Breast cancer screening

Fadwa J. Altaf, *FRCPC, FIAC.*

ABSTRACT

Breast cancer is a very common health problem in saudi females that can be reduced by early detection through introducing breast cancer screening. Literature review reveals significance reduction in breast cancer incidence and outcome after the beginning of breast cancer screening. The objectives of this article is to highlight the significance of breast cancer screening in different international societies and to write the major guidelines of breast cancer screening in relation to other departments involved with more emphasis on the Pathology Department guidelines in tissue handling, diagnostic criteria and significance of the diagnosis. This article summaries and acknowledges major work carried out before, and recommends similar modified work in order to meet the requirement for the saudi society.

Saudi Med J 2004; Vol. 25 (8): 991-997

Breast cancer is very common health problem in females, worldwide. Its incidence is very high in North America, Britain, Europe and Russia, however, intermediate to low incidence of breast carcinoma is noticed in Japan, China and Far East. Presence of breast cancer screening program (BCSP) in the developed countries increases the incidence of breast cancer due to improvement in breast cancer detection techniques, however, mortality rate of breast cancer has had a steady decline (30% less) in the United States of America (USA) since mid 1985 among women enrolled in breast screening program. Again, this improvement is related to marked improvement in breast screening techniques; health awareness and earlier diagnosis of the disease.[1] Breast cancer accounts for 30% of all cancers in canadian females and 18% of all cancer related death. One in 9 canadian women will develop breast cancer during her lifetime and one in 25 will die from this disease. According to the Canadian breast cancer foundation, the 5-years survival rate of breast cancer have risen from 70% in 1970 to 75% in 1980. This improvement in survival is related to improvement of breast cancer research, and treatment.[2] The magnitude of breast cancer in the Saudi society is difficult to determine, due to lack of annual global data registry in the Kingdom of Saudi Arabia (KSA), and due to lack of breast cancer screening program. According to the national cancer registry of KSA 1998 report,[3] Breast cancer is ranked number one in saudi females. Its incidence is 19.8% of all 5.231 newly diagnosed cancer cares. The median age of diagnosis was 46-years. The highest incidence was noticed in Riyadh, Eastern regions, Makkah and Qassim regions. Fifty percent of cases had regional involvement at the time of diagnosis, 21% were localized, and 15% had distant metastasis. Unknown stage was noticed in 11% and carcinoma in situ was detected in 3%. The most frequent histology was invasive ductal carcinoma 81%, and 19% are other histology of breast carcinoma.

General implications. Breast cancer screening program is highly required in our population, since breast cancer is highest in incidence. Such program requires cooperation of different departments in the hospitals such as family medicine, surgery, radiology and pathology. Each department has its own role in diagnosis. A working panel should be established including members of all these departments to write their own protocol and recommendation. In the United Kingdom, a multi-center study was established by the Department of Health and Social Security (DHSS)

From the Department of Pathology, King Abdul-Aziz University, Jeddah, *Kingdom of Saudi Arabia*.

Address correspondence and reprint request to: Dr. Fadwa J. Altaf, Associate Professor, King Abdul-Aziz University, PO Box 51241, Jeddah 21543, *Kingdom of Saudi Arabia*. Tel. +966 (2) 6401000 Ext. 17084. Fax. +966 (2) 6403975. E-mail: fadwaaltaf@hotmail.com

in 1981[4] to compare mammographically detected breast cancer and self examination. Their result was evaluated in 1988, they found mammographic detection is effective in pre and postmenopausal women,[5] which was concurred with other studies from Holland[6] and Sweden.[7] No benefit has been demonstrated from breast self-examination. The recommendation of the Ministry of Health working group in the United Kingdom was to establish a breast screening program on a national basis. This program showed 20% reduction in mortality in post menopausal women.[8] Similar programs can be initiated in the KSA in different hospitals from different health sectors such as the Ministry of Health, Ministry of Higher Education, Ministry of Defense, National Guard Hospital, and King Faisal Specialist Hospitals. To minimize the cost initially, the screening programs can be initiated in the high breast cancer incidence region according to the national cancer registry records. The median age of breast cancer in our population is 46-years, therefore, breast screening should be offered to the age group 40-65-years. Screening should start at 35-years to those patients with high risk. Re-screening should be offered between 3-5-years interval. Such a program will increase the workload tremendously in the departments involved in the screening, especially radiology and pathology. The total workload and cost should be determined by the working panel.

