous duct before reaching the nipple. The nipple contains a considerable amount of plain muscular tissue lying between and around the ducts. Traced backwards the ducts are found to commence in groups of saccular alveoli, the walls of which are lined by a single layer of epithelium which is columnar, when the milk is being produced within the cells it becomes flattened and may come out as it is discharged to fill the alveolus. In the resting gland, in the female there is a large amount of dense fibrous (or) adipose tissue between the group of acini.

I. SURGICAL ANATOMY OF BREAST

The breast is composed of three principal tissue types: epithelium, fibrous stroma and supporting structures and fat.

The relative amounts tend to vary with age, but there is even greater variability among individual women. In youth, the predominant tissues are epithelium and stroma, replaced by fat in the breast of older women. For this reason, mammography in women less than 30 years of age, whose breast tissue is dense with stroma and epithelium, produces images without much definition that are rarely useful clinically. Throughout the fat of the breast, coursing from the overlying skin to the underlying deep fascia, strands of dense connective tissue provide shape and hold the breast upward. These strands devoid of epithelial elements are called 'Coopers ligaments'. Because they are anchored into the skin, tethering of these ligaments by a small scirrhous carcinoma commonly produces a dimple on the otherwise smooth surface of the breast.

The glandular apparatus of the breast is composed of a branching system of ducts roughly organized in a radial pattern, which spread outward and downward from nipple areolar complex. These lactiferous ducts are so named because they carry the milk produced in the more distal lobular duct system. The subareolar ducts widen to form the lactiferous sinuses, which then exit

through 15 to 20 orifices on the nipple. These large ducts close to the nipple are lined with a low columnar (or) cuboidal epithelium.

In the opposite end of the ductal system and after progressive generations of branching the ducts end blindly in clusters of spaces that are called terminal ductules (or) acini. These are the milk forming glands of the lactating breast.

Under the columnar epithelium the entire ductal system in surrounded by a specialized myoepithelial cell of ductal epithelial origin which has contractile properties and serves to propel secretion of milk toward the nipple. Outside the epithelial and myoepithelial layers the ducts of the breast are surrounded by a continuous basement membrane containing laminin, type IV collagen, and proteoglycans.

II. SURGICAL PHYSIOLOGY OF BREAST

During adolescence the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. In the United States puberty begins at about 12 years of age, during which time there is hormone dependent maturation of the genital organs.

In the breast this process entails increased deposition fat, formation of new ducts by branching and elongation and the first appearance of lobular units. This process of growth entails cell division and is under the control of estrogen, progesterone, adrenal hormones, pituitary hormones and trophic effects of insulin and thyroid hormone. There is evidence that local growth factor networks are also important including epidermal growth factor, which can replace estrogen as a developmental hormone.

The resting breast contains fat, stroma, lactiferous ducts, and lobular units. During phases of the menstrual cycle or in response to exogenous hormone, the breast epithelium and lobular stroma undergo cyclic stimulation. In the late luteal phase there is accumulation of fluid and intralobular edema, which appears to correspond to the clinical complaint of breast engorgement that may be painful.

With pregnancy there is diminution of the fibrous stroma to accommodate the hyperplasia of the lobular units. This formation of many new acini (or) lobules is formed the adenosis of pregnancy and is influenced by high circulating levels of estrogen and progesterone and levels of prolactin that steadily rise during gestation. After birth there is sudden loss of the placental hormones and the high level of prolactin. This may be the principal trigger for lactation. Stimulation of the nipple appears to be physiologic signal for continued pituitary secretion of prolactin and for the acute release of oxytocin.

When the breast feeding stops, there is fall in prolactin and no stimulus for release of oxytocn. The breast then returns to a resting state and to the cyclic changes induced when menstruation begins again. Menopause results in involution and a general decrease in the epithelial elements of the resting breast. These changes include increased fat deposition, diminished connective tissue and the virtual disappearance of the lobular units. Sometimes the cycles may not be as symmetric and regular. This irregularity can induce functional nodularity and breast pain. When there is normal estrogen stimulation, diminished progesterone secretion. It acts as a inducing factor for development of a breast carcinoma. This is what is known as "estrogen window hypothesis" as proposed by Koreman in 1980. The basic assumption underlying this

hypothesis was that progestrone would act as an antiestrogen on breast epithelium in much the same way as it does on the endometrial epithelium.

III. BIOCHEMICAL BASIS OF BREAST DISEASES

There are more than 50 metabolic changes associated with oestrogen. The chief among them are enzymes of biological oxidation in mitochondria, on specific receptor protein in endoplasmic reticulum, and that of nucleus, governing specific pattern of RNA synthesis, especially RNA polymerase and enzymes on cell membrane permeability have been studied.

Estrogen dependent transhydrogenase have been recognised to trigger catalytic conversion of NADPH to NADP. Yielding the all powerful cyclic AMP from which high energy ATP – one essential for growth activities is formed.

IV. BIOLOGICAL BASIS OF TUMOUR FORMATION

Benign tumour can be formed under hormonal stimulus but all cases of benign tumour cannot be transformed into malignancy because of lack of induction factors. This process of malignant transformation has been divided into two phases, the induction and the promotion. Initiation is induction of neoplastic changes in a cell transforming it from one with normal growth characteristics to one with potential for uncontrollable growth and invasion. Initiation o\is often caused by a single agent with an immediate biochemical effect on the sequence of bases in the DNA. Once a transformed cell has been formed by subsequent action of other stimuli, i.e., the process of promotion, promoting factors may be chemical or hormonal or immunological.

AIM OF THE STUDY

1. To determine the factors which have good prognosis in females who develop carcinoma breast.

2. To determine whether tumour size or lymphatic permeation decides the prognosis.

3. To determine if secondary metastasis has a poor prognosis.

4. To determine the common age group at presentation.

5. To determine the disease awareness among the rural population.

CONDUCT OF STUDY

- This study was conducted between July 2003 to January 2006.

- Hundred patients were selected at random when they attended the breast clinic conducted every Wednesday.

- All the patients were subjected to the same tests and treatment modalities.

- The patients were followed up regularly and the factors for good prognosis determined.

MATERIALS AND METHODS

PATIENT FACTORS

1. Age

20-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	61-70 yrs	> 70 yrs
2	16	34	40	8	-

2. Menopausal Status

Pre menopausal	Peri menopausal	Post menopausal
12	30	58

Menopausal Status

12%

30%

58%

□ Pre menopausal □ Peri menopausal ■ Post menopausal
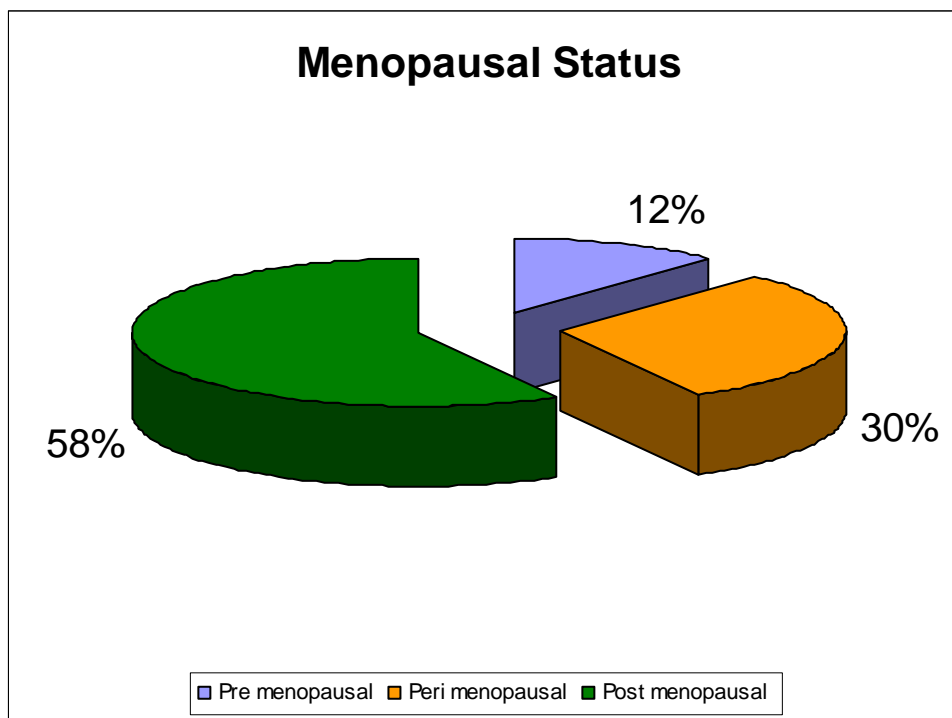
3. Parity

