CARCINOMA OF THE BREAST AS SEEN AT MUHIMBILI MEDICAL CENTRE

A CLINICOPATHOLOGICAL STUDY OF 100 FEMALE PATIENTS

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DECLARATION

I hereby declare that this study is original work done by me. I sincerely acknowledge and appreciate the contributions of other people used in writing this book. This work is a product of the collaboration and dedicated efforts of a wide range of people whom I wish to extend my sincere gratitudes.

Signature----------

Signature----------

*Certified by Dr. M. R. Aziz, the Supervisor

DEDICATION

This work is dedicated to my parents. My father showed me the road to education and made sure I followed it. My mother offered her support. It is dedicated also to my family who saw me through the struggle.

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CHAPTER I

INTRODUCTION

The female breast can be the seat of many pathologies, depending upon such - factors as age, socio - economic status of the population, hereditary predisposition and environmental factors. Neoplastic lesions and especially the malignant ones comprise the most - important clinical as well as social - problems concerning the breast. In relation to other breast pathologies, breast cancer is associated with far more significant morbidity and mortality. Management of breast cancer is fairly expensive for the poor Tanzanian woman and the state, it is quite demanding and often frustrating for both the patient and her doctor.

The disease is not a rare - entity in Tanzania. Between 1969 and 1987, 1356 cases of female breast - cancer were reported (1). Author of this work has seen 100 cases at Muhimbili Medical Centre alone in one year. Clinico - pathological pattern of presentation of this serious disease in our environment has not been sufficiently documented. Medical science knows many examples of similar pathologic entities presenting differently in differing environmental conditions. Is the clinico- pathological - pattern of presentation of carcinoma of the female breast in Tanzania different from other parts of Africa, Asia or Europe and North America. This is the question that prompted me to undertake this work.

Breast cancer is a major public health problem of great interest and importance to physicians in a variety of specialities. Furthermore, long-term results are now available from clinical trials initiated in 1970s and 1980s to evaluate the usefulness of early detection with mammography and physical examination, breast conserving treatment with limited breast surgery and irradiation adjuvant systemic therapy with hormonal therapy and chemotherapy.

In many parts of the world, cancer of the breast is the commonest cancer in females. Age adjusted - incidences of the disease vary from one continent to another and from one country of the same continent to another. Generally however, there are zones of high, intermediate and low incidences. Figures depicting incidence rates for 1976 in different parts of the world generally showed that high rates were recorded in North America; (Canada = 80.3, USA = 79.9) and Western Europe (U.K. = 54.5, Switzerland = 70.6). Eastern European countries had intermediate rates, (Poland = 31.5). Africa and Asia - showing the lowest rates (Nigeria = 15.3, India = 20.1 and Japan 12.1).(3)

The pattern of breast cancer mortality varies markedly when examined on an international scale. Age adjusted death rates for 1976, - indicated high rates for Western Europe (Denmark = 28.59) and the North America (U.S.A. = 22.45). Eastern Europe had lower rates when compared to Western Europe and North America, (Poland = 13.80, Bulgaria = 13.24). Still lower rates were recorded in

Asian countries, where Hong-Kong and Phillipines recorded rates of 9.18 and 5.81 respectively. Breast cancer is relatively rare in Japan. In 1976 Japan recorded a mortality rate of only 4.94. Other Asian populations have similarly low rates. Studies of breast cancer in Japanese women and their - descendants who migrated to U.S.A. indicate that the risk of breast cancer increases as the population migrates, giving further credit to the concept that environmental and cultural factors may contribute to the international variations observed. (4) Further, Black American women have been observed to have a higher incidence of breast cancer (57.9 in San Francisco) as compared to Black African women (Ibadan - Nigeria 15.3) - The black ladies in the U.S.A. thus seem to head for the higher rates characteristic of their white countrywomen, again giving further credence to the influence of the environment.(5)

In the majority of Sub Saharan African countries, its position as the most common malignancy in females is exceeded only by the larger incidence of cervical cancers, except in Sudan (6 - 12).

The disease is said to be advanced (stages III and IV) at the time of presentation in the majority of African countries (13), including Tanzania (14), the proportion of advanced cases being as high as 95.6 percent as reported by Kenda et al, (15). By the year 1985 the proportion of advanced breast cancer in the U.S.A constituted less than 20 percent.(15) A greater proportion of late cases fell amongst the black American women, and despite the same overall life time risk

of breast cancer between black and white American women, the risk of death is greater among young black women. The reasons for greater mortality among younger black women has been the subject of considerable speculation Possible factors sited include a later stage of diagnosis, a lower rate of positive estrogen receptor assay and differences in medical care or differences in histologic type of cancers diagnosed in blacks - compared to whites.(17)

Nearly 80 percent of women in Tanzania live in the villages (18), and have to go through an organised hierachy of medical services before they reach the regional or consultant hospitals where they are investigated and managed. Do they make their first appearance late? And does the health system play any role in delaying these patients? This work shall address these questions. It should be interesting to compare the stage at presentation of patients in different age groups. This could give an insight into whether younger patients are more concerned about their breasts.

Ever since it was recognised that breast cancer could be hormone dependent and that tumour regression by hormonal manipulation could be realised to the advantage of the patient it became a routine to treat most premenopausal patients by some kind of hormonal manipulation. Traditionally, this consisted either of hormonal ablative therapy or additive therapy. The invention by - pharmaceutical laboratories of an effective antiestrogen tamoxifen and the estrogen biosynthesis inhibitor aminoglytethimide has revolutionalised the

management of breast - cancer by hormonal manipulation. Surgical hormonal manipulation is now a matter of history. However, it became known later that not all patients are lucky enough to respond to hormonal manipulation. Thus determination of estrogen receptor (E.R.) status of breast cancer is now a routine procedure in the management of breast cancer patients. It has now become clear that determination of E.R. status is more useful in identifying those who are negative and thus spare them of unnecessary ineffective hormonal manipulation, which is after all very - expensive for the majority of patients. Currently, the antiestrogen tamoxifen is being used in Tanzania for both pre and - postmenopausal patients who can afford to buy it. This is done however, on empirical basis, without attempting to predict the chances that an individual patient will respond to such treatment. Is this a justifiable practice? The question shall also be addressed in this work. It might not be technically and economically, feasible to determine the E.R. status of every single patient in our setup, but at least we should have a baseline general knowledge of the E.R. status of the population of breast cancer patients in our environment, to be able to justify or otherwise our indiscriminate use of tamoxifen. Hormone receptors shall be discussed further in the section of literature review.

AIM OF THE STUDY

This is a prospective study whose principal goal is to document the clinico-pathological pattern of presentation of carcinoma of the female breast in Tanzania as seen at Muhimbili Medical Centre.

The working hypothesis is that most patients with breast carcinoma in Tanzania present late, when the disease is already advanced (stages III and IV), when chances of long term survival are almost non existent, and that a great majority of them are younger than their counterparts in the West. Should this be found to be true, then an explanation shall be sought. It is hoped that this work will come up with proposals and recommendations as to what can be done to increase the number of early presenters with the perspective of improving the survival and a better quality of life of breastcancer patients seen in Tanzania.

Estimation of the degree of oestrogen receptor positivity will be an important component of this study. The aim is to be able to recommend the type of systemic adjuvant therapy that our patients should be offered. This work shall offer a comparison of the clinico-pathological pattern of presentation of the disease in Tanzania as seen at Muhimbili Medical Centre with what has been documented from elsewhere in Africa and the world at large.

SPECIFIC OBJECTIVES OF THE STUDY

The general aim of this study is to attempt to establish the following specific objectives:-

1. To determine the mean age and range at presentation of women with carcinoma of the breast, and the age range of peak presentation. The age ranges shall be (a) below 20 years, (b) 20 - 30 years, (c) 30 - 40 years, (d) 40 - 50 years, (e) 50 - 60 years and (f) above 60 years.

2. To see whether breast carcinoma has equal predeliction for either of the breasts.

3. To determine whether breast cancer has a preferential area of location among the four quadrants (that is upper lateral and medial and the lower lateral and medial) or the central region of the breast.

4. To define the stage of the disease using the TNM staging system (U.I.C.C. - TNM Classification Atlas Third Edition - 2nd Revision 1992) for every patient in the study. It shall be presented in this work as stage I, II, III, and IV (Ref. To methodology).

5. To find out the reasons for delay in presentation. Do patients delay in presenting themselves or is the health system contributing to the delay?

6. This work shall also seek to determine whether family history of carcinoma of the breast is a prominent feature among breast cancer patients in our environment. The emphasis here shall be on first degree relatives from both the maternal as well as the paternal sides.

7. To determine the predominant histological type of the tumour, the two major groups being (a) Intraductal and (b) Lobular types.

8. To determine the oestrogen receptor status among our patients.

9. To describe the practice of lactation and the distribution of parity among breast cancer patients in our environment.

10. To establish whether or not contraceptives have any aetiological role in breast cancer cases seen at Muhimbili Medical Centre.

CHAPTER - 2

LITERATURE REVIEW

ANATOMY AND DEVELOPMENT OF THE BREAST

The breasts or mammae, are modified glands of cutaneous origin. They consist of three anatomical parts, a cutaneous layer, a stroma consisting of - subcutaneous fatty layer and a connective tissue supporting layer, and a parenchyma or glandular tissue.

Topography

The extensions of the breast are so variable in the adult female that precise topographic landmarks cannot be defined. Variations due to gravid state, menstrual cycle, obesity, age, and other factors all alter the topographic contours. The parenchymal tissue usually extends beyond the protruberance of the breast. From a surgical point of view, the breast topographically extends to the clavicle above, the midline medially, the seventh coastal cartilage inferioly and the margin of the latissimus dorsi laterally. The breast parenchyma frequently extends into the axilla - through an opening in the axillary fascia (foramen of langer) as the - axillary tail of Spence. The parenchymal tissue usually extends beyond the protruberance of the breast.

Structure

1. Cutaneous layer - It is thinner than the skin of the axilla. It is covered by downhairs associated with numerous sebaceous and sweat glands. Superficial veins may be prominent. It is more adherent to the underlying superficial fatty layer than in most areas, but is very flexible and elastic modifications of the skin are present over the centre of the breast, namely the areola and the nipple.

(a) Areola - consists of thin pigmented skin that varies with natural colouring of the individual and pregnancy. Elevations may be seen in the areola caused by underlying sebaceous glands and rudimentary milk glands (areolar tubercles of - Montgomery).

(b) Nipple - varies in shape and position. It contains many sebaceous glands and numerous smooth muscle fibres. The skin is wrinkled and pigmented - and contains 15 - 20 minute openings of the underlying lactiferous ducts.

2. Stroma It lies beneath the skin covering the whole gland except - under the nipple and areola. It consists of superficial fascia which also extends deep to the parenchymal tissue and is therefore termed the mammary adipose capsule. It interposes itself between the lobes and lobules and produces the smooth external appearance of the breast.

Other connective tissue elements consist of strands which extend from the apices of the lobes to the corium of skin, the retinacula mammae. They are especially well developed in the upper quadrants of the breast and are termed the - suspensory ligaments of Cooper.

3. Parenchyma This is a mass of glandular tissue, most prominent in the subareolar area. It is - composed of 15 - 20 lobes of irregular pyramidal groups of glandular material. The apex of each lobe points towards the nipple. Each lobe possesses a lactiferous duct, whose orifice is located in the nipple. Each duct is - dilated in its subareolar position to form a sinus lactiferous.

Arterial supply The main supply to the breast comes from the - internal mammary artery. The breast receives additional supply from branches of the axillary artery and aorta.

1. Internal mammary - is a branch of the first portion of the subclavian artery. The second and forth perforating - branches are most important in the blood supply to the breast.

2. Lateral thoracic is a branch of the second portion of the axillary artery and supplies the lateral and caudal portions of the breast.

3. Aortic intercoastals - may send small branches to the breast by its lateral cutaneous rami.

Venous drainage

The deep veins drain along routes roughly corresponding to the arterial blood supply. Thus one major route is through the anterior intercoastal perforating veins to the internal mammary veins. Another is by way of multiple branches to the axillary vein. A third route is by way of posterior branches anastomosing with the intercoastal - veins. This last route has special significance, since the intercoastal veins communicate with the vertebral veins. This anastomosis with the vertebral veins is the explanation for the often capricious metastasis of mammary cancer to the vertebral bodies or even the sacrum or pelvis without the presence of metastatic deposits in the lung.

Lymphatic drainage the lymphatics of the breast may be divided into cutanous and parenchymal drainage:-

1. Cutanous drainage - radiates from a circumareolar plexus
   (a) Lateral - to the anterior (pectoral) axillary nodes.
   (b) Superior - to the medial axillary nodes and the apical nodes
   (c) Medial - to the internal mammary nodes and to the cutaneous lymphatics of the opposite side

(d) Inferior - to the cutaneous lymphatics of the upper abdominal will and the liver.

2. Parenchymal drainage - receives channels from the breast proper as well as the skin of the nipple and areola. These afferent - channels drain into the subareolar plexus. From this plexus two main efferent channels arise:-

(a) Superior channel - receives tributaries from the anterior portion of the gland and drains into the anterior axillary nodes.

(b) Inferior channel - receives tributaries from the inner portion of the gland and drains into the anterior axillary nodes.

(c) Accessory channels - two major efferent channels extend from the subareolar plexus to the apical nodes of the axilla and to the lateral (brachial) nodes.

Histology of the resting mammary gland

Each lobe of the mammary gland is an independent compound alveolar gland. The mammary gland is a conglomeration of a variable number of such independent glands, each with its own excretory duct which has a separate opening on the surface of the nipple. The excretory ducts - measure from 0.4 to

0.7 mm in - diameter at the nipple surface and run perpendicularly through the nipple to turn and radiate out - toward the periphery of the breast. Beneath the areola they dilate into a short fusiform area called the milk sinus. Beyond the mild - sinus the excretory ducts begin to subdivide into smaller and smaller branches forming the lobules of the lobe. Within the lobules the ducts subdivide further, forming terminal, elongated tubes, the alveolar ducts, which are covered by round evaginations the alveolae. Lobules are peripheral and scanty in the nulliparous breast.

The walls of the alveolae and the alveolar ducts consist of a prominent basement membrane surrounding a layer of myoepithelial cells, which in turn lie beneath a layer of low columnar glandular cells. These cells take a spiral course - about the larger ducts and probably play a role in propelling milk from the acini to the nipple during lactation.

The collecting ducts are lined with a double layer of cuboidal to columnar epithelium until the milk sinus is reached. Here the lining changes to squamous epithelium. This continues through the milk sinus to the surface of the nipple.

Each lobule is surrounded by a coating of dense, firm, interlobular connective tissue, which is an intimate part of breast parenchyma. The lobules are separated by a lesser coating of less dense fibrous tissue, the interlobular connective - tissue. This layer represents the supporting stroma of the breast.

PATHOLOGY OF BREAST CANCER

The medical profession has laboured to classify breast lesions from the time of Hippocrates. The first classification was offered by Celcius at the time of Christ:-

1. Cocoethes - early or precancerous lesions
2. Carcinoma without ulceration
3. Fungating tumours.

This was a clinical classification which has now undergone modifications many times. It was essentially an anatomic diagnosis describing the extent of cancer. The product of those modifications, is the present day T.N.M. classification.

Another method of classifying breast lesions is the microscopic - appearance of the lesions. It should be noted that the time picture of the neoplasm is often modified by the varied response of the breast to the presence of cancer often - resulting in bizarre histologic alterations.

A good pathologic classification would essentially describe the intrinsic appearance of the lesion and the varieties of response by the breast. Such responses as lymphocytic or desmoplastic reaction, apparently a kind of defence mechanism, or absence of any such features in other tumours.

A classification should help create a communication between pathologists and clinicians on therapeutic - decision making and prognosis.

In the past when there was only one treatment for a cancer or non cancer of the breast, a diagnosis of malignant or benign lesion would suffice. Today however, there are alternative treatments both primary and adjuvant, a precise - classification is an important factor in the choice of therapy. The prevalence of treatment trials is another significant factor for a good classification. This is essential in the stratification that assures comparability.

In the International Histological Classification of Breast Tumours by the World Health Organisation, breast cancer is devided as follows:-

1. Noninfiltrating intraductal and intralobular

2. Infiltrating intraductal and Intralobular

3. Special Histological variants
   - (a) - Medullary
   - (b) - Papillary
   - (c) - Cribriform
   - (d) - Mucous
   - (e) - Lobular

(f) - Squamous cell

(g) - Paget's

(h) - Carcinoma arising in intracanalicular fibroadenoma

IN SITU VERSUS INFILTRATING CANCER

It is beleived that every type of cancer is fully malignant capable of metastasizing and killing, irrespective of whether it is infiltrating or not.