Steps implementation. General organization. The patient should fill a questionnaire (**Appendix 1**)*, all the patient demographic data is recorded by a nurse. In order to minimize the workload on general physician, a trained nurse can perform breast examination screening and selected cases are re-examined by a general physician, with emphasis on breast examination. The patient will proceed to mammogram after physical examination.

Radiological examination. Single oblique mammography is highly recommended by Forrest et al.[9] Selected cases may require another images. However, Blanks et al[10] recommended for standard mammographic examination to include 2-view mammography mediolateral oblique and cranio caudal projection of each breast. The use of 2 views in screening is more effective in detection of small (<15 mm) invasive cancer. Radiological criteria for case selection to have biopsy or surgical intervention will be determined by radiologist. All images should be filed in radiology department archives for future need.

Surgical interventions. Suspicious cases clinically on mammogram are presented to surgeons for surgical interventions such as true cut biopsy, lumpectomy, and segmental mastectomy etc. A pathologist or surgeon depending on the hospital set up can perform fine needle aspiration cytology (FNAC). Ultrasound or mammogram guided FNAC can be considered on selected cases. Criteria of selection will be determined by the working panel. Fine needle aspiration cytology and true cut biopsy can be performed before excisional biopsy is carried out. A high degree of diagnostic accuracy can be achieved by both techniques.[11]

Histopathology reporting. Gross specimen handling. A strict protocol is required to follow, in order to maintain uniformity of tissue handling procedures. It has to include adequate clinical information, and radiological interpretation of the findings. The nature of specimen should be recorded, if it is a true cut core biopsy, lumpectomy, or segmented mastectomy (**Appendix 2*** histopathology reporting form). Ideally, every breast excision specimen should be presented to the pathologist intact. The surgeon should be discouraged from cutting the specimen after excision. The orientation can be accomplished by inserted sutures at medial; anterior and superior margins.[11] The specimen is painted with colored ink. If the specimen has been incised previously or is submitted in 2 or more fragments, evaluation of the margins of excision may not be possible. The subsequent steps in specimen processing protocol depends on whether the excision was performed as of a palpable mass or a mammographic abnormality with needle localization.

Palpable mass. Specimen handling protocol described by Schnitt and Conolly[12] is very practical. It depends on the size of the excised specimen, if the breast tissue excised is 3 cm or less in greatest diameter, then after painting the specimen, it is palpated to determine the closest margin to the mass. The mass is cut at 3-5 mm interval, perpendicular to the closest margin. If the specimen is previously oriented, the closest margin is identified; the distance of the tumor to the nearest margin is described. The remaining tissue is grossly examined for any other abnormalities. For better assessment of the margins frozen section should be avoided, unless there is a specific margin that could be involved by gross examination, then frozen section of that margin is performed. Tissue submitted for permanent section should include not only the tumor itself but also to demonstrate its relationship to margins of excision and to the surrounding grossly uninvolved breast tissue. The size of the mass is very important in case frozen section is considered. If the grossly identified mass is ≤1 cm then no frozen section should be carried out and the tumor material is saved for permanent section to achieve adequate diagnosis. However if a mass is present >1.5 cm frozen section may be considered as well as tissue for estrogen receptors (ER) and progesterone receptors (PR) by biochemical assay.[11-13] If the specimen submitted is larger than 3 cm, then after painting it, one incision is applied to the closest margin detected by palpation. As indicated above frozen section of

**Full text including Appendix 1 and 2 is available in PDF format on Saudi Medical Journal webpage (www.smj.org.sa)*

Table 1 - Benign breast lesion, differential diagnosis, and subsequent risk of invasive carcinoma.