Nulli para	1 child	2 children	3 children	>3
2	0	30	28	40

4. Breast feeding

Never	0-6 mo	6 mo – 1 yr	1 -2 year
6	38	56	-

5. Family history

Mother	Sibling	maternal aunt	Paternal aunt	2° relative
-	-	1	1	-

Family history
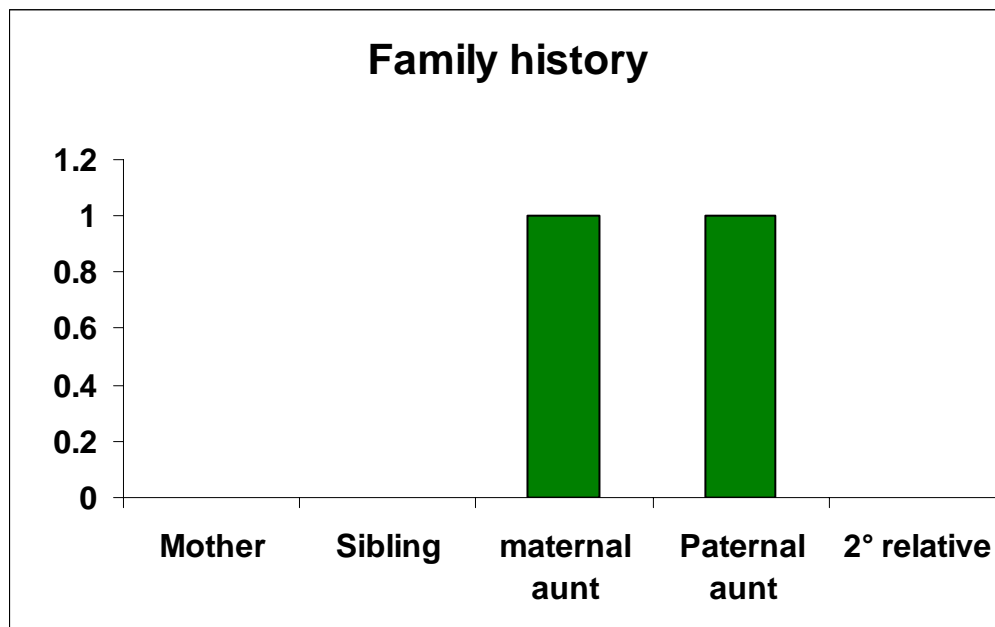
6. Socio economic status

High income	Middle income	Low income
2	22	76

7. Diet

Vegetarian	Non-vegetarian	High Fat diet	Alcohol
2	74	24	-

8. Previous breast diseases

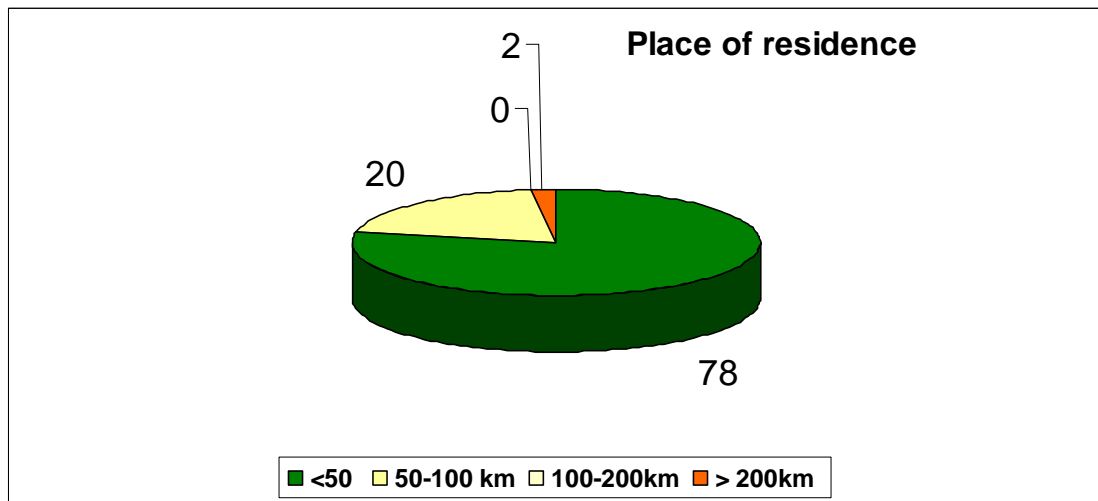| Cyclical Mastalgia	Non Cyclical Mastalgia	Fibro adenosis	Fibro adenoma	Lumpectomy	Ca.Opp.Breast	Previous breast biopsy	Previous Mammogram	Benign breast disease treated with hormone	Benign breast disease treated without hormone
2	1	2	1	2	0	2	2	0	0
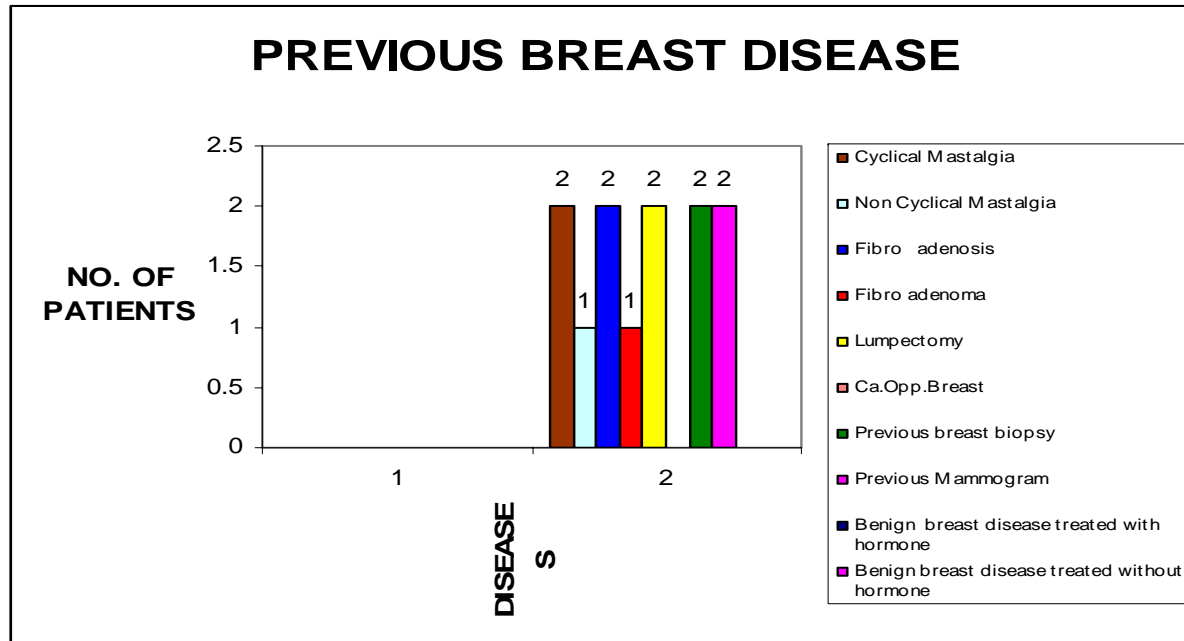
9. Place of Residence