During histological study of a tumour, if the malignant cells are not seen to penetrate the duct wall or invade the stroma at some points, it is not justifiable to conclude that infiltration has not taken place. It simply means that the cells are not - infiltrating at the sites studied. A more exhaustive classification has been presented by the pathology group of the National Cancer Institute (N.C.I.) Breast Cancer Task force.

Carcinoma of the Breast

Carcinoma of the nipple

- Paget's disease.

Carcinoma of mammary ducts

- Noninfiltrating - Intraductal carcinoma
  - Intracystic carcinoma
  - Solid duct carcinoma

- Infiltrating
  - Scirrhous carcinoma
  - Papillary carcinoma
  - Comedocarcinoma
  - Mucinous carcinoma
  - Medullary carcinoma

Carcinoma of mammary lobules

- Noninfiltrating lobular carcinoma in Situ
- Infiltrating lobular carcinoma

Rare carcinomas

- Tubular carcinoma
- Adenoid cystic carcinoma
- Inflammatory carcinoma
- Apocrine carcinoma

Lipid rich carcinoma

Carcinoma arising from fibro adenoma

Carcinoma with metaplasia.

- Osseocartilagenous formation
- Fibromyxomatons sarcoma like formation
- Squamous cell formation

Clear cell carcinoma.

Non - Paget's carcinoma in the nipple

Signet -ring cell carcinoma

Small - cell carcinoma

Individual carcinoma, even when a great many microscopic sections are studied, can only suggest in a general way whether or not infiltration has actually occurred. It cannot be regarded as decisive. (19, 20, 21)

Histologic Grading

Histologic grading of breast - cancer for degree of malignancy and prognosis has not been accepted unanimously. It is subjective, it varies from one pathologist to another, from specimen tissue blocks to tissue blocks, from area to area on the same slide and with the number of slides examined. Histologic grading is useful if used in light of the size of the primary lesion and the regional extent of the involvement. It can help together with many other factors to predict the behaviour of the malignant tumour.(22)

BREAST CANCER PRESENTING ON THE NIPPLE

Paget's disease

The lesion is sharply defined, the infiltrated area is dusky, erythematous, showing scaling, oozing and crusting at times extending to the surrounding skin. There are typical large Paget's cells in the epidermis of the nipple devoid of prickles with - round pale staining nucleus and a much lighter abundant cytoplasm scattered in groups or singly. The dermis shows moderately chronic inflammation. Paget's cells do not invade the dermis, but may extend along the lactiferous ducts of the breast. Recent study suggests strongly that the underlying ducts are the tissue of origin. (23)

CARCINOMA ARISING FROM MAMMARY DUCTS

Noninfiltrating Ductal Carcinoma (Intraductal carcinoma)

This is considered as carcinoma insitu of the mammary duct. Consequently the prognosis is good if adequate excision is made, even if multicentric. Cure is highly possible. This tumour has a segmental distribution in the mammary ducts involving large, medium or small segments.

The dilated lumens of the mammary ducts are partially filled by atypical ductal lining cells in single or multiple layers without well vascularized stalks. The obliterated lumens of the ducts do not have central necrosis, as do the

comedocarcinomas. The distinction between atypical intraductal papilloma and intraductal papillary carcinoma is extremely difficult in some cases.

Infiltrating Ductal Carcinoma

Scirrous carcinoma

This tumour is the most common and constitutes about three -fourths of all breast cancers. It is well - outlined and is stony hard, producing a grating sound when cut. When retracted from the surrounding tissue, the cut surface is greyish white, smooth and cartilagenous like with chalky streaks or dots.

The microcropic diagnosis is made more on disturbance of the normal mammary histologic pattern than - on the characteristic malignant cytologic features which could be blurred by the fibrotic process of the stroma.



Papillary carcinoma

The tumour is well outlined, but not encapsulated. It is soft, translucent, friable and sometimes bulky. Necrosis is common. Histologically, this tumour is similar to noninfiltrating intraductual carcinoma. the papillae are present, but composed of ductal epithelial cells with pleomorplnic and hyperchromatic nuclei in disorderly arrangement.

Comedo Carcinoma

The name of this tumour comes from its resemblance to the comedo of skin with slightly elevated, yellowish soft, "plugs" on a smooth, greyish, firm surface of the breast tissue. The plugs are necrotic tissue in the centers of solid enlarged mammary ducts filled with malignant epithelial lining cells. Their presence on a hard surface is unmistakable microscopically, enlarged, solid, mammary ducts are completely filled by large anaplastic epithelial lining cells with hyperchromatic, pleomorphic nuclei, and loss of polarity - Most of the comedo carcinomas are infiltrating.

Mucinous carcinoma (colloid)

Grossly, well outlined, bulky translucent soft gel-like lobules are in firm - whitish fibrous tissue, measuring an average of 1 cm in diameter. Gross appearance is typical, conveying a feeling of limited growth. Rarely may be mistaken for myxoid - degenerated fibroadenoma.

Microscopic appearance is that of well differentiated glands lined by columnar cells with some secretion in the lumens. Sometimes the tumour cells are not well differentiated and appear in clusters. Inflammatory reaction is seldom present.

Medullary carcinoma

These circumscribed tumours are large bulging, freshly, soft and greyish, measuring up to 10 cm in - diameter. It does not have the loose fibrous formation of scirrhous - carcinoma.

Microscopically, it is composed of an irregular mass of poorly differentiated epithelial cells arranged in sheets without any fibrotic stroma. Sometimes it is heavily infiltrated by lymphocytes.

CARCINOMA ARISING FROM MAMMARY LOBULES

Lobular carcinoma in Situ

There is no palpable or visible mass. The tumour is indistinguishable from ordinary breast tissue.

Microscopically, well circumscribed lobule or lobules are packed with - solid, enlarged, terminal mammary ductules filled with evenly spaced - enlarged epithelial lining cells. The shape of the mammary lobules is preserved, and the basement membrane of the ductules is intact. The lesion is not infrequently bilateral.

Infiltrating lobular carcinoma

The gross appearance of this tumour is like that of scirrhous carcinoma. It is greywhite, poorly outlined, and irregular. The cut surface is smooth and very firm, without chalky - streaks.

Microscopically, the tumour cells of the terminal ductules of the mammary lobules break through the basement membrane of the ductules, distort the lobular structure, and invade the surrounding stroma - in the form of strands, clusters or small sheets of poorly differentiated cells with hyperchromatic and pleomorphic nuclei. some pathologists emphasize the - presence of "indianfile" or rows of single cells in width in a fibrotic -

Stroma as an indication of lobular origin instead of ductal origin.

ETIOLOGY OF BREAST CANCER

The causes of breast cancer - remain unclear. There are however, predisposing environmental, hormonal genetic and nutritional factors which are of great interest - and speculation but are largely unsubstantiated. There is a high incidence of breast cancer in some families and this has served as sufficient reason for undertaking prophylactic subcutaneous mastectomies in some female - relatives. Some of these decisions are taken from fear and panic rather than the

calculation of risk factors. The development of breast cancer in certain families is common although genetic screening is rarely sought or utilised.

The alarming increase in breast cancer occurs in all industrialised nations. Epidemiologic studies have as yet to demonstrate a specific etiologic factor. The environment is more important than ethnic background, as the incidence of breast cancer in immigrants from the low - risk countries - approaches the risk of breast - cancer of the new host population - after one generation. (24)

With industrialisation, dietary changes also occur. Chief among suspected carcinogens is dietary fat. There is a direct correlation - between consumption of fat and rates of breast cancer. (24)

Premalignant lesions of the breast include lobular carcinoma insitu (lobular hyperplasia), intraductal carcinoma, a previous breast cancer, diffuse papillomatosis.

BREAST CANCER RISK FACTORS

The Concept of Risk Factors

Epidemiologists usually focus on risk factors in identifying means of disease prevention. Perhaps the best known example is the identification of cigarette

smoking as a risk factor for lung cancer. However, it is not always the case that an identified risk factor lends itself to a preventive intervention. For example, having a family history of cancer is known to be a risk for an individual, but there is nothing one can do to prevent having a family history of cancer.

Seidman et al (25) suggested that as much as 80 percent of breast cancer risk is not explained by known risk factors when considered either singly or in combination. They further demonstrated that most breast cancer patients do not have any of the known risk factors for the disease. The implication they drew was that "all women should be treated as at - appreciable risk for breast cancer.

Even if the risk factors do not allow one to predict with precision who might develop breast cancer, risk factors may have other important vises with respect to female breast cancer. for example, awareness of risk factors may motivate women to seek appropriate screening and detection services.

Risk should be distinguished from cause. A risk factor may not be a sufficient or necessary antecedent to the onset of disease. However, implicit in the concept of risk is the nation that the presence of the risk factor has a known-probability of association with disease occurrence. That probability can be so high as to nearly exclude other possible explanations of cause, such as with cigarette smoking and lung cancer. On the other hand, the association of a single risk factor with the disease occurrence may be so small as to require

consideration of a number of different variables as having potentially equal or greater contributions to disease etiology. The later situation tends to reflect the etiology of breast cancer where the range of possible risk factors includes demographic characteristics such as social class and ethnicity, family history of disease, reproductive history, diet and obesity, previous breast disease and exposure to a range of potential carcinogens including estrogens and ionizing radiation.

AGE AT MENARCHE AND MENOPAUSE

Women who start menstruating early in life (less than 12 years of age) have an increased risk of developing breast cancer (26). This finding has been confirmed in different countries with widely varying incidences of the tumour (27). In case control studies, the risk for women whose menarche occurred before 12 years of age is roughly twice that of those - whose periods started after 13 years. For those with both early menarche and a rapid establishment of regular menses, there is an excess risk of breast cancer which is nearly four fold (26).

The weight of evidence suggests that women with a late menopause also have an increased risk of breast malignancy (28). The rate of increase in the age - specific incidence rate of breast cancer slows at the time of menopause, the rate of increase in the postmenopausal period is only about one - sixth the rate of increase seen premenopausally. Women whose menopause occur before the age

of 45 years have a breast cancer risk one half that of those menstruating until 55 years of age (29). This applies to women undergoing either a spontaneous or artificial menopause.

OTHER REPRODUCTIVE FACTORS

Although cellibacy was first suspected, parity has been determined to be the relevant indicator of risk. Nulliparous women have significantly greater risk that parous women, but little additional protective benefit appears to result from additional pregnancies beyond the first (30). Age at the time of first live birth is also significant. McMahon has shown that breast - cancer risk increases with increases in age at which the women bears her first full term child (30). Women whose first delivery occurs after the age of 35 have a three fold greater risk than those first parous before the age of 18. Janerich has suggested that the protective effect of early first pregnancy may relate only to cancers occurring after the age of 40 (31). He suggested that early age at first pregnancy actually may promote the occurrence of breast cancer in younger women. Given that breast cancer in younger women is relatively - rare, even accepting Janerichs' hypothesis, the net effect of early age of first pregnancy on breast cancer - incidence has to be regarded as protective.(31)

A study in Brazil using multiple logistic regression analysis showed the following factors to be independently associated with increased risk of breast cancer:

(a) monthly family income,

(b) being a housewife,

(c) parity of less than six deliveries and nulliparous women. (32)

A Norwegian Study of 802,457 parous women aged between 20 - 56 years concluded that there is a non-linear relationship between breast cancer incidence and time since last birth and that part of the relation with age at last birth may be attributed to the association with time since last birth (38).

Data from a large, multicentric, population - based case control study were analysed to investigate the relation between multiple birth - pregnancies and subsequent breast -cancer risk in the gravidas. This study in USA failed to find neither protective nor detrimental effects of multiple births and subsequent development of breast cancer. (34)

BENIGN BREAST DISEASE

A history of benign breast disease has been shown to confer a two to threefold increase in risk for the subsequent occurrence of breast cancer. A prospective

study of 747 women was conducted by Coombs and Lilienfield at Roswell Park Memorial between 1957 and 1965. Follow up of this group and of a matched control population showed that the age adjusted incidence of breast cancer was three times higher in the benign breast disease group than in the control group (32). In another study to determine the rates of breast cancer in a group of 1489 women treated for biopsy proven benign breast disease, showed that 66 of the women subsequently developed breast cancer. This number was two times greater than expected on the basis of the risk of the general population (36). McMahon however points out that, it is not common for a breast cancer patient to report a history of benign breast disease (k). Only 5 percent of breast cancer patients report earlier benign breast conditions, further confirming the observation that most breast - cancer patients have no established risk factor.

Although fibrocystic disease and fibroadenoma are unlikely to be precursors to malignancy, they may be associated with epithelial changes that are premalignant (37). Most studies show an excess of subsequent breast malignancy in women with many patterns of benign breast changes, most notably multiple - cystic disease and lobular neoplasia (epitheliosis) (38).

FAMILY HISTORY

Familial breast cancer was recognised in the Roman Medical Literature of 100 AD (39). There is now substantial evidence that a subset (at least 5 percent) of all patients with breast cancer have hereditary etiology (40, 41).

It is important to distinguish between "familial" and "hereditary" breast cancer. Familial breast cancer is defined as an aggregation of breast cancer within a family which could be due to chance alone, to common environmental exposures, or which could even be a result of primary genetic - factors. Data however, are usually insufficient to ascribe a clear cut hereditary etiology (39). Hereditary breast cancer on the other hand is discussed when there is sufficient information within the pedigree to signify that primary genetic - factors are of major etiologic importance (42).

Certain clinical features aid immeasurably in assessing the significance of genetic factors - and they include the following:-

1. Significant early age of onset of breast cancer, with the average age being 44, as opposed to the - general population estimates of - about age 60 (43).

2. An excess of bilateral breast - cancer.

3. Hereditary breast cancer is heterogenous and may show differing tumour - combinations in kindreds which are intergral to specific hereditary breast cancer syndromes (44).

4. Hereditary breast cancer segregates within kinreds in accord with an autosomal dominant mode of inheritance, as evidenced by studies of segregation analysis (45).

A review of studies undertaken before 1963 showed that women with a female relative with breast cancer have a risk two to three times that of the general female population (46). This increased risk appears as great for paternal relatives as for those on the maternal side (47). More recent studies - have identified subgroups at even greater risk. The risk appears to be greatest for women with a first degree relative with bilateral or - premenopausal breast cancer. This - applies particularly to those aged less than 40. (48)

Further attempts to define those groups at risk have produced conflicting results. In a study of breast cancer patients from Los Angeles County Cancer Surveillance Program, it has been found that relatives of premenopausal women with bilateral disease have a higher risk than relatives of patients with unilateral disease (49). However, another group of researchers has shown that the risk of

breast cancer is higher for a woman whose first degree relative had unilateral rather than bilateral breast cancer. (34)

Despite controversy, there is little doubt that some women with a family history of breast cancer are at particular risk. This seems highest where there are two first degree relatives with breast cancer, particularly if the tumour developed premenopausally.(50)

Magnitude of hereditary breast cancer

In Creighton's oncologic clinic 225 consequtive patients with varified breast cancer were evaluated in an attempt to derive a crude estimate of the frequency of hereditary breast cancer. This study found that 13 percent of the patients fulfilled criteria for familial breast cancer, while 5 percent for hereditary. The remaining 82 percent were considered to be sporadic (41).

Heterogeneity in hereditary breast cancer

Detailed medical and genetic studies of breast cancer prone families with meticulous pathologic verification of cancer of all anatomic sites were initiated by Lynch and Colleagues in the mid - 1960s (51, 52) These efforts led to further understanding of hetoro - geneity in hereditary breast cancer through the recognition of a variety of syndromes wherein breast cancer showed an intergral association with cancer of differing - anatomic sites. The knowledge of heterogeneity is crucial to the understanding of the natural history of hereditary

breast cancer. It is definitely no longer sufficient to discuss hereditary breast cancer without defining a specific syndrome. Both hereditary breast cancer heterogeneity and its natural history are important phenomena the knowledge of which is indespensable for targeting the physicians' cancer - control program. It is important thus in certain kinreds cancer of - such sites as the ovary to be - given the same attention as that afforded to the breast when surveillance and management strategies are - implemented.

Compilation of family history and interpretation

In an ideal case, one should compile the history on all of the patients first degree - relatives - and informative second degree relatives (both paternal and maternal grandparents, aunts and uncles). Second degree relatives tend to be more informative genetically since they will be more likely to have gone through the cancer risk age. In view of heterogeneity, the family history must necessarily include cancers of all anatomic locations.

From a clinical point of view the information obtained from these interviews is often sufficient to recommend appropriate surveillance measures for that particular patients first degree relatives. When a patient presents with a pedigree showing several generations early onset of breast cancer, other cancers must be considered, such as carcinoma of the ovary, consistent with the - breast - ovarian cancer syndrome or sarcomas, brain tumours, lung and laryngeal cancers,

lymphoma, and leukaemia, and adrenocortical carcinoma, consonant with the SBLA syndrome (53).