Lesion	Differential diagnosis	Significance
Sclerosing adenosis	Radial scar/complex sclerosing Tubular carcinoma	No increase cancer risk
Microglandular adenosis	Tubular carcinoma	Slight increase risk 1.5-2X
Radial scar/complex sclerosing lesion	Tubular carcinoma	Slight increase risk 1.5-2X
Papilloma solitary multiple	Papillary carcinoma Carcinoma in situ Papillary or cribriform	Slight increase risk 1.5-2X
Florid epithelial hyperplasia	Atypical hyperplasia and carcinoma in situ	Slight increase risk 1.5-2X
Atypial epithelial hyperplasia	Carcinoma in situ ductal or lobular	Moderate risk 4X

margins is usually not performed unless to demonstrate the relationship of a tumor to the closest margin of excision. All other margins (medial, lateral, inferior, superior, anterior and posterior) should be examined on permanent section. If a segment of skin or skeletal muscle is present in the specimen, then sections from these structures with the tumor is taken to determine its relationship.

Mammographically detected excision. The most frequent mammographic detected abnormalities are microcalcification, soft tissue density or a combination of the 2. The specimen is typically excised with hook-wire or needle localization technique. Measure and examine the specimen intack, and then obtain radiograph of specimen. Blot dry the surface of the specimen and apply paint to surface, and blot dry again. The specimen is sliced 3-4 mm intervals ("breadloaf"). Obtain radiograph of sliced specimen, to identify the slice, which contain the calcification to be submitted totally for permanent sections. When the pathologist is examining microscopically, areas of calcification detected radiologically, he or she may not identify it depending of the biochemical type of calcification such as calcium oxalate will appear pale and refractile on histological examination and sometimes it is overlooked, but it will be better demonstrated by polarizable light, however, calcium phosphate will be really identified by routine hematoxyllin and eosin stain slide as hematoxyphilic density. Sometimes calcification does not appear on routine sectioning and deeper sections may be required. The use of frozen section for microcalcification with needle localization is strongly discouraged.[13] If a mass is identified grossly, and it is suspicious of malignancy, then the previous role of the size regarding submission of tumor tissue is applied.

Mastectomy specimen (MS). Mastectomy specimen should be handled within 2 hours of excision. At the laboratory, the fresh specimen should be sliced at one cm interval after painting the margins of significance. The size of the breast should be recorded, and the size of the tumor, and the distance of the tumor to the nearest margin of excision. Sections of the tumor are taken; one block/cm diameter of tumor. Sections from the closest margin are taken (if grossly identified). Sections should be taken from any suspicious lesion identified grossly, and from each quadrant at least one section/each quadrant. It is better to avoid fatty tissue, and sections are taken from the fibrotic stroma. Two sections are taken from the nipple. If a tumor was previously removed and the mastectomy specimen contains tumor cavity, then 3-4 sections should be taken from the tumor cavity.[12]

Axillary dissection specimen (ADS). Axillary dissection specimen that accompanied mastectomies or excisional biopsy should be examined carefully. Ideally axillary content should be divided into 3 levels (below, behind and above) based on its relation to the pectoralis minor muscle. In such cases, the specimen should be oriented or labeled by the surgeon. The specimen is cut into thin sections and examined carefully by the naked eye and by palpation. Sections are submitted from each lymph node identified.[12]

Microscopic examination. Although there are several aspects in microscopic reporting of breast screening specimen, yet determination of margins of resection, type of the lesion, and immunological markers are very important. Microscopic margins are the distance between the tumor, and the painted margin measured by mm. It is an arbitrary measure. Some investigators consider 5 mm as a negative margin,[14] while others consider a negative margin if

there are few adipocytes or collagen fibers separate the edge of the tumor from the margin.[15] Positive microscopic margin of resection does not guarantee the presence of residual tumor, and negative margins do not preclude it. Although some clinical studies[16,17] show increase incidence of recurrence of the malignant tumors in a margin positive cases, yet there are other contradicting ones.[18,19] Therefore, microscopic margins have some value but should not be considered as an absolute guide to the adequacy of the surgical excision. The microscopic appearance of the lesion is very important to identify. There are list of histological diagnosis that should be recognized, but it has no prognostic significance such as fibrocystic changes, duct ectasia, breast abscesses, adenomas, galactocele and phylloides tumor. In this article the histological criteria of diagnosing proliferative breast disease that has some prognostic significance, such as adenosis, florid hyperplasia, atypical hyperplasia (ductal and lobular), papilloma, radial scar and complex sclerosing lesion **(Table 1)** will be discussed. In addition, the histological criteria of subtypes of carcinoma in situ and invasive carcinoma will be also discussed.