Distance with regard to the hospital

<50	50-100 km	100-200km	> 200km
78	20	0	2

II. TUMOUR FACTORS

1. Side

Left	Right
66	34
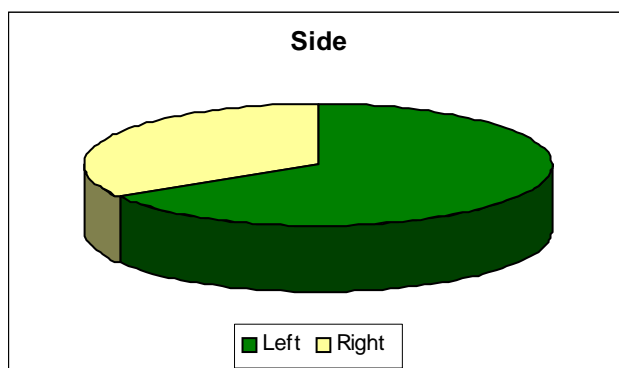
2. Quadrant

Upper outer	Lower outer	Upper inner	Lower inner
68	22	8	2
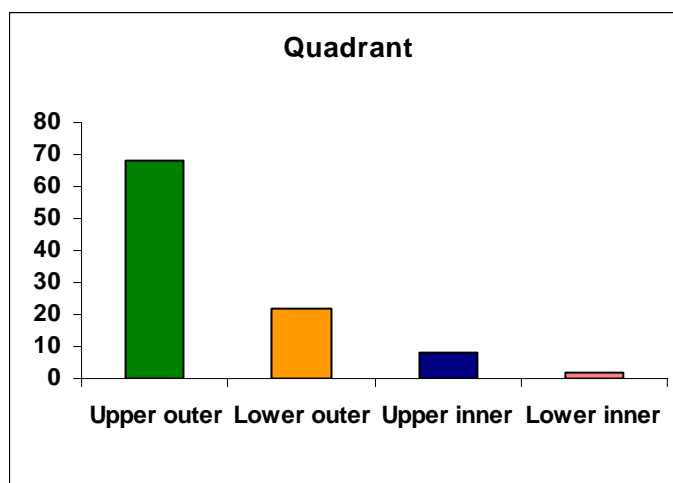
3. Size

<1cm	1-2 cm	2-4 cm	4-6 cm	>6cm
0	10	68	20	2
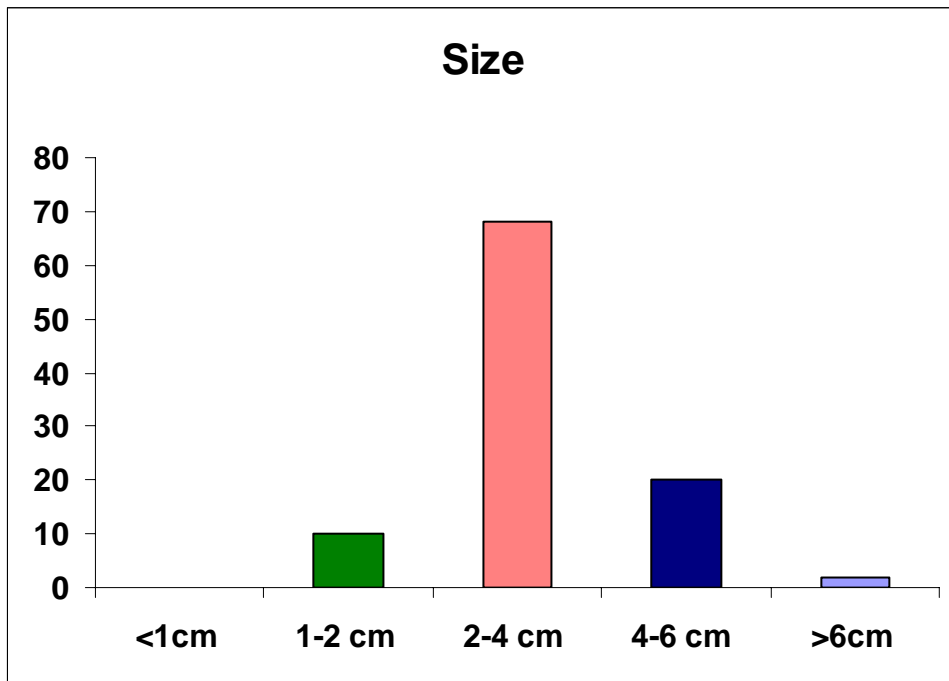
4. Fixity

Mobile	Fixed to deeper structures	Skin
82	10	10

Fixity
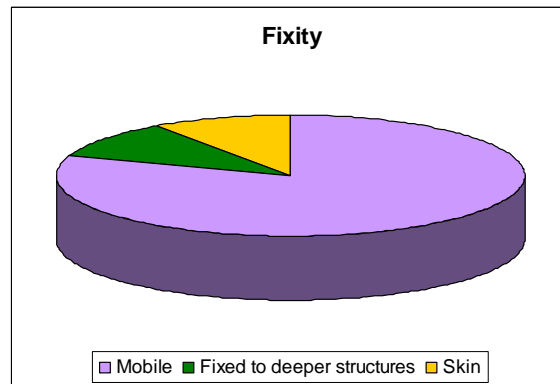
5. Nipple retraction

Yes	No
18	82

Nipple retraction
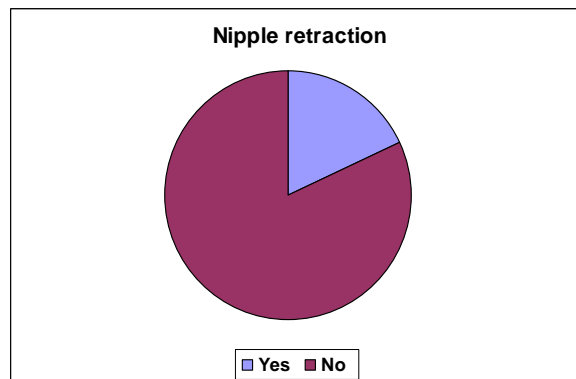
7. Histopathological Ex.

Insitu	Infiltrating ductal	Infiltrating lobular	Medullary carcinoma
-	97	2	1
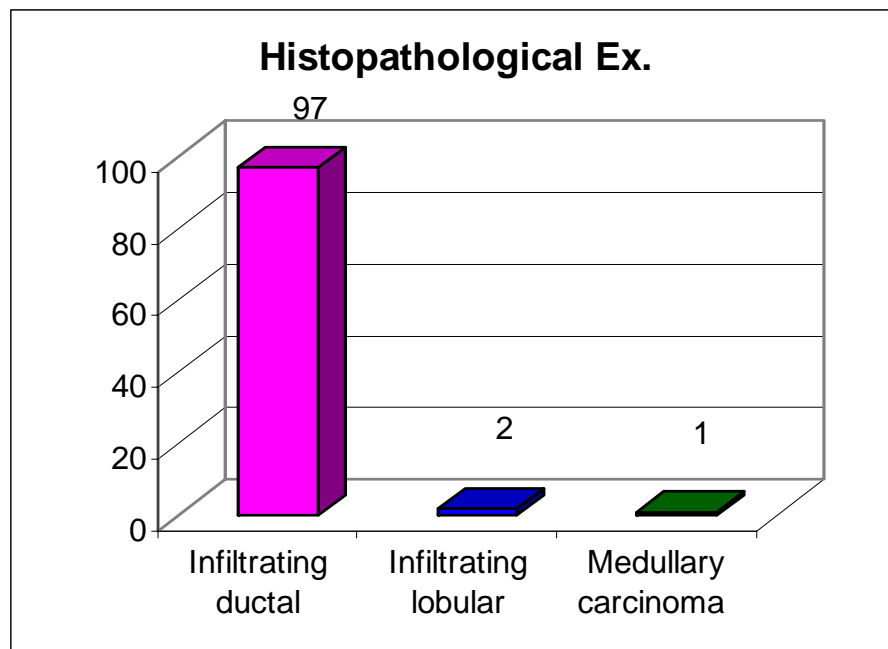
8. Grade