Oncogenes

Current dogma in the theory of cancer development suggests that specific genes, called oncogen, may induce some types of cancer and that normal host genes, proto - oncogens, that are required for cellular function can be converted to oncogens (54). When protooncogens are altered there appears to be an increased risk of malignancy. The structure or expression of these genes can be altered through a variety of mechanisms such as, amplification, mutation, deletion, and translocation. The abnormal occurrence of protooncogenes and oncogenes has been described for several breast cancer cell lines, as well as for human tumour specimens. The most thoroughly studied is the HER-2/neu oncogene. Other oncogenes frequently found in human breast cancer tumours are c - myc, int -2, and H -ras (55).

HER - 2/neu

Growth factors and their cellular receptors are believed to be involved in the abnormal growth characteristics of cancer CUIS. One such growth factor receptor is encoded by the gene HE - 2/neu, also identified as C - erbB - 2 and neu. As a member of the tyrosine Kinase family it is closely associated structurally to the epidermal growth factor receptor. Amplification of the HER - 2/neu oncogen or its - overexpression via mRNA transcription has been reported

in a large number of recent studies covering more than 1000 human breast carcinomas. Although there is considerable variation among the studies in the percentage of - patients showing the change, gene amplification has been found frequently, with an average of 18% of the tumour specimens showing additional gene copies (56).

Biomarkers associated with breast cancer - prone genotype

There is a dire need for recognition of biomarkers which should aid in the definition of breast cancer susceptibility genes. Because of the issue of hetero - geneity in hereditary breast cancer, any single biomarker may not be linked to all forms of hereditary breast cancer. One study of blood and 12 - hours daily urine samples which were collected throughout a single menstrual cycle in 30 - women at high risk for familial breast cancer (57). When compared with an equal number of control, abnormal estrogen conjugation was observed at the perioovulatory stage of the - menstrual cycle in the women who were at high risk for familial breast cancer. Plasma androsterone sulphate was significantly lower in these high risk subjects, while the plasma estrone and estradiol glucoronides showed a decreased trend.

Genetic counselling

When a patient is clearly at risk for - hereditary breast cancer, genetic counselling should be initiated. Genetic counselling involves a meticulous

delineation of the family history, interpretation of HS significance to the patient and her close relatives, diagnosis, treatment and prognosis.

EXOGENOUS ESTROGENS

Does the use of oral contraceptives affect the risk of breast cancer? A large number of women in Europe and USA are using oral contraceptives for family planning during their reproductive life. And increasing numbers are being convinced to use them in the developing countries world over. Such an exposure would be of public health concern if it was found that oestrogens have an effect on breast tumouringenesis. Fortunately, most published reports suggest little impact on breast cancer risk from the use of oral contraceptives. The Centres for Disease Control (CDC) has reported on the analysis of 689 breast cancer patients - compared to 1077 control subjects (58).

This study is significant not only for the number of patients involved but also for the fact that the pattern of use in a number of women dates back 15 years and there was an opportunity to examine long term exposure to oral contraceptives. The overall result was that oral contraceptive use had a relative risk of 0.9 compared to never having used oral contraceptives. The level of risk is not significant by less than 1.0 and it is not possible to assert a protective effect for oral contraceptive use, but the data dearly contradict the suggestion that oral contraceptive use may be associated with increased risk. Neither - duration of oral contraceptive use nor the length of time since the first use appeared to

influence breast cancer risk. It had been hypothesized that certain subcategories of women such as those with benign breast disease or a family history of cancer may be at increased risk of breast cancer when these risk factors are combined with oral contraceptive use. This hypothesis was not supported in the CDC data.

A 12 year study in England has reported on the effect of oral contraceptives on breast carcinogenesis (59). The findings were regarded as reassuring because few statistically significant differences in oral contraceptives use were found between breast cancer and control groups. No significant association between the use of oral contraceptives and the risk of breast - cancer was found in a study conducted in several large hospitals in - Connecticut by Kelsey et al (60).

With regards to this subject thus the current data are inconclusive. A case control study of 314 women with breast cancer aged less than 37 years at diagnosis and a control group of 314 women, demonstrated that long term use of oral contraceptives before the age of 25 years is associated - with an increased risk of breast cancer, this is particularly so if a preparation with a high progesterone content has been used (61).

An analysis of 1176 women aged 16 - 50 with breast cancer and 1176 women as control group, has found no important statistically significant differences in oral contraceptive use between the breast cancer and the - control group (62). A more recent study by the same investigators reported that, more patients in both

groups had been exposed to oral contraceptives, and there appeared to be an excess in the breast cancer group. There was an excess of exposure to the "pill" before first term pregnancy among the cases in the new study compared with the control. These results were very different from those published previously by the same authors using similar methodology. This suggests a latent period before the development of breast cancer after oral contraceptive exposure. Alternatively, there may either have been a subtle unrecognised bias or the results may depend on chance. When the - type of "pill" used was examined, an association between high "progesterone potency" and increased risk was not found (63).

A number of other studies have in general failed to establish a relationship between oral contraceptive use and breast cancer (64). Others have suggested increased risk in certain subgroups, principally young women using the "pill" before their first pregnancy. However, it has been - pointed out that if the increased risk is confined to prolonged use in young women prior to their first full - term pregnancy, current studies may only just be starting to show the effect, as this - pattern of oral contraceptive use was common only after 1970. They caution that further follow up of long - term studies is needed, before final conclusions can be drawn (63).

Another paper was published in 1985, which reported the results of a case control - study on the relationship - between breast cancer and oral -

contraceptives in young women. This was a population based case - control study in women aged less than 45 years. 2088 cases were enrolled with an equal number of control of the same age. There was no significant change in risk of breast cancer, by age, according to prior oral contraceptive use. The cumulative risk form 20 to 44 years of age for everusers compared to never - users was 1.1 (95 percent confidence limit 0.9 - 1.3). Analysis of these results according to the duration of use of high progestogen pills before 25 years of age or use of oral contraceptives before first pregnancy, failed to show a significant increase or decrease in risk (65). Authors of this study conclude that the study suggests that oral contraceptive use has no - significant effect on risk of breast cancer in women under 45 years of age.

Several studies have examined the possible relationship between breast cancer and the use of estrogens - following menopause. Reported data on risk of breast cancer following exposure to estrogen replacement therapy have been reported. In four longitudinal cohort studies, the risk of breast cancer for estrogen users was reduced in to (66, 67), unaffected in one (68) and raised among long term users in one (69).

The Drug Epidemiology unit in Boston compared patterns of conjugated estrogen and other forms of non-contraceptive estrogen use among 1610 women with breast cancer and 1606 control subjects (70). This study did not support the hypothesis that noncontraceptive estrogen use represents a source of risk for

breast cancer. No effects were evident among premenopausal or postmenopausal women, among persons with benign breast disease, or among persons with a family history of breast cancer. No combination of noncontraceptive estrogen use and any other known risk factor for breast cancer suggested an interaction that resulted in increased risk.

RADIATION EFFECTS

Exposure to ionizing radiation - increases the risk of breast cancer in women. This has been shown in a number of studies. 63,275 female Nagasaki and Hiroshima atomic bomb survivors were followed up (71). A dose - response relationship to neutron and gamma radiation that yielded an overall absolute risk per rad of 1.9 excess cases per 1 million women years at risk was observed. Women 10 to 19 years old at the time of exposure experienced much greater excess risk of breast cancer than did women older than 35 years at the time of exposure.

Shore et al followed 571 women who had been treated with x-rays for acute postpartum mastitis (72). Compared to a control population, the relative risk of exposure to a mean dose of 347 rads to both breasts rose to 3.6 20 years following exposure. In this study the excess risk was estimated to be eight to ten excess cases per rad per million women years. In another study 1047 women who received an average of 102 - fluoroscopic examinations were followed over a period of several years as part of their course of tuberculosis therapy (73).

It was estimated that the excess risk of this exposure was 6.2 excess "cases" per rad per million women years. Higher risk was observed for women whose exposure to repeated fluoroscopic examinations - initially occurred - before the age of 30.

Exposure to relatively high doses of ionizing radiation significantly elevates breast cancer risks. Furthermore, there is some consistency in the data suggesting that exposure during adolescence poses greater risk that exposure at later ages. The evidence concerning the effects of - radiation on breast carcinogenesis has been important in evaluating the risk and benefits of mammography. Because of the very low doses - involved in mammographic examinations relative to other studies of radiation carcinogenesis, there are no direct estimates of risk based on the observation of women exposed to routine mammographic examinations. However, extrapolations of risk based on the high dose data when combined with the benefits estimated to be derived from early detection of breast cancer from mammographic examinations, suggest that the far greater effect of mammography is to increase life expectency (74).

WEIGHT AND DIET

Dietary factors have recently become objects of intensive research with respect to their role in the etiology of breast cancer. Part of the basis for this - enthuthiasm is the fact that international variations in breast cancer rates suggest substantial differences which may be attributable to dietary differences. Of greatest interest has been the possible role of dietary fat in elevating breast cancer - risk.

Such an interest in the role of dietary fat and breast cancer has been stimulated by experimental data involving the study of mammary tumours in mice or rats. It has been shown that animals exposed to the carcinogen 7, 12 dimethylbenz(a) anthracene (DMBA) and fed diets containing 10 and 20 percent by weight of corn oil developed more mammary adenocarcinomas than animals fed as percent and 5 percent corn oil diets (75). The high fat diet rats bore more tumours per rat, more rats bore tumours and the tumours began to appear more rapidly among the high fat diet group. It has also been shown that fewer tumours are produced in animals fed saturated fats than those fed - unsaturated fats.(76).

The high unsaturated fat diet known to be associated with promotion of rat mammary tumours has been suggested as reflecting the average American diet in which 40 percent of the calorie intake is from dietary fat. Indeed age adjusted mortality rates of breast cancer exhibit a high correlation with international pattern of per capita fat consumption (77). It has also been suggested that - within the United States, the lower risk of breast cancer among black women may be attributable to their less frequent intake of fats and oils (78). Similarly, seventh - Day Adventists, who have a lower than average fat intake because of vegetarian dietary practises, have been shown to have lower cancer death rates than the general population. (79) It is not clear whether the risk factor is dependent on body weight or fat per se. Diet has yet to be established as a definite risk factor. For instance, it has been shown that the low incidence of breast cancer in Seventh Day Adventists is matched by that in Mormons who are not vegetarians and who do not avoid fat in their diet (80).

Under the hypothesis that diet might affect cancer risk by influencing circulating lipid levels, the association of breast - cancer with serum cholesterol has been investigated. A cohort of 95,179 women for whom serum cholesterol, lipoproteins - and total lipid measures had been obtained has been studied. Follow up - revealed 1035 cases of breast cancer. It was observed that the level of blood lipids has no value in predicting subsequent breast cancer risk. (81)

Under the hypothesis that breast cancer and gallstone disease share intake of dietary fat as a common etiologic factor, Admi et al studied breast cancer incidence in a cohort of 11,678 women who had undergone choleystectomy. Follow up after 11 to 14 years of observation revealed an incidence of breast cancer not - significantly greater than that among comparably a women in the general population (82). These data thus, suggest that breast cancer does not share etiologic factors with gallstone disease, and that if dietary fat is related to one disease it is possibly not related to the other.

There is a wealth of epidemiologic reports on the relation of body weight to breast cancer. However studies are not easy to compare because the authors use different indices of overweight. There are studies which reported the association of excess body weight and breast cancer separately for premenopausal and postmenopausal women. A single study (83) reported a statistically significant reduction in breast cancer risk among premenopausal women weighing 58 kgs

or more. On the other hand, premenopausal patients were thinner than controls in some studies (84). The picture is different among postmenopausal women. Many studies found that postmenopausal women weighing more than either 60 kg. or 64 kg are at increased risk of breast cancer (85). Postmenopausal patients with breast cancer have been shown to have consistently higher weight than controls. The study of Choi et al (84). Suggests that this excess body weight really appears in the later years, around the onset of menopause. Thus, taking the consistency of study findings as criterion for inference, the evidence for an influence of excess body weight on the development of breast cancer is weak among premenopausal women but more - substantial among postmenopausal women.

From the standpoint of the biologic plausibility of the association in relation to the concepts of carcinogenesis, there is weak evidence for a potential protective effect of overweight in premenopausal. Women, but more evidence in favour of an increased risk of breast cancer in overweight postmenopausal women. Overweight could be related to a lower risk of breast cancer during the premenopausal years because it is associated with a lower proliferative activity of the mammary gland because of lower levels of progesterone and increased prevalence of amenorrhoea. (86)

On the other hand, the biologic plausibility of an effect of overweight on postmenopausal breast cancer is better supported. There is evidence from

metabolic studies and from animal studies of a promoting role for overweight in the development of postmenopausal breast cancer. The mechanism may be hormonal, involving enhanced synthesis of tumour - promoting estrogens, increased availability of biologically active estradiol, and a higher concentration of estrogen receptors (87) After - menopause, ovarian hormonal secretion ceases, and the plasma estrogens are derived almost entirely from the enzymatic aromatization of androstene dione to form estrone in adipose tissue. Thus, estrone levels in postmenopausal women are positively correlated with body weight (88). Moreover, breast adipose tissue contains the enzyme - responsible for converting estrone to estradiol, and the conversion rate is positively correlated with body weight. Also in obesity, the plasma sex hormone binding gobulin concentration is reduced, and as a consequence, there is an increase in the biologically available albumin - bound and protein free fractions (89)

Thus the increased exposure to biologically active estrogens, as well as the higher prevalence of estrogen - receptors, among overweight postmenopausal women may stimulate the growth of existing preneoplastic lesions.

Overall, the association of excess body weight with breast cancer is unlikely to be a strong one in either premenopausal or postmenopausal women. The largest - reported odds ratios did not exceed 0.5 in premenopausal women or 3.0 in postmeno pausal women. Such a weak association can be highly sensitive to confounding, because body weight is related to education, income, alcohol use,

and reproductive factors also associated with breast cancer, such as age at menarchs, and age at first delivery (90).

LACTATION AND BREAST FEEDING

The idea that lactation confers a - protective effect on women has been prevalent for much of this century. However, several studies in the 1960s show that there is little or no beneficial effect although all were conducted in areas of high breast cancer incidence (91). One study from Japan, a low - risk area, suggests that breast - feeding is protective, an effect that might be related to the prolonged lactation that is usual in that country (92). However in a separate study of Tokyo women, one quarter of whom had a history of lactation exceeding five years, with some having lactated for more than 10, prolonged lactation failed to show any protective effect (93).

A population based case - control study of breast cancer with a focus on premenopausal women under 45 years of age, conducted in three geographic regions of the U.S.A., enabled the evaluation of risk in relation to varying breast - feeding practices. Among premenopausal parous women (1,211 cases and 1,120 random - digit dialling controls), a history of breast feeding for two or more weeks was associated with a relative risk (RR) of 0.87 (95 percent confidence interval (CI) = 0.7 - 1.0). This relationship was altered substantially by removing from the reference group - women who had problems with breast feeding in the first two weeks, - including those with insufficient milk

production. Risk was not related - substantially to number of children breastfed or length of breastfeeding, although a relatively low risk was observed among those breastfeeding for the longest duration examined. Women who began to breast feed at a young age (∠22 years) - experienced the greatest reduction in risk.

ALCOHOL CONSUMPTION

Little attention has been paid to any potential relationship between - consumption of alcoholic beverages and breast cancer. One study has reported an excess of alcohol drinkers among breast cancer patients relative to women with cancer at other sites. (94) Subsequently, another study in 1982 reported on a case control study of 1152 women with breast cancer and two control groups (519 with endometrial or ovarian cancer and 2701 with non-malignant conditions). A positive association was reported to be evident for beer, wine and spirits and supports the hypothesis that alcohol consumption, or related dietary factors, increases the risk of breast cancer (95).

CIGARETTE SMOKING

It has been shown that urinary levels of endogenous estrogens are about 30 percent lower in smokers than in nonsmokers during the luteal phase of the menstrual cycle (96). Authors of this work have suggested that this might reduce the incidence of breast cancer. A case control study, where there were 2160 women aged 30 - 65 with newly diagnosed breast cancer and 717 controls

consisting of women with malignant conditions judged to be unrelated to smoking was subsequently done. The smoking habits of the breast cancer patients were similar to those of the control group. Results of this large study did not support the hypothesis that smoking might reduce the incidence of breast cancer (97) Many other previous studies have yielded conflicting results. In a follow up study of 45,000 women, one study found that the incidence of breast cancer was higher in smokers than in nonsmokers (98). Conversely another study found that mortality from breast cancer was lower in smokers (99).

Overall, the current evidence does not confirm a negative link between breast cancer and smoking and suggests that if there is such an effect, it is likely to be quite small.

STRESS

A hypothesis has been put forward that stress disturbs the body's - homeostatic mechanisms which prevent the development of cancer (100) One large prospective study has examined the effect of stress on subsequent development of cancer. In this population study, the subsequent - registration and mortality from cancer among those whose spouse had died recently were evaluated. Despite - the various methods of analysis, the data provided no support for the concept that death of a spouse (rated as the most stressful life event) increased the risk of subsequent cancer (101) Analysis of breast cancer deaths also failed

to show an excess in widows. Overall the hypothesis that stress increases risk of developing breast cancer remains unproven.

PROGNOSTIC FACTORS

The course of an individual patient with breast cancer is still mostly unpredictable. Survival of patients is variable. Where as some die of metastatic disease within one year, others survive several decades. This marked variability in clinical course has prompted - considerable interest in identifying the important characteristics predictive of tumour behaviour. This interest has been intensified by the recent advent of promising strategies for adjuvant therapy in patients without involved lymphnodes.

Tumour size

Knowing the extent of disease at the time of diagnosis is crucial for an accurate assessment of a patients prognosis. Survival expectations and tumour size has been the subject of many studies. Larger tumours are associated with shorter intervals before disease recurrence or death. In a representative sample consisting of 24,740 patients, survival data collected by the Surveillance, Epidemiology and End Results (SEER) program of the US National Cancer Institute have - confirmed the importance of tumour size. (102)

The relation between tumour size and survival at 5 years was linear regardless of nodal status, although for node - negative patients, the adverse - effect of size on

survival was less than for node - positive patients. Five year survival rates, adjusted for age - expected mortality, ranged from 45% for tumours more than 5 cm in size with involved lymphnodes to 96% for tumours smaller than 2 cm with no involved nodes. Similar findings were reported in another work which incooperated data on pathologic features in 644 patients with a median follow up period of 18.2 years (103). Tumour size was more important in predicting recurrence than was nodal - status or histopathologic grade. A very favourable prognosis was implied for patients with tumours less than 1 cm, for whom the probability of relapse was 12%, compared with 28% for patients with tumours of 1 to 2 cm. When analyzed by decade, however, tumour size was not found to be of significance in disease recurrences after 10 years.

The efforts devoted early detection of breast cancer as well as the designation of minimal cancer for those lesions measuring less than 5 mm, and the recognition that almost three - fourths of the - patients with tumours larger than 5 cm - have nodal metastasis when first examined conveys the prognostic importance of tumour size. There is a dichotomy of findings with regards to the - significance of tumour size in survival. Some studies have disclosed a direct relationship between tumour size and survival, yet on the other hand others have failed to observe such a relationship. The reasons for such a - dichotomy of findings is not clear. An appreciation of the various histologic types and grades of malignancy of cancers appears to be sufficient to recognise that the doubling times or growth rates of all breast cancers may not be similar. As an example, a

study by Bloom (104) could find no - correlation between tumour size and prognosis in those cancers regarded as being of low or high degrees of malignancy, although a poor prognosis was encountered in patients with lesions greater than 2 cm that were of an intermediate grade of malignancy.

A study by Fisher indicates a consistent correlation between tumour size, when expressed as greatest diameter by pathologic measurement, and treatment failure rate. Tumours greater than 5 cm had a higher incidence of treatment failure than those measuring 2.1 to 5.0 cm, which in turn had a greater failure rate than those measuring equal or less than 2 cm (105).

Stage

The characteristics of the primary tumour, and the presence or absence of axillary lymphnode involvement and its degree are strongly correlated with survival. These account for two elements of the TNM staging system, the third being metastasis. A study by Paterson of over 3000 patients, reported on the usefulness of TNM staging in prognosis, and a clear correlation between the risk of recurrent disease and increasing stage was documented. Clinical stage at presentation exerted little or no effect on the disease process after the diagnosis of the first metastasis. When taken together this means that stage does not exert effect on the disease process itself, butt is a temporal prognostic indicator representing the age of the tumour from its inception. However in a study of the nature from the same institution, patients with stage I disease who developed

locoregional recurrence had longer - survival than those presenting with stage III disease who also had a locoregional relapse.

In general, five year survival rates presently, of patients with which modalities of treatment breast cancer by stages is about as follows:- Stage I - 84%, Stage II - 44%, Stage III - 24% and Stage IV - 0 + %. (106).

Axillary Nodes

The number, location and gross vice pathologic detectability of axillary nodes has a most significant influence of prognosis. Berg (107) has shown that the number of axillary nodes involved is inversely proportional to the patients - survival. In addition, the level of axillary nodes involved is of great importance. Involvement of a few nodes in the lower axillary group has a good prognosis but positive nodes in the upper or superior apical group has an extremely bad prognosis. It has been noted that if metastatic node involvement can only be detected microscopically the prognosis is much better than when it can be detected grossly (108). In a study of occult metastasis by Pickeren (109) found by doing multiple serial section of axillary nodes initially judged free of tumour by routine pathological examination, he noted that the five year survival rate was no different than in the patients with nodes free of cancer.

Christopherson (110) presented the - following five year survival statistics related to axillary node involvement.

Axilliary nodes	5 year survival
Negative nodes	83.2%
Positive nodes:	
Level I Lower	65.2%
Level II Middle	44.9%
Level III Apical	28.4%.

The importance of the number of nodes involved has been emphasized. The five year survival rate for patients with positive nodes was 49%. The rate was 62% for 1 - 3 positive nodes and 35% for those with 4 or more positive nodes. A study by Cutler (111) who investigated the axillary node status of patients as to whether they were negative, homolaterally involved and/or heterolaterally involved, in 100 patients with bilateral palpable axillary nodes, he found superior survival rates, which was attributed to host defence.

There is a substantial difference between clinical and pathological evaluation of the status of lymphnodes. The pathological data is a much superior index of prognosis than the clinical assessment. In one study it has - been found that among cases having clinically negative nodes 38 percent - were positive on pathological examination - and in cases with clinically positive nodes 37 percent were pathologically negative (112). the same investigator has reported a five

and ten year survival rates for patients with pathologically - negative nodes of 84 percent and 70 percent and in the clinically negative nodes of 74 percent and 58 percent. In the pathologically positive group the five and ten year survival rates were 52 percent - and 33 percent and in the clinically positive group 58 percent and 38 percent.

Histologic types

Prognosis in general is influenced by whether the cancer is invasive or not, by the histologic type and by the grading or degree of differentiation of the cancer. Non invasive carcinomas such as lobular carcinoma insitu, intraductal (comedo) carcinoma without stromal invasion, Paget's disease confined to the nipple and areola (non-invasive without a mass), non invasive papillary carcinoma and intracystic carcinoma have a truly excellent prognosis - approaching the 100 percent category for five year survival.(110)

A number of reports assert on the better prognosis of certain histologic types of breast cancer, namely colloid, medullary with lymphoid stroma intraductal (comedo) with minimal or no invasion.

Nuclear grade

The nuclear grade of the invading cancer cells is one of the criteria for histologic grading of breast cancer. Broaders (113) in 1920 attempted to estimate the degree of malignancy by certain features of cancer cells including the

characteristics of the nuclei. Cancers were grouped into four grades of malignancy (I, II, III, IV). the more removed from normal in appearance - the worse the prognosis (Gr.I) and the - closer to normal (Grade IV) the better the prognosis. In a study of 1067 women with proved cancers of the breast a positive association has been reported between patient survival and the degree of nuclear differentiation of the primary tumour (114). The essential features of this system of nuclear grading are as follows:- Nuclei showing marked variations in size and shape, prominent nucleoli, chromatin clumping and numerous mitotic figures are considered to be minimally differentiated and graded as 0 to 1. Nuclei that are quite similar in size and appearance to those of the - homologous noncancerous cells are considered as differentiated and graded as 3 to 4. Nuclei whose appearance is intermediate between the two - extremes are graded as 2. Cancers with grade 0 - 1 have a poor prognosis as opposed to crack 3 - 4.

Although a good correlation between tumour grade and survival rates has been reported, more recent data suggest less impressive results. In a series of 1400 patients, many followed for 20 years or more. After 10 years follow-up, the mortality rate in patients with - high grade tumours, although initially high, approached that of the general population, whereas patients with grade I tumours continued to succumb from their cancers (115) This suggests that, in grade I tumours, metastasis, presumably present but undetected at the time of diagnosis, only - manifest themselves after along period of time. Histological grade may

therefore be useful in predicting early relapse rather than long - term disease free survival.

Data regarding histological grade and response to hormonal therapy are conflicting. Several studies have found no relationship, whereas others have suggested that good - grade tumours are more likely to respond to this type of treatment. (116)

Blood vessel and lymphatic invasion

The growth of Neoplastic cells into, the lumina of blood vessels, has been thought by some authorities as being an ominous sign. It occurs in nearly 50 percent of patients with breast cancer. Its prognostic importance seems to be related to the clinical stage of the disease and Christopherson considers blood vessel - invasion meaningless from the stand - point of prognosis unless at least one lymphnode is involved with cancer (110)

In another study however, a striking correlation between survival and the presence or absence of vascular invasion. In this study of 242 patients, 126 have were shown to have vascular invasion with or without axillary lymphadenopathy. Only 34 of these patients survived (27 percent) survived five years (117)

The possible importance of lymphatic invasion has become better appreciated recently. In about one third of 1000 patients with breast cancer lymphatic - invasion was confirmed - in one study. Because of its association with other poor prognostic factors this was felt to represent an unfavourable feature. In studies of patients without axillary node involvement around 10 percent have - been shown to have lymphatic involvement in the tumour. Overall the prognosis seems poorer in these patients. (118)

Lymphoid infiltrates and sinus histiocytosis

Patients showing a marked sinus histiocytosis reactivity of the axillary lymphnodes are considered to have a better prognosis. (119), and this is considered as a manifestation of host resistance. Basically it is the extent to which the sinusoids of the axillary lymphnodes are distended by elongated histiocytes. When the sinus reaction is minimal or absent it is graded as SH 0-1. When there is evidence of a high sinus - reaction graded SH 3 - 4 the prognosis is good. A study of 777 female cancer cases by Cutler, confirmed previous reports -indicating that sinus histiocytosis as well as nuclear differentiation are favourable prognostic factors. (114) It is felt that the biological behaviour of - cancer is the result of tumour - host interaction and that nuclear differentiation is an index of tumour malignancy while sinus histiocytosis is a structural representation of host resistance.

That an inflammatory infiltrate in the stroma of a carcinoma implies a good prognosis has been - reported by many (120) This inflammatory infiltrate is composed of plasma cells, lymphocytes and occasional histiocytes in the stroma of the carcinoma. Very seldom granulocytes or eosinophiles are part of the infiltrate. It is thought to be a manifestation of host resistance and is more meaningful when it is dense and located at the tumour periphery.

Age, Breast Size and Configuration Pregnancy and Nursing

Evidence regarding the prevailing belief that the prognosis of - breast cancer is less favourable in younger women is at great variance. There is no substantial evidence to show, however, that breast size or configuration influences prognosis. Factors causing confusion in the problem revolve around stage of diagnosis, histologic type, and pregnancy and lactation.

Mc Divitt and Stewart (121) noted that breast cancer behaves differently in children that in adults, seeming to run a much more favourable course. In a study of - 8,396 breast cancers in Connecticut, Ryan and associates found that the prognosis in the younger women was equal to that in the older women.

However, in the study of 53, 452 females with breast cancer by Mersheimer and Heise it was noted that women under 35 experienced - lower survival rates even among surgically treated patients with - localised disease. They concluded that

it is possible that breast cancer in these younger women may in some way be biologically different from breast - cancer in older women.(122)

The overall poor prognosis in breast cancer associated with pregnancy and lactation has for years been blamed on the increased hormonal titers of estrogen and progesterone. However, it is more likely due to the lack of early diagnosis and to the marked increase in vascularity and in - lymphatic permeability in the pregnant and lactating breast.

Treves and Holleb (123) in a review of comparable age groups of pregnant and nonpregnant women found that for this stage and histologic type of cancer the prognosis of cure was as good for the pregnant woman as for the non - pregnant counterpart if the axillary nodes were negative, but it - was much worse if the nodes were positive.

Body weight

A correlation between survival and body weight and serum cholesterol in women with breast cancer was sought by Tartter et al. In a retrospective - study, it was shown that heavier women have a worse prognosis(124). The five year disease free survival rate among 374 women was 67 percent for those weighing less than 150 pounds and was reduced to 49 percent for those weighing more than this. Cholesterol did not - act as an independent prognostic - factor, but the

was associated with the worst prognosis, with five - year disease free survival of 32 percent.

Thymidine labelling Index

Incubation of fresh tissue with radiolabeled thymidine has been used to measure the number of cells incorporate the thymidine into DNA, synthesis (S - phase) of the cell cycle. Actively growing cells incorporate the thymidine into DNA, and the proportion of cells involved in DNA synthesis can be - calculated by antoradiography. This proportion, the thymidine labelling index is a measure of the rate of cellular proliferation and has been found to be related to the risk of relapse. Tubiana et al prospectively measured the index for 128 patients and correlated its measure with the patients clinical course over a period of 10 years. The thymidine - labelling index was found to be a better predictor of relapse than was tumour size, the number of axillary nodes, or histologic grade. (125)

The thymidine - labelling index of a tumour although has a value as prognostic factor, unfortunately the technique is not practical.

Flow cytometry

This is a faster method to assess the growth characteristics of a tumour. Flow cytometry also has the advantage of measuring nuclear DNA content by using a different DNA - specific fluorescent stain. The DNA index is quantitative measure of the degree of aneuploidy and can be calculated from DNA -

histograms. The proliferative capacity of a tumour measured by flow cytometry is defined as the portion of cells in the S - phase and usually is reported as the S - phase fraction. Although the findings were not entirely consistent, aneuploidy was associated with those characteristics already established as predictors of shorter survival. Thus aneuploidy has been correlated with increasing tumour size, poor differentiation, and the presence of nodal metastasis. There have been conflicting reports on the relation of ploidy to hormone receptor status. Some investigators have reported a higher aneuploidy rate in estrogen receptor negative tumour (126) and progesterone receptor negative tumours, where as others have found no significant relations.

THE CONCEPT OF EARLY AND SYSTEMIC BREAST CANCER

The biology of breast cancer is a complex phenomenon, that it should not be taken simply as a stereotyped, time - related progression of events. This simplification portrays a cancer that grows with time and subsequently spreads to the regional lymphnodes and then with time spreads systematically. A cure therefore can be anticipated if this cycle is interrupted early enough before systemic dissemination occurs. Such an understanding ratifies to many the value of so - called early detection and/or treatment.

Although one cannot deny that primary tumours take time to grow, relating regional and subsequently - systemic spread to time is according to more moderate tenets and experiences, not only misleading but inaccurate. Presently,

there is no doubt that breast cancer presents a heterogenous group of neoplasms, and that the cells comprising individual breast cancer are biologically heterogenous. This lack of uniformity however, does not rule out the presence of certain principles that apply to the growth of cancers, including those of the breast. This further provokes scepticism concerning clinical designations of "early" or late in relation to breast cancer at the time of diagnosis.

It is well appreciated that most - breast cancers cannot be palpated until they are atleast I cm in size, or 1 billion cells. According to tumour cell Kinetics such a size requires 30 population doubling. Considering that a doubling time might mean 30 to 200 or more days, it - becomes apparent that a tumour that is regarded as clinically early is in truth biologically late, requiring only 10 to 20 more doubling before killing the host. A small 0.5 cm breast cancer detected by mammography is clinically - regarded as early, but it has already traversed through 27 doubling, and biologically therefore a late tumour. The most crucial consideration however, is when will the tumour metastasize, if it consists of cells having phenotypic potential to do so. Most evidence suggests that when metastasis occur, they do so in the first 10 to 20 doubling times, that is at a stage undetectable by prevailing screening methods. It has been estimated that 50 per cent of women with a breast cancer 1 cm in size already have systemic disease (127)

It is difficult to rationalize the experiences noted in some women with untreated breast cancer with the concept of early breast cancer or the effects of delay in diagnosis and treatment. Thirty five percent of women with untreated breast cancer have been noted to survive for 5 years. Sixty eight percent who presented with localised disease and were untreated survived at least this long. (128) Results obtained in Protocol 4 of the National Surgical Adjuvant Breast Project (NSABP) certainly refutes the significance of delay in diagnosis and surgical treatment on survival. No difference is disease free survival has been observed in this cohort of patients when these latter patients were grouped according to duration of symptoms, that is 0 - 3, 3 - 6, 6 - 9, and longer than 9 months (129) It has been observed that survival rates are comparable between patients with occult micronodal metastases and those without it.

These considerations thus reveal an important shortcoming of the - conventional concept of tumour biology. Experimental studies have clearly shown that the so called barrier - function of lymphnodes, a fundamental feature in the conventional view is incorrect. Tumour cells may so beyond the nodes either through the efferent lymph channels or - lymphaticovenous communications, which as well as passage through interstitial spaces, occurs with alarming frequency (130) Removal of lymphnodes therefore, is for proper staging of the Neoplastic disease rather than for removing the tumour per se and thwarting subsequent metastases

This has led to an alternate hypothesis, which emphasizes that the positive regional lymphnodes is not an instigator of tumour cells dissemination but an - indicator of a host - tumour interrelationship that permits the development of metastases. Regional lymphnodes are of biologic rather mechanical importance. In a large proportion of instances, operable breast cancer is already a systemic disease, so it is unlikely that variations in locoregional treatment will affect survival rates.