Low grade	Intermediate grade	High grade
52	42	6
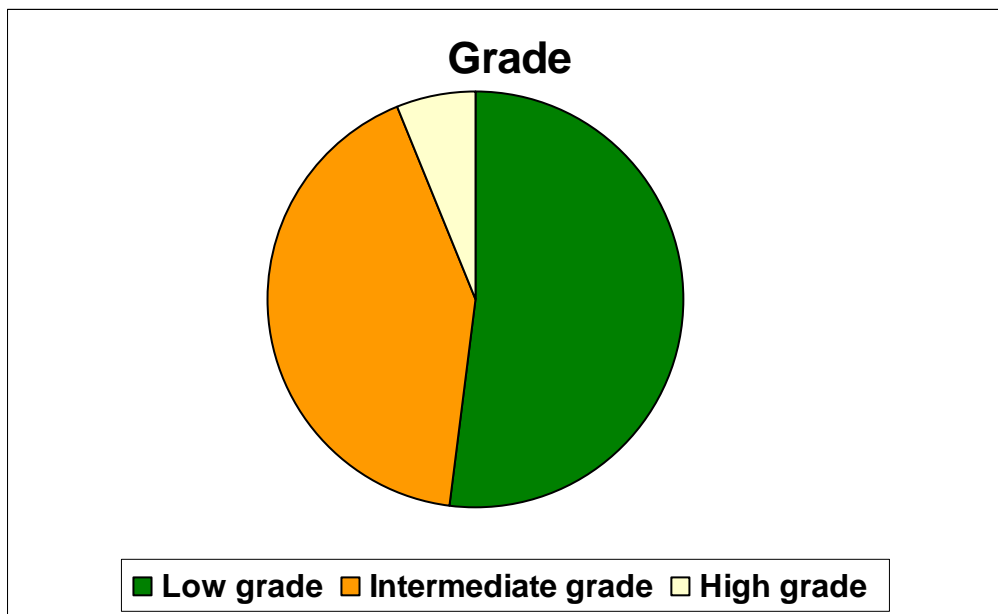
III. NODE FACTORS

1. Number of Nodes

0	1-3	>3
28	66	6

Number of Nodes
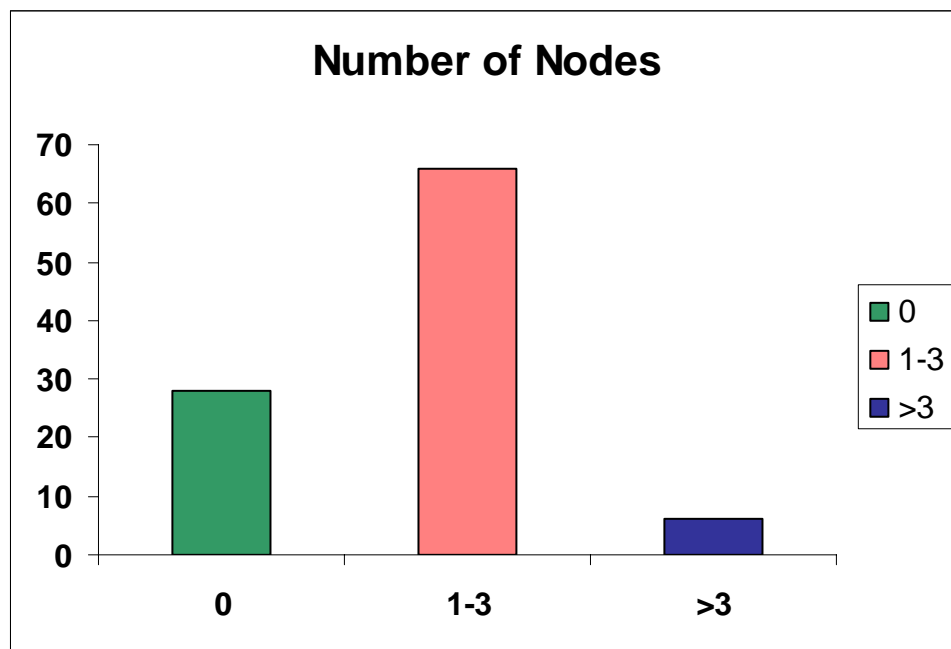
2. Level of nodes

No nodes	Level I	Level II	Level III
28	64	8	0
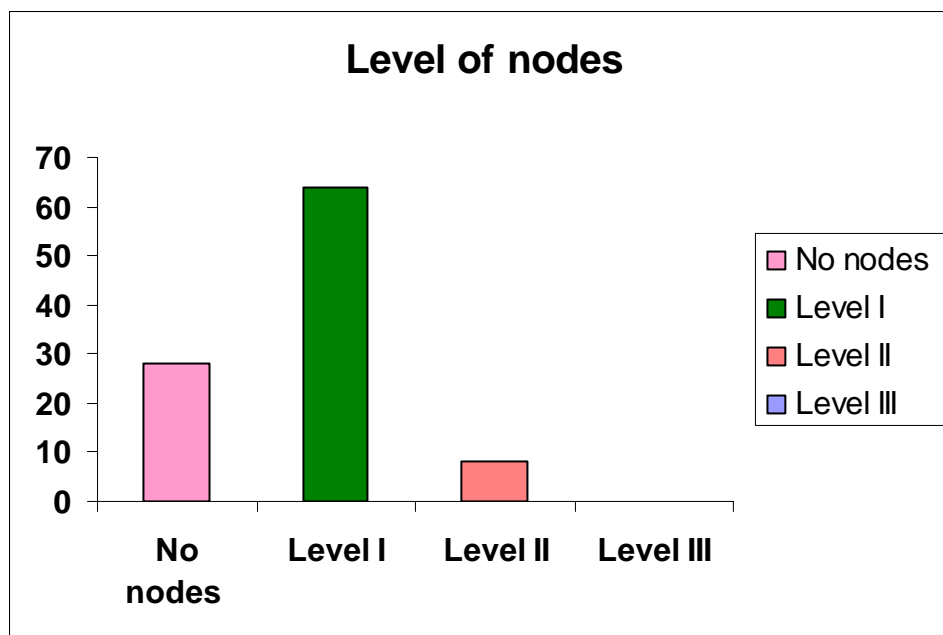
3. Fixity