Theoretically, reduction or elimination of tumour burden is significant if defensive host response, or chemotherapeutic agents are to be maximally effective. It is still to be demonstrated however, whether this will be of benefit, during adjuvant therapy for all patients or just certain individuals considering the heterogeneity of breast cancers.

Hormone Receptors

The hormone dependency of human breast cancer has been known since 1896, when Beatson first observed tumour regression in premenopausal patients following oophrectomy.(131)

Traditionally, endocrine treatment of breast cancer consists of hormone ablative and hormone additive therapy. The former involves the removal of endocrine glands such as ovaries in premenopausal patients, and adrenals and pituitary, which secrete hormones potentially involved in supporting tumour growth, in postmenopausal patients. Hormone additive therapy consists of administration of pharmacologic doses of hormones such as estrogens, androgens progestins and glucocorticoids.

A major milestone in the ability to treat breast cancer has been the introduction of newer forms of endocrine therapy such as the antiestrogen, tamoxifen and the estrogen biosynthesis inhibitor, aminoglutethimide. These are affective and safe and have virtually replaced the surgical procedures such as adrenalectomy and hypophysectomy.

Two features of endocrine manipulation are specially attractive. The duration of remission observed in responsive patients averages nearly 1½ years. Secondary is the lack of significant side effects. Endocrine therapy however, will benefit only approximately one third of unselected patients with metastatic breast

carcinoma (132) It is desirable therefore, to identify those patients who can benefit from this treatment. In 1971, it was reported for the first time by Jensen et al that presence of estrogen receptors in a - tumour biopsy specimen predicted response to endocrine therapy (133)

Factors affecting estrogen receptor status

Approximately 60 percent of human breast carcinomas contain a measurable amount of cytoplasmic estrogen receptors (134) Tumours from premenopausal patients tend to be less frequently estrogen receptor positive, and even when positive tend to have a lower receptor concentration (135) One possible explanation is that the higher plasma estrogen level in premenopausal in premenopausal patients may occupy the receptors and translocate them to the nucleus, thus making them unavailable for measurement in most essay systems, which only detect unoccupied cytoplasmic receptors.

Estrogen receptor status also seems to correlate with tumour histology. There are studies which have reported that tumours that are well differentiated are estrogen receptor positive more frequently than poorly differentiated tumours (136) Correlation has also been found between estrogen receptor status and cell kinetics. It has been observed that estrogen receptor negative breast cancers have a larger fraction of cells in the S-phase than do their - estrogen receptor positive counterparts, which points to the more aggressive biologic behaviour of estrogen receptor negative tumours.

Primary tumours tend to be estrogen receptor positive more frequently than metastatic tumour. This suggests that in some cases breast cancer may change its biologic behaviour at the time of recurrence. In an individual patient however, the concordence in receptor status between primary and metastatic tumours is nearly 80 percent (137)

Intervening Endocrine Therapy

Systemic therapy and particularly the endocrine one, has also been found to affect estrogen receptor status. Several investigators have observed that following endocrine therapy, estrogen receptor - positive tumours manifested a decrease in their receptor content (138) This can be explained best by a heterogenous population of receptor - positive and negative cells - coexisting in the same neoplasm. Endocrine therapy, is supposed to affect only the receptor - positive subpopulation, thus leaving predominantly hormone independent cells.

Predicting Response of Metastatic Breast Cancer to Endocrine Therapy

Rondomly treated patients with metastatic breast cancer have about 30 percent - chance of responding to endocrine - therapy. It has now been firmly established that the likelyhood of response to endocrine therapy is between 50 and 65 percent when estrogen receptors are present, whereas it is at best 10 - percent when they are absent (139) Thus estrogen receptor measurement is particularly accurate in identifying patients with hormone independent, estrogen receptor

negative tumours, who should be spared unnecessary endocrine manipulations and treated instead with - combination chemotherapy. It is not clear why some (very few) estrogen receptor - negative tumours regress after hormonal therapy.

Positive estrogen receptor status is less accurate in predicting response to endocrine therapy, since at least 35 - percent of tumours harbouring estrogen receptors will not benefit from hormonal therapy. Tumour cells heterogeneity may be a likely explanation. It is possible that a tumour composed primarily of estrogen receptor - negative cells, and thus hormone independent, may possess enough estrogen receptor rich cells to produce a positive biochemical essay.

It is possible also that in the process of dedifferentiation, some tumours may retain the ability to bind estrodiol and thus be estrogen receptor - positive, but they may have lost the ability to carry on subsequent steps of estrogen action, - such as migration of the estrogen receptor complex to the nucleus, stimulation of messenger RNA, and initiation of - mitogenesis.

Predicting Response of Breast Cancer to Cytotoxic Chemotherapy

Cytotoxic chemotherapy is generally, more effective against rapidly deviding cells. Considering the fact that estrogen receptor negative tumours have a higher growth fraction than their estrogen - receptor positive counterparts, it is logical to question whether estrogen receptor negativity would be predictive of response to cytotoxic chemotherapy. In one retrospective study it has been observed that

patients with receptor - negative tumours did have a much higher response to cytotoxic chemotherapy than patients with receptor positive tumour (140) On the contrary, another study reported a higher response to - chemotherapy in patients with estrogen - receptor positive tumours (141) Thus at present it is fair to summarize that estrogen receptor status has no predictive value in terms of response to cytotoxic chemotherapy.

Estrogen Receptor Status as a Prognostic Variable

Since the original publication on the importance steroid hormones in breast cancer, numerous articles have appeared supporting their value as prognostic factors. An undetectable or low estrogen - receptor value in a tumour is predictive of earlier recurrence and shorter overall survival than in patients with an estrogen receptor - positive tumour, regardless of the nodal status, tumour size, menopausal status and adjuvant treatment used. This concept is further supported by the observation that estrogen receptor - positive tumours tend to be histologically more - differentiated and have slower growth rate (136) An important clinical implication is that women with node negative - (stage I) tumours, traditionally considered to have a better prognostic outlook, those who are estrogen receptor - negative, and thus at higher risk of relapse, may benefit from early - aggressive adjuvant therapy.

Progesterone Receptors

It has been observed that synthesis of progesterone receptors is dependent upon estrogen action. This has made measurements of progesterone receptors very attractive in a bid to test the functioning of the estrogen action pathway. It was logical therefore to - expect that the presence of progesterone receptor in addition to the estrogen receptors could more accurately identify hormone response of tumours (142)

It is now well established that - tumours lacking both estrogen and progesterone receptors have virtually no chance of regression following hormonal therapy. In contrast, the likelihood of response to endocrine treatment is between 75 and 80 percent in patients with both estrogen and progesterone receptor positive tumours. It is worth noting however, that at least 20 percent of - tumours positive both for estrogen and progesterone receptors still fail to benefit from endocrine therapy. The reason for this lack of response is presently not understood.

Cancer of the Opposite Breast

The most frequent second cancer to develop in patients treated for breast carcinoma is a cancer of the other breast.

Any consideration of cancer of the second breast must first distinguish - between metastasis from the first - cancer and a true second primary. Any non -

invasivecarcinoma or invasive cancer of a histologic type or nuclear grade distinct from the first cancer - may be considered a second primary.

Second primary breast cancers may be either synchronous or metachronous. The reported incidence of synchronous bilateral breast cancer varies widely and depend highly on the diagnostic capabilities. If clinical criteria alone are used (presence of a palpable mass) about 0.5 percent of breast cancers are bilateral. If mammographic screening is added, 3 to 4 percent of patients will be found to have contralateral cancer. Finally, if screening biopsy of the opposite breast is routinely done at the time of treatment for the first cancer, as many as 12.5% of biopsied patients will be found to have a cancer of the other breast (143)

Where facilities are available, all patients with a clinical cancer in one breast should undergo mammography - preoperatively. This is particularly - important to evaluate the second breast and rule out the presence of suspicious areas which could be a guide for localization of the - contralateral biopsy.

Bilateral breast cancer is an important part of the hereditary breast cancer syndromes natural history. Thus careful assessment of the opposite - breast is imperative, especially in the patient who refuses prophylactic therapy.

Three approaches are possible for - management of the other breast at the time of treating the first cancer.

1. Observation only (serial physical examination and mammography)
2. Contralateral biopsy
3. Prophylactic mastectomy

None of the above is appropriate for all patients and each case should be treated on its own merits, considering of course, patients condition and presence of associated diseases and patients ability to - comply with surveillance.(144)

PREOPERATIVE ASSESSMENT OF THE PATIENT WITH BREAST CANCER

History and physical examination are important first steps in assessing a patient with a breast mass. Below 20 years of age a mobile, nontender mass in the breast is nearly always a fibroadenoma. Excision under local anaesthesia usually suffices. It is sent for histopathological examination as a routine. An intermittently tender mass if cystic will need simple - aspiration in a 30 years old lady. If the cyst doesn't refill and no residual hump remains, everything ends there and the _ patient is usually cured. Bloody aspirates however, should be submitted for cytologic examination. Cysts are frequently the cause of masses in premenopausal women and become more frequent as the menopause approaches (145) Cysts which refill and have bloody aspirates raise suspicions of intracystic carcinoma and should be taken seriously.

Aspiration of solid masses

Failure to aspirate cyst fluid indicates that a lump is solid and this calls for fine - needle aspiration and cytologic examination. This procedure has provoked much interest as a convenient alternative for open biopsy and has produced - extensive literature detailing the technique and comparing its results with those of histologic examination of breast lumps. A study conducted at the Mayo - clinic - and comprising of 10,917 cases, concluded that the results of fine needle aspiration could provide an added measure of confidence in the diagnosis of benign breast lesions, act as an additional safeguard against misdiagnosis of malignant nodules, and reduce the cost of managing breast cancer (146) Overall accuracy of up to 95 percent has been - reported, however the range of false negative (up to 35 percent) and false positive results (up to 18 percent) was a matter of concern (147)

It is generally conceded that there is a learning curve with fine needle aspiration. Optimal results are achieved only with careful technique and evaluation by experienced cytopathologist. Among the limitations of the procedure is its inability to differentiate invasive from non invasive carcinomas and lymphomas from poorly differentiated carcinomas with confidence. False positive results are caused usually by epithelial proliferations, duct papillomas, fibroadenomas, fat necrosis, mastitis, gynecomastia and radiation changes.

In relation to core needle biopsy, fine needle aspiration is said to be quicker and less invasive, it requires no special equipment and may be more reliable in identifying cancer owing to more extensive sampling, offcourse in good hands (148).

Mammography

Even in the presence of an obvious breast cancer, mammography still constitutes an essential method of examining women with apalpable breast lump. Those below 20 years of age and pregnant women are excluded. Mammography is performed to evaluate the breast for possibilities of occult lesions either in the same breast or the opposite one. Multiple cancers and bilateral synchronous cancers are known to exist and mammography is the best way to search for them.

In general, structural details of the breast in question are significant factors in the success of mammography. Breasts in postmenopausal - women are predominantly fatty. This makes accurate interpretation relatively easier than the dense, fibroglandular breasts of younger women, particularly nulliparous. Good radiologic technique is essential.

All the characteristics of malignancy can be mimicked by benign conditions and vice versa. A mammogram merely supplies the interested physician with

additional diagnostic information leading to the decision of whether to explore surgically.

Ultrasonography

This is not very useful in the - evaluation of palpable breast masses. It cannot distinguish benign from malignant masses. A fluid - containing mass (cystic) can be readily distinguished from a solid one, whowever, needle aspiration is quicker, less expensive and nearly equally accurate, and furthermore it serves a therapeutic - purpose for a cyst.

CT and Magnetic Resonance Imaging (MRI)

These two methods have not earned an established place in evaluating palpable breast masses. They can both distinguish a cyst from a solid mass, but in this, aspiration and sonography are quicker and cheaper. The - differences indensity upon which CT depends is not distinctive of cancer. A CT is expensive, involves high doses of radiation exposure and the results are comparable to the conventional mammography. Exposure to radiation is avoided with MRI but this method is cumbersome and expensive. (149)

Open Biopsy

This is the final court of appeal in deciding whether a breast lump is benign or malignant. A one step procedure where biopsy was done in theatre under general anaesthesia, diagnosis made by examination of frozen sections and

cancers - treated at the same sitting used to be practised in many countries where such a system was technically feasible. Today however, a two step technique is recommended, where by diagnosis and treatment are two separate procedures. This offers an opportunity for staging the disease and consultation. In - well organised clinics biopsy can be done as an outpatient procedure under local anaesthesia. This minimizes costs and is convenient.

Frozen sections can still be used under certain circumstances. To allay a patients anxiety, to diagnose cancer so that appropriate biochemical tests can be performed on fresh tissues, or to ensure that the specimen removed is adequate.

Incorrect diagnoses based on frozen section examination should be rare if decisions are differed in the event of doubt.

COMMON SITES OF METASTATIC DISEASE

Breast cancer can metastasize in principle to almost any site in the body. The most common sites of metastatic disease however, are the bones, lungs, mediastinal lymphnodes and liver.

Lung metastasis can occur in two general patterns, related to the initial mode of spread. Blood borne metastasis being the commonest, form nodular masses in the lung parenchyma having traversed the walls of pulmonary capillaries. These are not visible on routine screening films until they become 1 to 2 cm in size.

Metastatic breast cancer in the - mediastinal lymph nodes can spread in a retrograde fashion into the peribronchial lymphatics, thus producing a lymphangitic pattern of spread on the chest radiograph. In this situation, the chest radiographs are characterized by a diffuse interstitial infiltrate that is difficult to diagnose until the tumour has spread rather widely throughout the lung. Nodular lesions - usually produce no symptoms until the lung is largely replaced with the tumour.

Metastatic lesions in the mediastinal lymph nodes are not seen on chest radiographs until they reach 2 cm in size. This is because the lesions tend to blend with other mediastinal structures. They are usually asymptomatic until the - tumour invades adjacent structures having gone beyond the nodes.

At autopsy the commonest sites of metastatic disease are the bones, and at least 20 percent of patients with operable breast cancer develop clinical evidence of osseous metastases before they die (150). They occur from blood borne metastases either - systematically through the lungs and left heart or via the intercoastal veins and dissemination through the vertebral veins. The pelvis and spine are the most frequent sites. Within the spine, the lumbar spine is the commonest site, followed by the thoracic spine, sacrum and cervical spine. Other sites in order of decreasing frequency, are the femur, ribs, skull, humerus, scapula and clavicle.

Four types of bony metastases have been identified. The commonest is the osteolytic lesion that destroys bone mineral. This lesion appears on the radiograph as an irregular focus of bone destruction. At least 60 percent of bone material must be destroyed for the lesion to be visible on a radiograph. Osteoblastic lesions constituting 5 to 10 percent produce irregular dense focuses on the radiograph. Malignant cells growing directly into the bone marrow form the third type and produce no signs - radiographically. Any combination of the above mentioned three forms constitute the fourth type of osseous metastases.

Clinically bony metastases remain asymptomatic until they invade the periosteum when they produce pain, or fracture the invaded bone.

Liver metastases are present in 60 - 70 percent of patients dying of metastatic breast cancer (151) They reach the liver via the hepatic artery. Symptoms when they occur are either due to distention of the Glissens capsule causing pain or to obstruction of the billiary system manifesting in jaundice.

Routine Screening Procedures

In any patient with suspected or proven breast cancer, some investigations are generally indicated, independent of the disease stage. A conventional chest radiograph is inexpensive and almost harmless to the patient. Although occult pulmonary, mediastinal, pleural or - bony metastases are not commonly seen,

the chest films should be searched for radiographic evidence of nodular lesions in the parenchyma, mediastinal widening, pleural effusion, osteolytic or osteoblastic lesions on the bones visible on chest radiograms.

A Serum alkaline phosphatase (ALP) assay is another important routine screening procedure. This - Isoenzyme originated in the liver, bones, intestine, kidneys and placenta of pregnant women. Elevations of the ALP are most often due to increased amounts of liver and bone fractions. It has been demonstrated that serum ALP is elevated in 58 to 90 percent of patients with liver metastases. It is not a specific indicator of metastases however, and a number of other hepatobiliary disorders, as well as inflammatory processes in bone, metastatic lesions in bone, normal bone growth and osteoparotic bones.

However the ALP assay has been demonstrated to be an effective screening procedure for either bone or liver secondaries if other liver enzymes are taken into - consideration (152) Significant elevations of the ALP in the presence of a normal billirubin and serum glutamic oxaloacetic transaminase are suspicious enough of bone or liver metastases to indicate the need for additional skeletal and hepatic studies.

Assessment of Liver metastases

Modern technology has equipped physicians with three effective methods of screening the liver for occult metastases.

1. Scintigraphy after injecting radioactive colloids
2. Computed tomography and
3. Ultrasound.

Scintigraphy is performed following - injection of a sulphur colloid - labelled - technetium - 99 m. The colloid particles are taken up by the reticulo - endothelial system, and since Kupffer cells of the liver represent at least 90 per cent of reticuloendothelial activity in the body, the radioactivity in the colloid particles provide a means of screening the liver. Metastases appear as focal filling defects.

On the basis of a number of studies it can be said of scintigraphy that it can detect up to 80 percent of liver metastases in advanced metastatic cancer, but it cannot - be used routinely for screening purposes due to its low - efficiency in early operable cancers. It is however, indicated if serum ALP is significantly elevated.(153)

It has been demonstrated that accuracy of screening the liver for metastases increases by combining scientigraphy and determination of serum carcinoembryonic antigen (CEA) (153). Thus the CEA assay appears to be

quite useful in further defining the etiology of focal defects demonstrated by liver scientigraphy. If the focal defects are associated with CEA levels greater than 5 mg per ml, liver metastases are - considered to be present. Focal defects on the liver scintigram not coupled by a significant CEA elevation should be further evaluated by ultrasound. If the lesion is cystic, it is not a metastasis. Solid lesions need further evaluation by CT, percutaneous needle biopsy, peritoneoscopy or laparotomy.

CT studies are the most accurate way of detecting metastases. Thus CT studies are indicated in any patient with elevated ALP or CEA, and patients with stage III disease.

Bone scans

The law yield of positive results (<5%) reported by a multiple of studies make this type of investigation not cost effective in screening patients for osseous metastases in stages I and II disease. In stage III disease nearly 20 percent of patients will have positive bone scans (154). It is thus indicated in stage III disease.

CHAPTER - 3

PATIENTS AND METHODS

This study was a prospective study conducted at the Department of General Surgery of Muhimbili Medical Centre, the largest consultant and university teaching hospital in the country. Over a period of 14 months between January 1996 and February 1997, a total of one hundred cases with carcinoma of the breast were collected. During this period all women referred to Muhimbili either from the district hospitals in Dar es Salaam or from any other hospital in the regions, upcountry, with a clinical diagnosis of carcinoma of the breast became the subject of this study. Patients admitted for other causes but later found to have lesions suspicious of breast carcinoma were also entered. Patients were seen at the surgical outpatient clinics of the three surgical firms and admitted to the wards or were admitted through the casualty.

As a resident in surgery during the period of this study, I was personally involved in the management of these patients. I regularly visited the female surgical wards of the department to make sure no patient was missed. I evaluated these patients, investigated them as necessary and counselled them with regards to their disease and finally in most cases participated in their management in the form of surgery and or later presenting them at the tumour board meetings for discussion as to their further management.

HISTORY TAKING

A detailed history of the disease was taken from every patient enrolled in the study, a questionnaire relevant to a diagnosis of carcinoma of the breast was filled for each patient (Annex I)

PHYSICAL EXAMINATION

This consisted of the examinations of both the breasts and their respective regional axillary and supraclavicular lymphnodes, and a general physical examination in search for evidence of secondaries.

BREAST EXAMINATION

A. INSPECTION

The breasts were first inspected usually in a sitting and occasionally in a standing position having asked the patients to strip to the waist. This was carried out:-

(i) With the arms by the side of the body

(ii) With arms raised straight above the head.

(iii) With the hands on the hips and patients asked to press and relax and

(iv) With the patients bending forward from the waist so that the breast fall away from the body.

Inspection in these standard positions was made to reveal lumps, nipple retraction or dimples which would usually be accentuated and become more

obvious. In most cases however, there were conspicuous breast masses and did not require any special techniques to reveal them. The nipple, areola and the skin over the breast were inspected, and such features as elevation and retraction of the nipple, its size and shape or ulceration were noted in each case. Features of Paget's disease of the areola and nipple such as cracks, fissures, weeping ulcers and eczema were noted. Special attention was given to the skin over the affected breast, where peua d' orange, satellite nodules, ulceration and fungation were noted if present. The arm and the thoracic wall on the affected side was finally inspected where brawny oedema or cancer encuraisse were noted.

B. BREAST PALPATION

This was done in the classical way. Small breasts were palpated in a sitting position, while large ones in a recumbent position. In the later position, a pillow was put under the scapula on the side being examined, and the homolateral arm raised above the head. The apparently normal breast was first examined systematically, each of the four quadrants and the central area were palpated using the flat of the hand. The same was repeated for the affected breast. During palpation, if a lump was detected, its location, size, shape and surface were defined. The consistency of the lump and the character of its margins were also noted. The lump was also tested for fixisity to skin, breast tissue, underlying fascia, muscles and the chest wall.

REGIONAL LYMPHNODES EXAMINATION

A thorough palpation of both the axillae and the supraclavicular fossae was then conducted as an important part of staging of the disease. The subscapular and supraclavicular groups were examined form behind. The characteristics of the lymphnodes, including the number, size, consistency, fixation to each other and the chest wall were noted.

GENERAL EXAMINATION

This was done in an attempt to look for secondaries. It was also part of preoperative assessment of the patients. Special attention was devoted to the Liver, Lungs and bones.

SPECIAL INVESTIGATIONS

A Biopsy of the tumour:

Histological confirmation of the disease was important both for subsequent management of the patient and for the purpose of this study. Biopsies of breast lumps were usually done in the wards in the presence of a pathologist. Deep seated small tumours were biopsied in theatre. Under strict asepsis, the biopsy site was infiltrated with one or two mls of 0.5% lignocaine and a wedge of tissue of about one cubic centimetre was excised from the tumour. Two or three deep skin sutures of 2 - 0 silk were then applied for both haemostasis and wound closure. Specimens were not fixed, but immediately taken by the pathologist who froze them for subsequent determination of the histological type and the

hormonal status of the tumour. It should be noted that biopsies were always done at such a site and direction that would not interfere with subsequent surgery.

B. Other Investigations:

A conventional chest radiography in the postero-anterior view was done for every patient. All patients were taken for abdominal ultrasonography, the liver being the main target in search for secondaries. Blood samples were also taken for quantitative determination of serum alkaline phosphatase.

STAGING OF THE DISEASE

The T.N.M. staging system was employed where T stands for primary tumour size in cm, N for status of the regional lymphnodes and M for distant metastasis (According to U.I.C.C. Manual for Staging of Cancer, Third Edition, 2nd Revision 1992)

(A) Tumour size

This was assesed as follows:-

T_1 - tumour 2 cm or less in greatest dimension

T_2 - tumour between 2 and 5 cm in size

T_3 - tumour more than 5 cm in size

T_4 - tumour of any size with direct extension to chest wall or skin.

(B) Nodal Status

Regional lymphnodes were assessed only clinically, where:-

N_x - When nodes couldn't be assesed

N_o - Homolateral axillary nodes not considered to contain growth

N_1 - Mobile discrete homolateral axillary lymphnodes considered to contain growth

N_2 - Fixed ormatted homolateral axillary lymphnodes considered to contain growth

N_3 - Homolateral supra/infraclavicular nodes considered to contain growth or oedema of the homolateral arm

(C) **Distant metastasis**

During physical examination, if there was no evidence of metastasis, patients were evaluated as Mx. Following special investigations named above, patients were evaluated as Mo when there was no distant metastasis located and M1 when there was evidence of metastasis.

Patients will be presented and belonging to stages I, II, III, or IV, where stages I, and II represent early disease, where as stages III and IV represent advanced disease. The stage gouping shall be as presented below:-

Stage I - $T_1 N_o M_o$

Stage II - $(T_o - T_2) (N_o - N_{1)} M_o$

i.e. - $T_o N_1 M_o$

	-	$T_1 N_1 M_o$
	-	$T_2 N_1 M_o$
STAGE IIIA	-	$(T_o$ to $T_3)$ $(N_o - N_2)M_o$
	i.e.	$T_oN_2M_o$
		$T_1N_2M_o$
		$T_2N_2M_o$
		$T_3N_oM_o$
		$T_3N_1M_o$
		$T_3N_2M_o$
Stage IIIB		Any T, N_3, M_o
		Any T_4, Any N, Mo
Stage IV		Any T, any N, M_1

TYPE OF STUDY, SELECTION OF PATIENTS AND SAMPLE SIZE

This was not an analytical epidemiologial study. It was more of a hospital based descriptive type of study. There was no randomisation during selection of patients. Patients have were picked on convenience basis. The method of sampling used in this study is hence called CONVENIENCE SAMPLING. The figure one hundred for the sample size did not originate from an epidemiological formula. It was based on availability of patients and as a convenient figure.

RESULTS

1. The Median age in the group was 44.5 years. The youngest patient was 21 years old while the eldest was 78 years old. From 21 years onwards, the number of patients increased steadily to the first peak between the ages 30 to 40 years. The highest peak recorded however, was between the ages 50 to 60 years. From this peak, the number of patients fell sharply with advancing age. Fig 1.

2. When grouped by their menopausal status, the premenopausal group (aged below 50 years) consisted of 48 patients, while the postmenopausal group (aged above 50 years) consisted of 52 patients. The two groups thus, were nearly equal in size. Fig 2

3. Fifty five patients had left sided breast tumours as compared to the 45 tumours found in the right breast. Fig.3

4. There were considerably more tumours located in the upper lateral quadrant (UL =49) than in the other quadrants. Seventeen patients had their tumours in the upper medial (UM) quadrant. Ten patients harboured their tumours in the lower medial (LM) quandrant, while only 4 had their tumours in the lower lateral quadrant (LL). The sub areolar area (SA) harboured tumour in 6 patients (SA). There were 14 patients with tumours too big to be assigned to any of the breast area, these were named as generalised (GEN). Fig.3

5. Out of 100 patients only 2 had stage I disease. 5 patients had stage II disease. While 14 patients had stage III. The remaining 79 patients had stage IV disease. Fig.4

6. When stage of the disease was related to menopausal status, there was no premenopausal patient in stage I where as there were two postmenopausal patients in that stage. There was only one premenopausal patient in stage II disease, while there were four postmenopausal patients in that stage. In stage III disease, there were seven patients in each group. Seventy nine patients, forty premenopausal and thirty nine postmenopausal were in stage IV disease. fig.5

7. Serum alkaline phosphatase was elevated in thirty three patients. The remaining sixty seven had normal levels of the enzyme in their sera. Fig.6

8. Eight patients only (8%) had a positive family history of breast cancer among their first degree relatives. the rest denied such history. Fig.7

9. there were ninety six (96%) patients with invasive ductal carcinomas. Only four (4%) had invasive lobular carcinoma, type of histology. Fig.8

10. Fifteen patients (15%) agreed to have used oral contraceptives before. The remaining eighty five patients (85%) denied to have ever used oral contraceptives in the past.

11. Eighty three out of one hundred patients (83%) were parous. The average parity was 3.5. All those who were parous, had lactated and breastfed their children. Seventeen patients (17%) were nulliparous and had therefore not lactated.

12. Only fifty two had their tumours evaluated for estrogen receptors status. Twenty four of these (46%) were scored as positive, while twenty eight of them (54%) were scored as negative. Fig.9

13.31 patients delayed for less than 3 months, 29 for 3 to 6 months and 40 patients for more than 6 months. The median value was 9 months. The median of delay by the health system was 4 months.

DISCUSSION

This study shows that a substantial proportion of women suffering from breast cancer are young. 34% of them being in their twenties and thirties. The cumulative percentage of premenopausal patients (those below 50 years) was 48%, which was nearly half of all the patients in the group. The median age of the patients in the group was 44.5 years. This was similar to the results reported in previous works; (Abioye et al (11) Mukhatar (7). This reaffirms the fact that in general, breast - cancer patients in Africa South of the Sahara, Tanzania included are on the average 10 years younger when compared to the median age of breast cancer patients in - temperate countries which is 58 years (148)

It has been reported that incidence rates are the same among younger black and white American women, but among the older women, white female rates are greater than those of black females (149). Austin et al however, heave shown that the - incidence rates for blacks and whites do not differ for women born after 25, suggesting that the incidence differential observed among older -

women may disappear in future years.149) This gives more credence to the possibility of under - representation of the older age group among the black women rather - than a genetic bias for younger black females. Under representation of the older age groups among the blacks can be explained by such factors as short life expectancy. We could not expect larger proportion of patients in their 7th or 8th - decades of life when the average life expectancy for a Tanzanian woman is 52 years. Greater - proportion of younger patients is thus a result of having a younger population than anything else. With better and longer life and access to better medical services the incidence of breast cancer in - older black American women is approaching that of their white counterparts, we should probably expect the same trend among our patients later if should there be improvements in the socio - economic status of African populations.

There were no patients in this study belonging to the age groups 0 - 10 - years and 11 to 20 years, thus reaffirming the fact that breast cancer is a probably rare disease below 20 years of age.

This study shows two peaks of age specific incidence rates (Fig.1) A lower peak in the fourth decade and a higher peak in the sixth decade. Studies from other African countries (6,7,8) and earlier studies in Tanzania (157), show a single peak of age specific incidence between 4th and 5th decades of life, followed by a gradual fall with advancing age. The rise in the lower peak could be associated with the prime of - hormonal activity on the breast tissues at that age, followed

by a fall of incidence rates probably during the hormonal changes associated with menopause. Following menopause, the incidence rates continue to rise steadily though not as steeply as before - menopause in temperate climates, where as there is a gradual fall with advancing age in this study, probably associated with longevity in the former and shorter life span in the later case.

Location of tumour in the breast (side)

The finding of slightly more tumours occupying the left breast (55%) in relation to those occupying the right breast (45%) in this study is in - agreement with the general trend - elsewhere.

The number of tumours found in the different areas of the breast is interesting. Nearly half (49%) of all the tumours were located in the upper lateral quadrant. Generally, distribution by quadrants in this study resembles those of most other authorities. The smaller number of tumours in the subareolar area in this study is - probably due to the advanced local disease, when in some instances (14 patie nts) it was not possible to specify the quadrant.

It has repeatedly been reported that tumours located in the outer quadrants have a better prognosis than those in the medial quadrants, which is not however true when the axillary lymph nodes have been involved (158), as has been the case in most patients in this study.

Stage of the disease

This study reaffirms that majority of breast cancer patients in our environment present with advanced disease, stages III and IV. Ninety three patients were in this group and obviously these patients have very slim chances of long term survival. This indeed is a very gloomy picture. When grouped by age there was almost no difference in the stage at presentation between different age groups, most patients in all age groups being in the late stages of the disease.

Considering the breast as a - symbol of feminity, one would expect the younger patients to have presented earlier than their older counterparts. This however was not the case and it appears that younger women are not in the least more sensitive to their breasts than the elder ones. Both pre and post menopausal groups mostly presented with the characteristic fungating or ulcerating lesions. In fact out of the seven patients who presented with early breast cancer, only one was premenopausal, the remaining six were elderly postmenopausal patients.

Patients delay defined in this study as the time lapse in months between observing a breast lump and reporting to hospital for the first time, was considerable for many patients. The median delay was 9 months. It is not simple to explain such a long delay, for it seems the factors responsible are multiple and complex, each contributing its own share to the total delay.

One principal factor is lack of information. When asked whether they had any knowledge of breast cancer before they were admitted with it, 56% of the patients had no idea what it - was, they had not heard about it. these patients did not have the slightest idea that their breast could be the seat of this terrible disease.

Absence of pain is another significant factor. Most patients agreed that they did not come earlier because it was painless. It was interesting to find that even those who claimed to know breast cancer, expected it to be painful. Absence of pain is probably the main culprit. Had breast cancer been painful from its onset as a breast abscess is, there would probably be less late cases, for with an abscess they hardly stay a week before seeing a doctor.

Access to medical advice also has a role to play. Medical advice is not easily accessible to the majority of women in the villages. Tanzania is a vast country and women have to travel long distances to seek medical attention. But why would they travel long distances to see a doctor for a breast lump which is not worrying them (they don't know it could be cancer), and after all which is causing no trouble (it is painless)? This is why they don't seek medical advice until there is fungation, ulceration or pain. Accessibility of medical services however, cannot explain why women from within big cities like Dar es Salaam, also - present late, and such cases are not rare. Zanzibar is a small place where

medical services are within easy reach of the population, but still early breast cancer is a rare finding.

Psychological factors could also play a role in delaying our patients to report o hospital. An inherent tendency to deny a bad possibility for themselves is characteristic of humans. Some of the patients are very knowledgeable about breast cancer, but when they observe a lump in their breasts, they would rather think it was anything else but not cancer. One of the patients in the series of this study was a medical laboratory technologist, who presented with an inoperable tumour already fixed to the chest wall and was painful, and a pathological fracture of femur. We failed to explain her delay.