Yes	No
10	90

Fixity

Legend: □ Yes ■ No
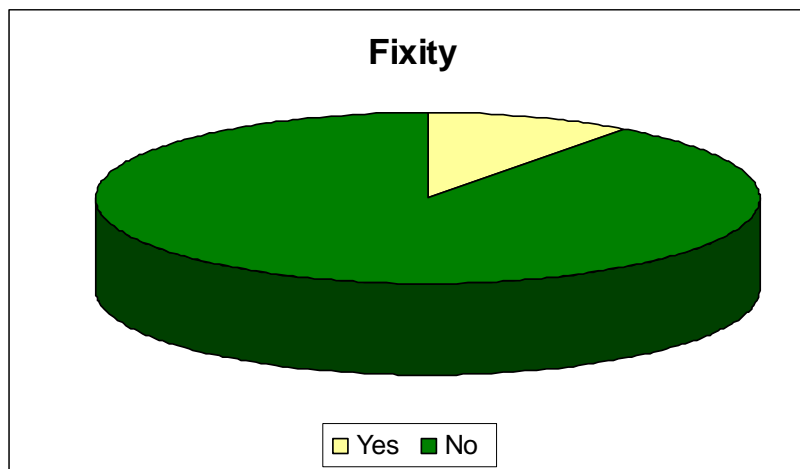
4. Internal mammary

Yes	No
0	0

6. Secondaries

Supra -clavicular	Liver	Bone	Pleura
1	1	-	1

Secondaries
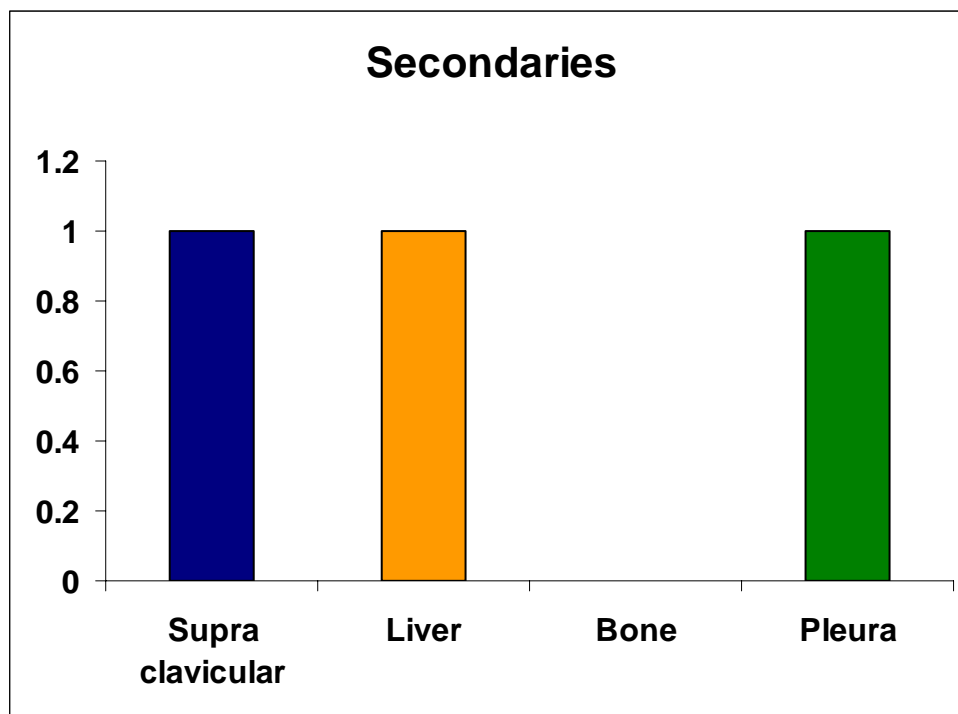
OBSERVATION

1. AGE :

From this study of 100 cases of cancer breast in females it was observed that patients present with carcinoma breast more in 50-60 years. The patients presenting at an older age have a better prognosis than the younger women.

Of the 100 cases 58% were postmenopausal and 30% were perimenopausal. The menopausal status in a woman is important prognostic factor in carcinoma breast.

The incidence of breast cancer increases with age and steadily after the age of 50. Thus 75% of all cases of breast carcinoma are diagnosed. In postmenopausal women. The risk of developing breast cancer is one in 19,608 at 25 years, 1in 33 women at 55 years and in 8 for women living in to their 80's.

2. MENOPAUSAL STATUS :

Engodenous exposure to oestrogen and progesterone likely accounts for majority of breast cancer risk. This is demonstrated with the known risk factors

of early menarche, latemenopause, delayed child birth, difficulty in conception, postmenopausal obesity.

In my study 58% were post men opausal and 30% were perimenopausal and 12% of premenopausal

3. PARITY :

99% of women were multiparous. Only one patient was unmarried and nullipara.

4. BREAST FEEDING :

Except for three all women breast fed their children ranging till 6 month to 1 year.

5. FAMILY HISTORY : is a strong predictor for breast cancer.

Despite known hereditary risk factors, the majority of breast cancer are increased in women with no such risk factors 10-20% of breast cancer patients have a family history suggestive of hereditary susceptibility.

In my study one woman had a positive family history of carcinoma breast in her maternal aunt and one woman had a positive family history of carcinoma breast in her paternal aunt.

6. SOCIO ECONOMIC STATUS :

Despite breast cancer being common in women of high socioeconomic status 90% of women in my study belonged to low socio economic status with an occupation as a manual daily wage earner with an income around 1200/- per month.

Their education status was elementary school in 4% and 6% attended upto VI std.   90% of my patients were illiterate.

Family support was not very forthcoming to almost all the subjects.

97% of patients are from nuclear family with nobody to look after their family during their hospital visit.

Affordability was very difficult for all the patients including blood and histopathological tests.

The disease awareness and importance of breast self examination was absolutely nil in all patients except one patient.

All the patients were surprised to hear about cancer breast and the various treatment modalities.

7. DIET :

A high fat diet consisting of ghee and oil in vegetarian and red meat once a week in non vegetarian was a observed in 24% patients.

None of my patients were found to use alcohol.

None of my patients were smoker. None of my patients had external estrogen supplementation

8. PREVIOUS BREAST DISEASE :

3% had treatment for mastalgia in younger days with analgesics and water restriction. 2% had cyclical mastalgia and 1% non cyclical mastaligia. 2% had treatment for fibroadenosis with analgesics for one month. One patient had fibroadenoma which was excised at her 20 years of age.

Two patients underwent lumpectomy. One in her younger days –
pathology report not available.

Another the lump came as carcinoma and was admitted for surgery. Two
patients had mammogram prescribed by their general physicians with positive
report.

9. PLACE OF RESIDENCE :

78% were found to reside within 50 km of this referral hospital.

20% around 50 -100km radius.

One patient with positive lumpectomy finding was referred here from
>200km far away place.

I TUMOR FACTOR

1. SIDE:

Of 100 patients 66% had lesion in left breast and 34% in right breast.

Left more common than right.

2. QUADRANT :

- o 68% had lesion in upper outer quadrant which is more common.
- o 22% in lower outer quadrant
- o 8% in upper inner quadrant
- o 2% in lower inner quadrant

3. SIZE :

- o No patients presented to hospital with a lesion <1cm.
- o One patient came after lumpectomy and she was categorized as T_x.
- o 10% had lesion of 1-2 cm and the lesion was discovered on pain of lump.

- 68% came with lesion 2-4 cm. The presenting symptom was pain, nipple discharge lumpiness.

- 20% had lesions 4-6 cm in size. These patients came to the hospital late with lymphnode metastasis. These patients also delayed coming even after the lump was brought to their notice. 2% came with lesion more than 6cm.

4. FIXITY :

- 82% had mobile lump.

- The lump were found to be mobile irregardless of size in large breasts smaller breasts tended to have early fixity to pectoral fascia and muscles.

- The skin involvement was seen in10%.

- The skin involvement was in the form peau-de-orange edema, and ulceration in 4%.

- 10% had tumour fixed to deeper structures.

5. NIPPLE RETRACTION :

- 18% had nipple retraction 12% had lesions in upper outer quadrant but with size 3-4 cm with edge of tumour near the nipple areola complex.

o 4% had lesion in lower outer quadrant, 2% had it in upper inner quadrant.

6. HPE STATUS :

o All the 97% had infiltrating ductal carcinoma.

o This seemed to be more common in my study.

o 2% of patients had infiltrating lobular carcinoma.

o 1% of my patients had medullary carcinoma.

7. GRADE :

o 52% had low grade or well differentiated tumor

o 42% had intermediate grade

o 6% had high grade.

o Of this 2 patient had 3-4 cm lesion.

o 4 patients had 1-2 cm lesion in high grade or poorly differentiated tumour.

o It was seen that these tumours tended to disseminate to lymphnodes early irrespective of the tumour size.

o The metastasis was upto level II.

o The lymphnodes were fixed and 3-4 in number.

III NODE FACTORS

1. NUMBER OF NODES :

- o 28% had no nodes.

- o These patients had tumours of either well differentiated variety and the lesion was 1-2cm.

- o 66% had 1-3 lymphnode involvement.

- o These lymphnodes were tender and usually involved the anterior axillary group.

- o Only 8% had more than 3 lymphnodes involvement.

- o This was seen in either large tumors with late presentation and in poorly differentiated tumours.

2. LEVEL OF NODES :

- o 28% had no nodal involvement.

- o 64% had level I group of nodes involved.

- o 8% had level II node involvement

- o 6% had moderated differentiated tumour

- o 4% had poor differentiated tumour

3. FIXITY :

- 90% had no fixity to each other or surrounding fascia.

- 10% had fixed nodes.

- 4% had poorly differentiated carcinoma with lymphnodes metastasis extending up to level II.

- 4% had mode rarely differentiate carcinoma with involve of level II nodes.

- 2% had well differentiated carcinoma extending upto level II.

4. INTERNAL MAMMARY NODES :

- None of the patients in my study had internal mammary node involvement.

5. SECONDARIES :

One patient had supraclavicular node involvement. This patient had level II fixed node of tumour size 3-4 cm, well differentiated.

1% had pleural involvement. This patient had fixed level II nodes with tumour in upper inner quadrant and, moderated differentiated 2-3 cm tumour. 1% had liver secondaries 2 cm lesion in right lobe segment VII. This patient had 4-5cm mobile tumour with level I mobile node with moderately different infiltrating ductal carcinoma.

DISCUSSION

1. AGE :

Carcinoma breast usually occurs in women over 40 years. If at earlier onset it may be familial. The incidence of breast cancer increase with age the incidence of breast cancer increases with age and steadily after age 50. Thus 75% of all cases of breast carcinoma are diagnosed. In postmenopausal women. The risk of developing breast cancer is 19,608 at 25 years, in 33 women at 55 years and in 8 for women living in to their 80's.

2. MENOPAUSE :

Early menarche (before 12 years), nulliparity, late menopause (after 55 years) are known to increase breast carcinoma risk. Increase exposure to estrogen. Increase risk for development to carcinoma.

Text book of clinical oncology says breast cancer may be 2 separate diseases.

A premenopausal disease influence by genetic, hormonal and reproductive factors. A post menopausal disease influenced heavily by diet, body habitus and endocrine factors.

Breast tissue and breast malignancy are dependent on estrogen for their growth. A post menopausal breast cancer is far less common in Asian countries than in western countries.

3. PARITY :

Women who complete their first full term pregnancy after age 30 are 2-5 times more likely to develop breast carcinoma than those before age 18 years. Carcinoma breast is common in nullparous

Oxford text book of oncology says nulliparous women have a greater risk of breast cancer **(Mustachi 1961).**

Multiparity and full-term pregnancy before 20 years of age protect women from the disease **(Mac. Mahon et al, 1970).**

Women who had oophorectomy before 40 years of age have reduced risk of breast cancer **(Lieinfeld, 1956).**

Androgens have been proposed as a possible carcinogenic factor in breast carcinoma. This hypothesis is mainly supported by fact that incidence of breast cancer is higher post-menopausal women, where androgenic levels are high.

Administration of androgens for cystic disease has been shown to increase the risk of breast cancer **(Veronesis and Frizzocaro 1968).**

4. LACTATION :

Cancer breast is common in and women who have not breast fed their babies.

There is a decreased risk of breast carcinoma in women who nurse for a long duration. Longer lactation period decrease total number of menstrual cycles and are protective.

Breast feeding does appear to have a small protective effective (decreased relative risk).

5. FAMILY HISTORY :

Majority of breast cancer are increased in women with no such risk factor. 10-20% have family history suggestive of hereditary susceptibility 5% breast cancer attributed to known genetic defect in women of Jewish desent with diagnosis of breast cancer about 25% have genetic mutation.

Identifying hereditary risk for breast cancer is a 4 steps process that includes

1. Obtaining complete multigenerational family history
2. Assessing the appropriateness of genetic testing for a particular patients
3. Counselling the patient
4. Interpreting the results of testing

A hereditary risk of breast cancer is considered in a family if it includes two or more women who developed breast cancer before age 50 years.

Any women diagnosed with breast cancer before age 50 years is asked about first, second and third- degree relatives on either side of the family.

Approximately 5% breast cancer cluster tightly in what appears to be a hereditary fashion.

Numerous studies have shown that the risk of breast cancer increase if a first degree relative (mother, sister daughter) has been diagnosed with breast cancer. Relative risk in range 1.5-2 have been reported on these increase to five fold if two 1° relatives have been diagnosed with cancer breast.

If a mother or sister has been diagnosed premenopausally with bilateral breast cancer the absolute risk to other 1° relatives approaches 50%.

A postmenopausal diagnosis in the affected relative poses less of a risk than premenopausal diagnosis. It appears that the risk continues to decrease as the index case ages and women whose mothers were diagnosed past age 60 have a relative risk of 1.4 compared with women whose families are free of breast cancer.

Relative risks association with a family history of breast cancer.

Family history	RR
One 1° relative	1.5-2.0
2 1° relative	55.0
if 1° relative had B/L	
post menopausal carcinoma	~10.0
if 1° relative had B/L	
premenopausal carcinoma	~20.0

6. SOCIO ECONOMIC STATUS :

Carcinoma breast occur more in women with western life style.

This disease is prevalent in women of high socio-economic status.

The factors which went in to assessing the socio-economic status was

1. **Occupation :** Of both husband and wife. Three fourths of my patients were daily wage earners, with a work of hard labour. Loss of a day's work by a hospital visit will result in loss of income.

2. **Education:** The patients were barely literate many of them could only write their names and read few words slowly. Almost all had only primary education. This had an effect in not knowing about the disease, not able to make a choice of treatment preferred, not able to decide if the patient wanted treatment or not. Much effort had to be put in to making them understand the nature of their disease.

3. **Family support:** Family support was not very forth coming. The patients had to make arrangements for their children care before hospital visit. But, since most of my patients were post-menopausal the hospital visit was delayed due to family functions and religious restrictions.

4. **Disease awareness:** Almost all my patients were not aware of carcinoma breast. They did not know about. Breast self-examination and the importance of diagnosing the disease in the early stage itself. All the patients were not aware of the definitive treatment for cancer breast.

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7. DIET:

A diet with reduced phytoestrogenus and fibre diet and high fatty diet with alcohol is a predisposing factor.

A high fat diet leads to obesity and in post menopausal women conversion of androstenedione to estrone by adipose tissue with increase in estrogen exposure.

Finally evidence suggests that chronic consumption of food with high fat content. Contributes to an increased risk of breast cancer by increasing serum estrogen levels.

Alcohol consumption is known to increase serum levels of estradione.

Meta – analysis of 12 studies that included 10,000 subjects found a positive correlation of fat – intake and breast cancer for postmenopausal women.

Breast cancer rates are higher in urban population than rural within the same country.

Incidence rates have greatly increased in countries like Japan where major life style changes occurred. Factors include diet and body habitus toward a western life style of high fat diet, more junk and fast food, and use of food decreased in phyto oestrogens.

In my study there was increased incidence in rural population and low socioeconomic status probably due to high fat diet and the higher socio economic group preferring the private centres.

Alcohol consumption has been associated with breast cancer risk in a number of studies and is now an established factor effect is more pronounced in post menopausal women who consume more than 2 or 3 glasses of wine per day.

Recent studies have shown that ethanol ingestion can increase sex steroid hormone levels in non alcoholic premenopausal, women by an unknown mechanism.

In my study no women was an alcohol consumer may be due to social taboos and religious restrictions.

8. PREVIOUS BREAST DISEASE:

Relative risk for invasive breast carcinoma based on pathological examination with benign breast disease.

1. Slightly increase risk of 1.5-2 times in seen in hyperplasia moderate or florid, solid or papillary.

   Papilloma with a fibrovascular core.

2. Moderately increase risk (5 times) is seen in atypical hyperplasia (ductal or lobular).

Hyperplasia with atypia in a proliferative disease is associated with 8% risk of developing invasive breast carcinoma with patients in negative family history and 20% risk in patients with positive family history.

Papilloma, sclerosing adenosis lobular carcinoma in situ known to increase risk.

It has been long recognised that a history of benign breast disease increases a woman's risk of breast cancer.

Infact, a woman who has had a biopsy for any lesion of benign diagnosis appears to have an increased relative risk of breast cancer of approximately.

1.5 to 2 compared with women who have had no diagnostic procedure performed on the breast beyond a mammogram.