African women's attitudes - towards their breasts have not been explored sufficiently. But there could be some unknown factors in this area which could at least in part account for late presentation.

System delay is defined here as the time taken by health personell to suspect a carcinoma from the day a woman presented with a lump in her breast. It is presented in months. This study has revealed that 56% of obvious advanced breast cancer were not suspected to be malignant at initial presentation. These patients were treated with antibiotics for 2 to 3 months.

Thus the health delivery system also contributes to the problem of late diagnosis. But here again there is a multiplicity of reasons. Most women in the villages do not have an opportunity to see a doctor. They are seen by rural medical aids, medical assistants and even nurse auxilliaries, whose knowledge about breast cancer is questionable. The issue of availability of facilities for early diagnosis is also important. Facilities for cytological and histopathological examinations are not available in most rural, district and even some of the regional hospitals. Because of such a lack of facilities even if the doctors do recognise the need to do biopsies, it is simply not feasible. They could possibly send their biopsy specimens to the consultant hospitals, but these are so underequipped and understaffed, that they cannot cope with such a burden. In fact there are patients within Muhimbili Medical Centre who have been reffered from upcountry, who have to wait for several months for histological reports of their biopsies. It would not be possible to refer all patients with breast lumps to the consultant hospitals, because breast lumps are common, and only a small percentage of them are malignant. Afzelius et al have studied 7608 patients with breast cancer to see the effect of patients' and doctors' delay on survival. Their observation is that a long patients delay (more than 60 days) was associated with an unfavourable outcome, as compared with a short delay (0 - 14 days). On the contrary, the prognosis was better for patients - with a long doctor's delay compared to that of a short doctors delay. They suggested that all causes of delay should be kept at minimum (152).

Serum Alkaline Phosphatase

This was elevated in 33 patients, among whom 5 had liver metastases detected by ultrasound. There was only one patient with a liver metastasis and whose serum alkaline phosphatase was normal. This enzyme is not a specific indicator of liver metastases. It could be elevated in osseous metastases. Thus these patients who have elevated levels of the enzyme but no liver metastasis, might either have small liver secondaries that ultrasound could not detect or a possibility of bony metastases.

Family history

The 8% of patients in this study with family history of breast carainoma is in agreement with the figures - presented in literature, where up to 13% are said to be familial. This study did not attempt to differentiate between familial and hereditary cancers.

Histological type

The predominating histological type was invasive ductal carcinoma (96%), with only 4% of invasive lobular carcinomas. This finding is in agreement with other studies both in African and elsewhere in the world.

Oral contraceptives, parity and breast feeding

Contraceptives may induce precancerous breast changes, though this question is still controversial. Oral contraceptives use however is not a predominant

feature among breast cancer patients in our environment. It was reported in only 15% of patients in this study. Nulliparity is said to be associated with a higher incidence of breast cancer, while women with 3 or more children have a lower risk. Only 15% of patients in this study were nulliparous and therefore, had not lactated. The remaining were all parous with an average parity of 3.5 characteristically lactation and breast feeding proceeded for nearly 2 years for every child. Thus it seem that parity and lactation probably have no association with breat cancer in our environment.

Estrogen receptor (E.R.) Status

It is generally agreed that - estrogen receptor positivity offers a favourable prognosis. This study has revealed that nearly half of all the tumours studied were E.R positive. Estrogen receptor negativity, observed in almost half of the patients tested in this study, is said to be associated with poor differentiation of the cancer cells and a higher degree of malignancy. This could in part contribute to the late presentation by some of the patients, due to faster growth rates and earlier dissemination of E.R. negative tumors.

Fig. 1:

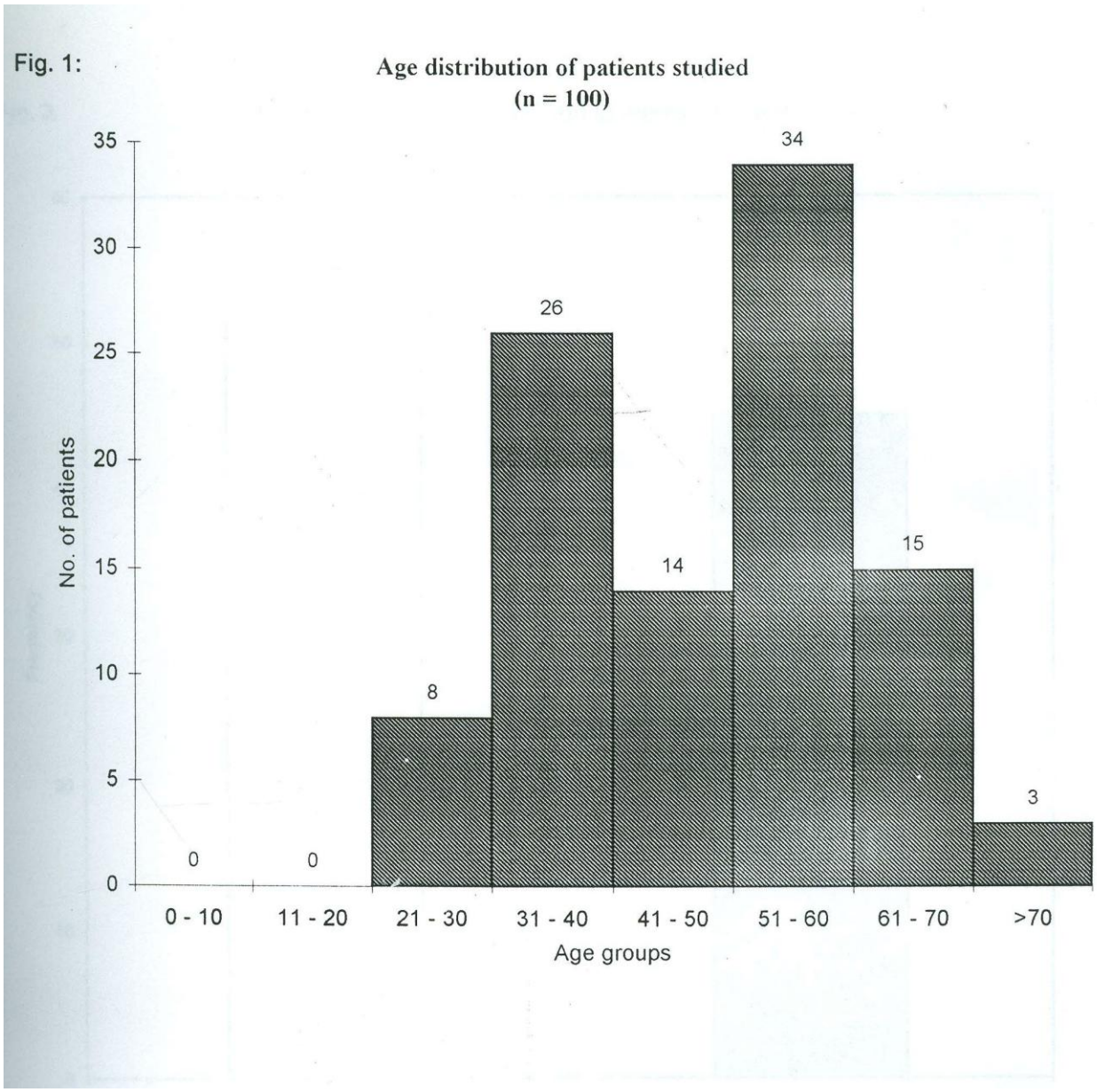

Age distribution of patients studied
(n = 100)
No. of patients
35
30
25
20
15
10
5
0
0
0
8
26
14
34
15
3
0 - 10
11 - 20
21 - 30
31 - 40
41 - 50
51 - 60
61 - 70
>70
Age groups

Fig. 3 Frequency of tumour location in the two breasts

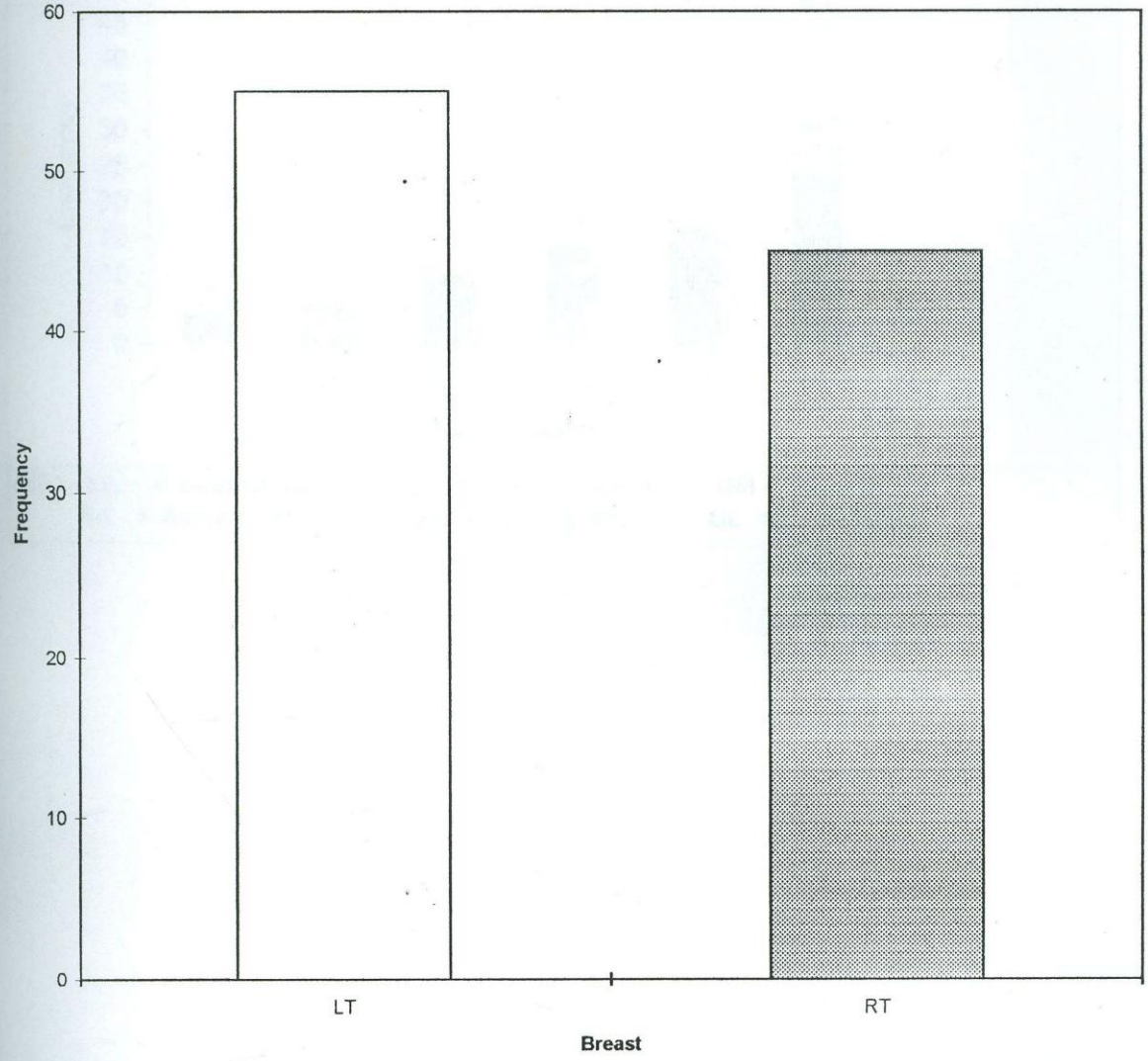
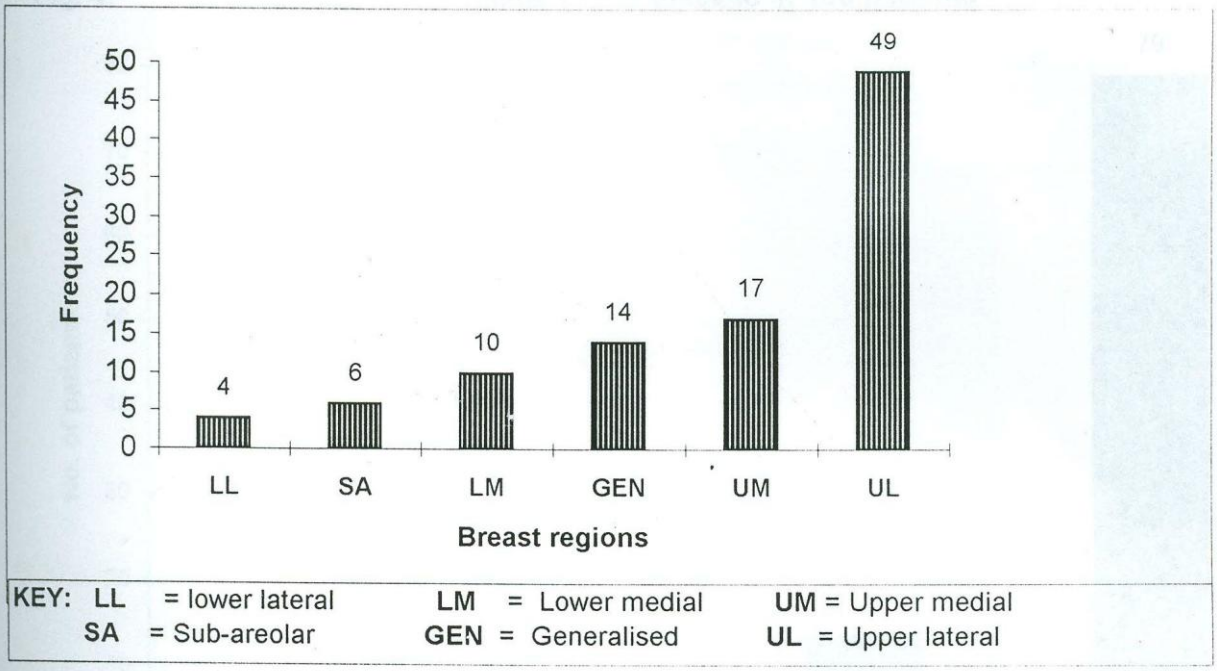


Fig. 3

Frequency of tumour location in the different regions of the breast



KEY: **LL** = lower lateral **LM** = Lower medial **UM** = Upper medial
SA = Sub-areolar **GEN** = Generalised **UL** = Upper lateral

Fig. 4:

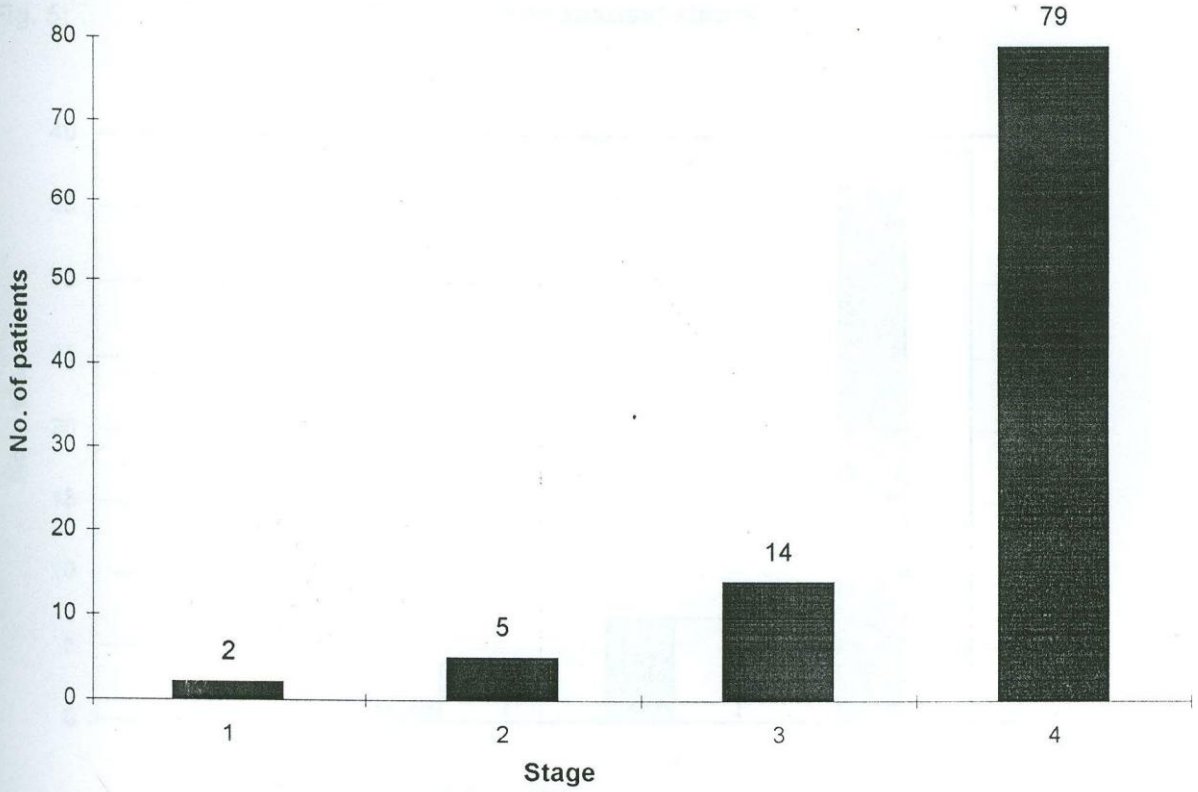

Stage of the disease in 100 patients
No. of patients
80
70
60
50
40
30
20
10
0
2
5
14
79
1
2
3
4
Stage