It appears that women who have a benign biopsy showing proliferative changes such as ductal or lobular hyperplasia have a relative risk of 1.5 to 2 compared with unbiopsied women.

Where 5-10% of women with atypia (atypical ductal hyperplasia or atypical lobular hyperplasia) have increased relative risk of 3 to 5.

The study of **Dupont and Page** shows that if a woman with atypical proliferative changes also has a family history of breast cancer then her relative risk increases even more up to 11.

This is a significant risk factor. In several studies women who had mastectomy the subsequent development of cancer in the remaining breast has been estimated 0.5 to 0.8% a year.

9. PLACE OF RESIDENCE :

Women with better access to a hospital tend to present in early stages.

The mode of conveyance, charges to reach the tertiary referral hospital has significance in a rural population filled city in a developing country like India.

The women who presented in early stages came from villages within 50 km of the hospital where the study was conducted.

II TUMOUR FACTORS

1. SIDE :

Breast lesions present more on left side.

2. QUADRANT :

Carcinoma breast occurs mostly in upper outer quadrant due to more amount of fibro fatty tissue

Bailey and love text book of surgery says

60% in upper outer quadrant

12% upper inner quadrant

10% lower outer quadrant

6% lower inner quadrant

12% behind upper aueola complex

In my study too the findings were similar.

in upper outer quadrant	68%
upper inner quadrant	8%
lower outer quadrant	22%
lower inner quadrant	2%

3. SIZE :

The risk of recurrence increases linearly with tumour size for patients with fewer than to lymphnode involvement with metastasis.

Effect of tumour size on prognosis is by following SEER 5 year survival data.

The size of primary carcinoma is of great importance in the prognostic assessment.

Kaseilny et al study data form 2648 cases follow up for 10-25 years – a direct relationship between the increase in tumour size and worsening of prognosis was found.

Adair et al (1974) found a considerable difference in survival, both in patients with negative and with positive node, according to size of primary carcinoma.

Russo et al (1987) n a multivariate analysis of different characteristics of 646 breast carcinoma describes the size of primary tumour as one of the must important independent prognostic variables.

Valagussa et al (1978) showed that the 5 year relapse rate was 37% in patients with positive nodes and small primary tumour less than 2 cm and 79% in patients with positive nodes and large primary tumours (> 5 cm).

Mernon et al (1992) showed that cases with clinical axillary presentation without palpable or mammographically detectable primary carcinoma have a relatively good prognosis inspite of extensive axillary involvement and the undifferentiated character of the axillary metastases.

In my study the size of the primary tumour was taken in to account and it showed that the axillary nodal status depended on the size of tumor and also the size of breast. A small tumour in a small breast had early locoregional spread and fixity than a large tumour in large breast.

4. HPE STATUS :

INFILTRATING DUCTAL CARCINOMA - This is the most common type of breast cancer, occurring as an irregular, hard nodule averaging 1 to 2 cm. Histologically, the tumor is composed of malignant ductal cells disposed in cords, solid cell nests, tubules, anastomosing sheets, and various mixtures of all these. Tumors are graded according to the degree of nuclear atypia and histological (tubule) differentiation.

INFILTRATING LOBULAR CARCINOMA – This accounts for 5% of invasive carcinomas, more frequently multifocal and bilateral compared with other breast carcinomas of duct origin. It appears as a rubbery, poorly circumscribed mass composed of small uniform cells forming strands of infiltrating tumor cells arranged concentrically about ducts.

MEDULLARY CARCINOMA – 1% of a carcinoma it is large soft well – circumscribed tumour 2-3cm in diameter .

Histologically

1. Absence of desmoplasia

2. Moderately tense lymphoplasmacytic infiltrate

3. Large pleomorphic tumour cells growing in solid syncitium like anastomotic masses

Only when tumour has all above features does it follow a less malignant course.

5. GRADE OF TUMOUR :

Tumor grade is an important prognostic variable. The Nottingham combined histological grade is recommended by the AJCC staging system.

A tumor is graded by assessing three morphological features

i) Tubule formation

ii) Nuclear pleomorphism

iii) Count of mitosis

Histological grading shows significant correlation with prognosis (**Boom & field 1971, Contesso et al 1989**), **Freedman et al 1979** following up 1759 patients with infiltrating ductal carcinoma over ten years, showing a statistical difference in survival from 56% (grade I) to 33% (grade III).

A multivariate analysis showed that simple mitotic count is the best single prognostic predictor followed by tumour size, lymphnode invasion and skin invasion.

Tumour grade is an important prognostic value, text book of clinical oncology says

A value of 1 (favourable) to 3 (unfavourable) is assigned to each feature.
Higher the grades worse the prognosis
Grade I – 3-5 points
Grade II – 6-7 points
Grade III – 8-9 points

III. NODAL INVOLVEMENT :

Nodal involvement is a greater prognostic indicator for breast cancer recurrence. 10 year survival is 90% in node negative tumour less than <1 cm.

The prognostic significance of axillary involvement is well documented.

Preliminary observations reported **high survival rates** in **node-negative patients - 70-75%** and low survival rates in node-positive patients 25-30%.

This assessment in based on number of metastatic nodes **(Fisher et al).**

Salvaderi et al, Cascnell et al study shows that if one single axillary node is involved then the prognosis is very close to that of node negative patients.

But if ten nodes are metastatic then the prognosis is more ominous.

The level of axillary invasion plays an important role the prognosis is much worse when level III is involved **(Schottenfeld et al, Veronen et al 1993).**

Regional lymphnodes our harbingers of systemic disease and not barriers to tumour spread. Patients with axillary lymphnode metastasis have a higher rate of relapse and distant metastases than patients without nodal metastasis despite complete removal of all local tumour.

INTERNAL MAMMARY NODE :

Internal mammary node involvement is an important diagnosis factor **(Veronei et al 1983, Lancone et al 1987).**

In a series of 1110 patients prognosis when axillary or internal mammary nodes are involved separately are similar.

The prognosis is excellent when both nodal stations are free of metastases and it is very grave when both an involved **(Veronen et al 1985).**

DISTANT METASTASIS

The most common sites are lungs, bone and liver.

They rarely present at the time of 1st diagnosis and in majority of cases they appear after treatment of primary.

The distribution is influenced by biological and haematodynamic factor.

Liver and bone metastasis may be present in the absence of macroscopic lung metastais suggesting that malignant cells may easily go through lung filter.

An analysis of 3000 patients by institute breast Gustave over a 15-30 years period has shown relationship between pathological tumour size, number of axillary node metastasis, histological grade and subsequent probability of distant metastasis and death.

This is a blood borne spread in relation to the development of a primary breast cancer and spread to axillary lymphnode.

SUMMARY

A postmenopausal woman of 50-60years with 2 or more children, breastfed upto 6 months of age with no previous family history of breast or ovarian cancer from a disease aware middle to high socio economic status on a low fat diet with no history of previous benign breast disease, residing within 100 kms of our institution had good prognosis.

A T 1 lesion 1-2 cm, mobile, not fixed to deep structures with infiltrating ductal carcinoma of low grade variety, or well-differentiated tumor with no lymphnode involvement or level - I mobile lymphnode, no internal mammary, no secondaries had less chance of recurrence and very good prognosis.

CONCLUSION

GOOD PROGNOSTIC FACTORS

1. Carcinoma breast in a woman between 50-60 yrs of age has a better prognosis than in women younger.

2. A post menopausal woman has better prognosis than pre menopausal.

3. A multiparous woman with 2 or more children, who has breast fed her children atleast up to 6 months of age has better prognosis than women who have never breast fed.

4. A woman with no previous history of breast carcinoma in her family and a woman from high to middle socio-economic status with a good disease awareness and taking a low fat diet with a low body mass index (BMI) had a better prognosis.

5. Though women with history of previous benign disease and treatment with hormone were more prone to breast carcinoma, in my study that history of could not be clearly elicited due to less educational status and less disease awareness among my group of patients.

6. Women residing within 50 km of the hospital where my study was conducted had a better prognosis due to reaching the hospital earlier and in early stages of disease.

7. Carcinoma breast was found to be more common on left side than on right side and were more common in the upper outer quadrant confirming with the incidence worldwide and they behave better than inner quadrant Tumors.

8. AT1 lesion 1-2 cm in size in a good prognostic factor due to lesser tumour tissue micro invasion.

9. Lesions that were mobile, not fixed to underlying pectoral fascia, muscles had better prognosis due to easy complete removal of tumour and less chance of recurrence.

10. Lesion with no nipple retraction or skin involvement had better prognosis due to lesser lymphatic permeation.

11. In my study infiltrating ductal carcinoma was the most common type of tumour.

12. Lesions that were low-grade variety or well-differentiated types have better prognosis due to higher mitotic rate and nuclear pleomorphism.

13. Lesions with no lymphnode involvement had the best prognosis.

14. Lesion with axillary lymphnodes affecting level I group and mobile lymphnodes are better prognostic indicators.

15. No patients in my study group had internal mammary node involvement. Though book says there is no difference between internal mammary

lymphnode positive and axillary lymphnode positive, the removal of affected internal mammary node has higher morbidity.

16. Patients with carcinoma breast without any secondaries have a better prognosis but it depends on their 'T' stage and nodal status.
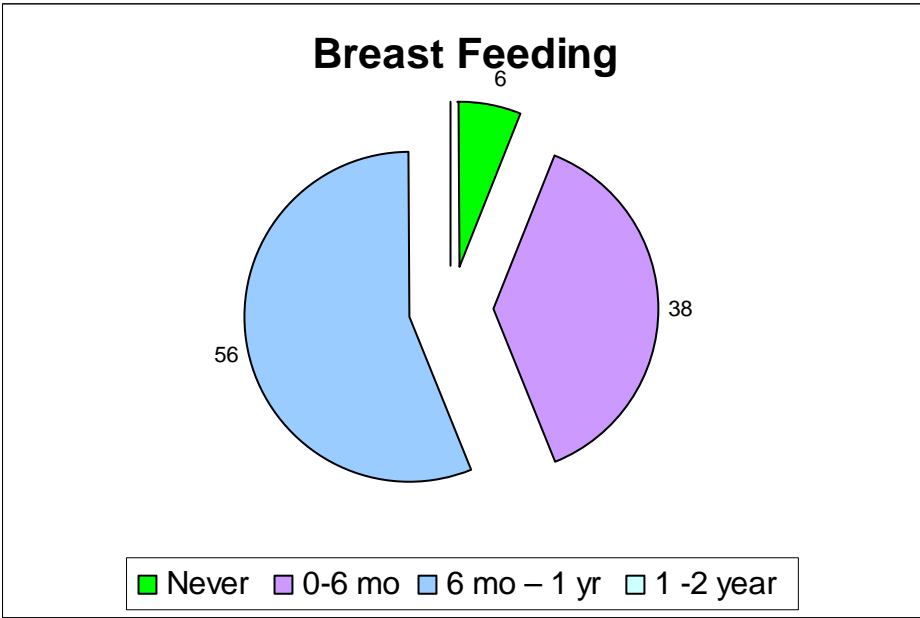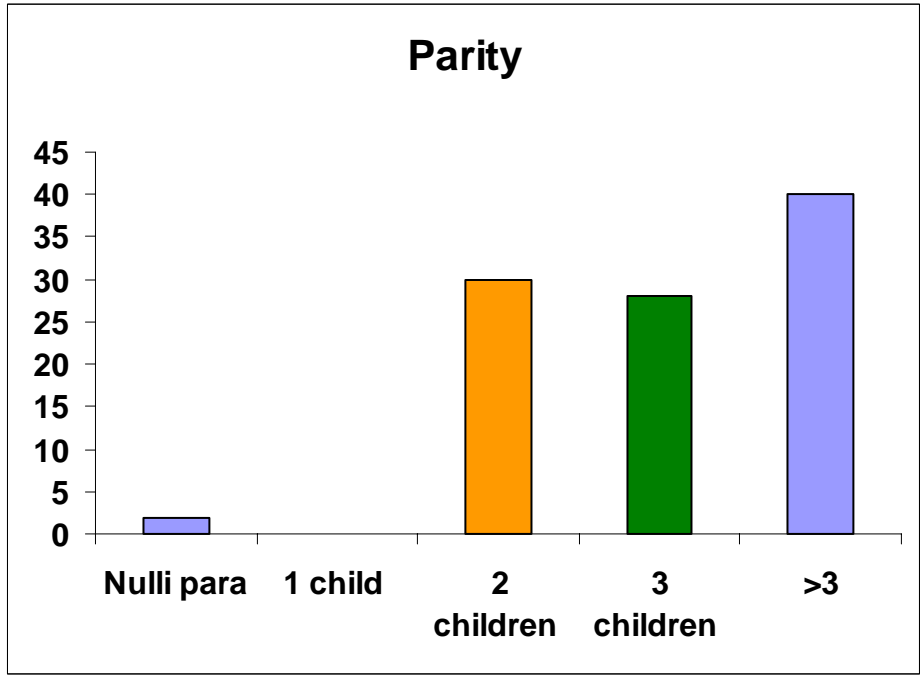
17. Patients with liver secondaries, single have a better prognosis than pleural secondaries.

18. Patients with bony secondaries present early with symptoms but high clinical suspicion index is necessary for earlier treatment and better prognosis.
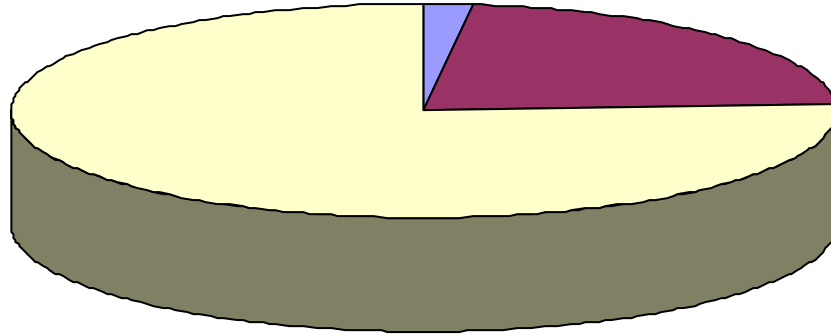
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PROGNOSTIC FACTORS IN CARCINOMA BREAST IN FEMALES – 100 PATIENTS
PROFORMA

Name :   Age :   Menopausal Status :

Parity   :

Breast Feeding   :

Family History   :

Socio Economic Status   :

Diet   :

Previous Breast Disease   :

Side of Tumor   :

Quadrant of Tumor   :

Size of Tumor   :

Fixity to Pectoral Fascia/Skin :

Nipple Retraction   :

Histo Pathology Type   :

Grade of Tumor   :

No. of Axillary Lymphnodes :

Level of Nodes   :

Fixity   :

Internal Mammary Nodes :

Secondaries   :

Parity

45				
40				
35				
30				
25				
20				
15				
10				
5				
0				

Nulli para   1 child   2 children   3 children   >3

Breast Feeding

6

38

56

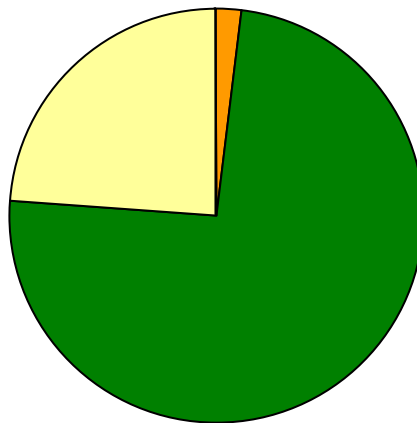Never   0-6 mo   6 mo – 1 yr   1 -2 year

Socio economic status

☐ High income ☐ Middle income ☐ Low income

Diet

☐ Vegetarian ☐ Non-vegetarian ☐ High Fat diet ☐ Alcohol