Fig. 5: Stage and menopausal status

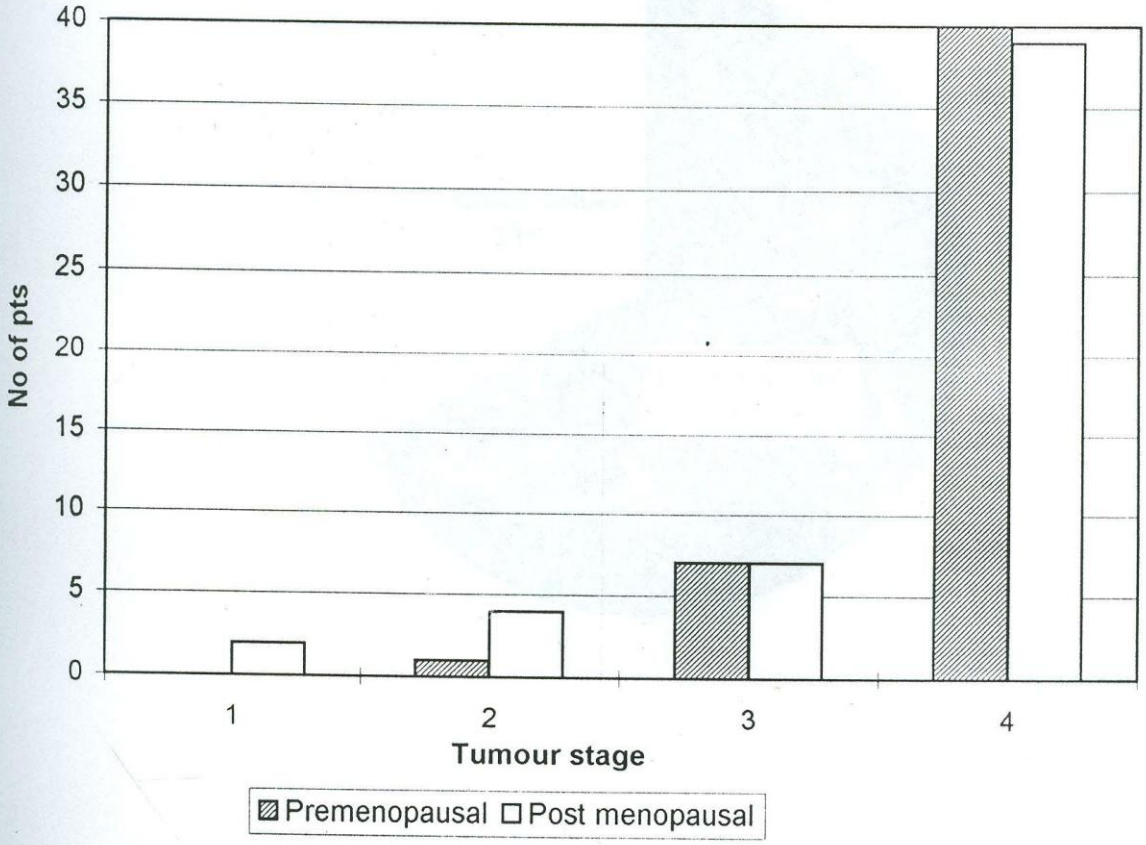


Fig. 6: **Serum alkaline phosphatase levels (n=100)**

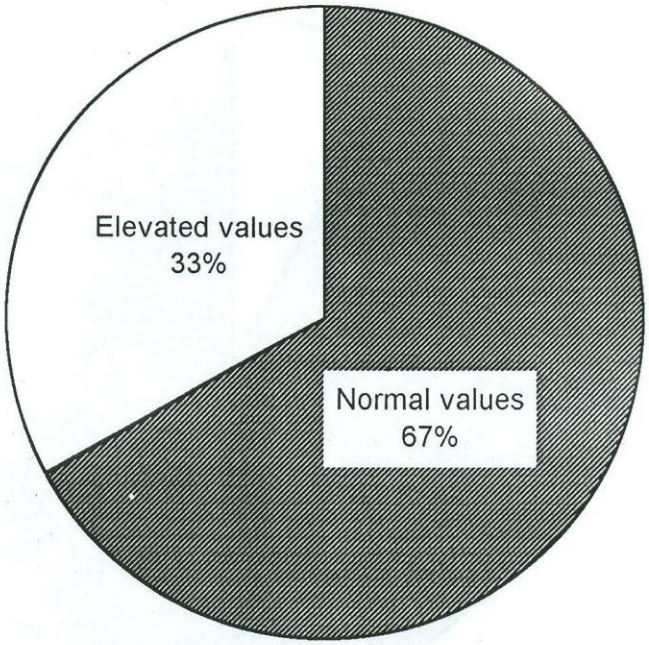


Fig. 7

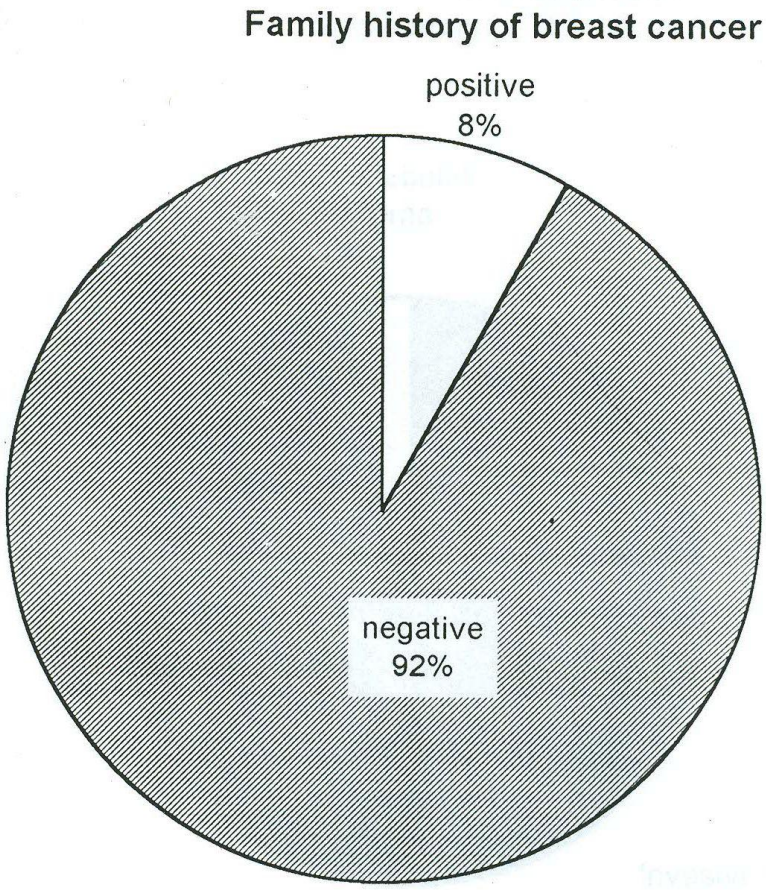


Fig. 8: **Occurance of invasive ductal and lobular carcinomas**

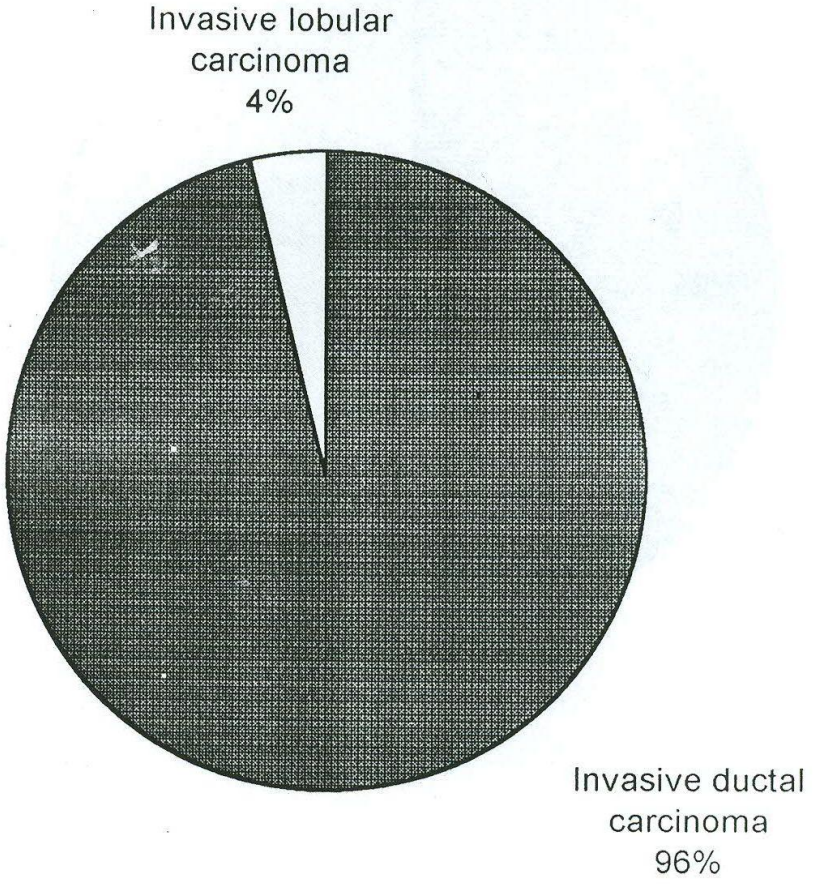
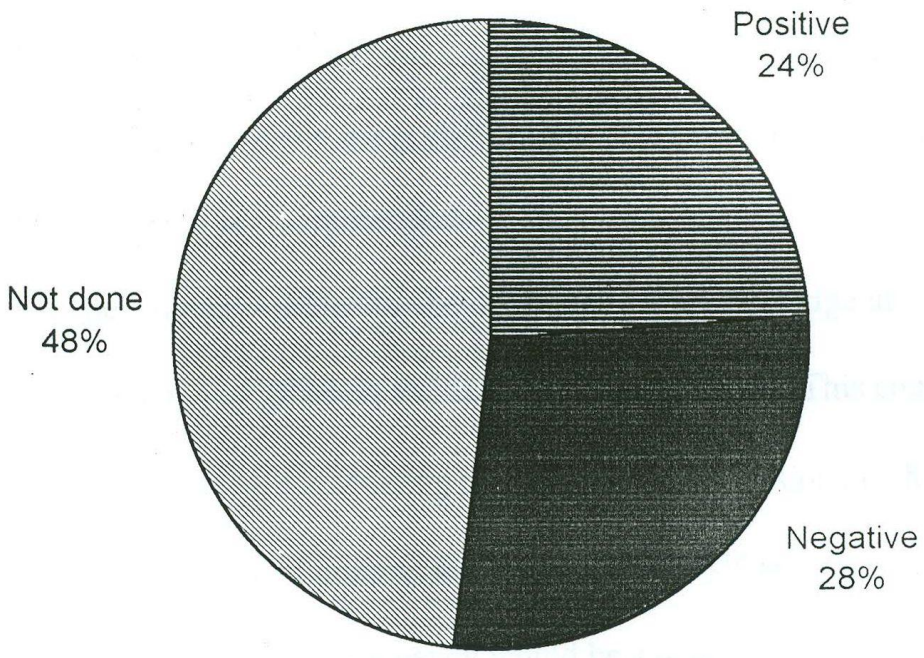


Fig. 9

Oestrogen receptor status of the tumours



RECOMMENDATIONS

I To reduce the proportion of patients presenting with late breast cancer, the following is recommended:-

1. The Ministry of Health should disseminate knowledge about breast cancer to reach women of different walks of life in the society. This could be done by:-

- Conducting special discussion sessions with pregnant women and nursing mothers attending MCH clinics. One session for each pregnancy would be sufficient.
- Breast Self Examination (B.S.E.) - should be propagated and taught. This has been shown to be effective in reducing the number of late presenters and it is being practised in many countries B.S.E. however would only be successful if women were strongly motivated and made to believe that breast cancer is a potential hazard. This is rather difficult in a developing country - like Tanzania. Nevertheless it should be given a trial. We could start with a pilot project in one of the regions or districts and then assess its outcome.
- M.C.H. staff could conduct sessions of health education in secondary schools for girls in their corresponding areas.
- Media of mass information (TV, Radio and Newspapers) should be used more effectively to disseminate this information.

2. Equipment and personell should be made available in the regional hospitals so that each could cater for the biopsy specimen sent to them from the peripheral hospitals in their areas.

3. Mammography is unlikely to be a cost - effective approach to early diagnosis in a developing country like Tanzania, especially considering its low effectiveness in young women who form the majority of our patients. It is t . . recommended, but only for tertiary health centres, i.e. consultant hospitals.

II. Determination of serum alkaline phosphatase should be routinely used to screen patients for the possibility of hepatic or osseous metastasis Abdominal ultrasound and radio isotope bone scans should only be done for those patients with elevated levels. This will reduce the work load for the few radiologist we have and will not compromise the staging of the disease.

III. Estrogen receptor (E.R.) status should be defined for all breast cancer patients treated in consultant hospitals. Because E.R negative patients have limited chances of responding to hormonal manipulation (see lit - review), they should be treated with chemotherapy - The antiestrogen tamoxifen could still be used however, to treat patients without knowing their E.R. status, taking into consideration the fact that nearly half of the patients studied in this series were positive and that tamoxifen - is also effective in some E.R. negative patients.

SUMMARY

This prospective study was conducted with an aim of finding out the clinico - pathological pattern of presentation of carcinoma of the female breast in 100 patients who presented at Muhimbili Medical Centre.

It was found that a great proportion of patients suffering from the disease were young ladies below the age of 50 years. They constituted 50% of patients in the study. The median age was 44.9 years. This finding is in agreement with findings of previous studies conducted here in Tanzania and elsewhere in Africa South of the Sahara. It was however, in sharp contrasts with the age distribution of patients in the temperate climates where the median age is about 60 years. In this study as it is in such studies conducted elsewhere in Africa the age specific incidence falls sharply with advancing age, whereas in Europe and North America the incidence rates rise progressively with age.

Most patients, (93%) presented in advanced, stage of the disease, that is stage III and IV independent of age of the patients. Early presentation was rare finding.

The study revealed that there is considerable delay by patients to report to hospital from the moment they observed an abnormality in their breast, principally because they are ignorant about the disease and because the disease is painless. The study also recommends a research into women's attitudes

towards their breast which might find out some hidden causes of this prominent delay in presentation. The health delivery system also contributes in the delay.

Breast cancer in our environment is often associated with multiparity, prolonged lactation and breast feeding, and that oral contraceptives use is not a predominant risk factor among patients with breast cancer in our environment.

Breast cancer occupies the left breast more than the right. The upper lateral quadrant is a preferential location of breast cancer in comparison to other quadrants.

Nearly half of the patients examined are estrogen receptor (E.R) negative. This study recommends determination of these receptors for every breast cancer patients when ever this is possible. It recommends chemotherapy for those who are negative. Because tamoxifen has been shown to be active against some E.R. negative breast cancers, it can still be used imperatively on every patent when E.R. determination is not feasible.

Histologically most tumours were of the invasive intraductal type (96%). Invasive lobular carcinomas constituted only 4%. Such a finding corresponds to findings elsewhere in the world.

PROTOCOL annex I

1. Patients - Name
2. Age (yrs) - prem/post M
3. DOA
4. DOD
5. Parity (N)
6. Did she breast fed her children (±) (how long)
7. Has any of her first degree relatives suffered from breast cancer? (±)
8. The period that elapsed between noticing the disease and reporting at hospital for the first time.
9. What happned on reporting to health facility for the 1st time - tumour recognised (REC) unrecongnised and treated as inflammatory. (UNREC)
10. After what period was she reffered to MMC?
11. Breast involved (R/L)
12. Quadrant involved - UM/UL/LM/LL/SA/GEN
13. Size of tumour in cm.
14. Skin involvement (±)
15. Fixation to chest wall (±)
16. Homolateral regional nodes status NI/N2?N3
17. Presence of tumour in the opposite breast (±)
18. CXR - for lung secondaries (±)
19. Liver ultrasound scan (±)
20. Serum alkaline phosphatase N/H

21. Histological type IDC/ILC

22. Eostrogen receptor status (±)

23. Contraception (±)

24. Did she know breast cancer before admission? (±)

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