Adenosis. When this term is used, it indicates an increase in the glandular unit whether acini or ductules. It includes sclerosing adenosis (SA), microglandular adenosis (MGA), and blunt duct adenosis (BDA). The later has little diagnostic usefulness, while sclerosing adenosis and microglandular adenosis have some significance. Although sclerosing adenosis was reported as lesion with slight increase risk of carcinoma,[20] yet subsequent reports show no significant increase cancer risk.[21] Sclerosing adenosis represent proliferation of lobular acinar unit with preservation of organized lobular architecture. The glands are lined by epithelial and myoepithelial cell layers. Early lesion of sclerosing adenosis can be cellular, and later ones are sclerotic. The acini may infiltrate adjacent connective tissue, nerves and blood vessels that can lead to an erroneous diagnosis of malignancy. Calcification may be present in sclerosing adenosis.[22] Microglandular adenosis is a histological pattern of increased numbers of glands which is not lobulocentric, extending through stroma and fat. The glands are lined by epithelial cells with myoepithelial cell layer, and its cytoplasm contains glycogen, and often the lumen contains mucin that stain with periodic acid schiff, (PAS) mucicarmine and alcian blue positive eosinophilic hyaline material. No nuclear pleomorphism or atypia is present in microglandular adenosis.

Radial scar or complex sclerosing lesion (RS/CSL).[11,22] These lesions represent a stellate, or nodule composed of central firm fibrous tissue. Radial scar is usually <1 cm while complex sclerosing lesion is >1 cm in size. Microscopically both lesions show central fibroelastotic zone, from which radiate out tubular structure lined by 2 layers of epithelium and myoepithelium. The ductules may show epithelial proliferation.

Papilloma.[11,22,23] Papilloma is defined as a tumor composed of papilli (fibrovascular core covered by epithelium). There is an inner myoepithelial layer and outer epithelial layer. Foci of epithelial hyperplasia may be present but no atypia. Apocrine metaplasia may be present as well as squamous metaplasia especially seen in areas of infarction or sclerosis. Papilloma could be solitary involving subaleolar ducts or multiple involving terminal ducts.

Florid epithelial hyperplasia (FEH).[11,22] Cellular proliferation more than 4 cell thickness but with tendency to distend the involved space and crossing of the space by the hyperplastic cells. The involved space contains irregular intracellular spaces, often slit-like, and mostly present at the periphery of an involved space. Streaming or swirling of the cells around the space is also noticed. Solid pattern of growth is rarely seen.

A typical epithelial hyperplasia (AEH). This term includes both atypical ductal and lobular hyperplasia. Atypical ductal hyperplasia (ADH) is diagnosed when some of the features of CIS are present. The diagnosis of CIS include cytological and architectural criteria. The cytological features include 1. Uniform population of cells, 2. Smooth geometric spaces between cells or micropapillary formation with even cellular placement, 3. Hyperchromatic nuclei. These cellular changes should involve at least 2 major ducts of 2 mm size in diameter. If the lesion has 2 criteria and suggestive of the third and, the size of the duct involved is less than 2 mm then a diagnosis of ADH is suggested. Implementing these criteria sound very simple, however, practically it is very difficult to apply and there is great controversy between pathologist in this diagnostic entity. Atypical lobular hyperplasia is diagnosed when uniform population of cells are found in lobular unit but less than half of the acini in a unit are filled, distorted and distented. This lesion represent 2% of non-malignant biopsy from unscreened women.[11,22]

Carcinoma in situ (CIS).[11,22,23] Carcinoma in citu of breast is divided into 2 major categories, which is ductal CIS and lobular CIS. The former represent a heterogenous group of histological and cytological abnormalities that involve membrane bound space larger than 3 mm in its greatest diameter. Ductal carcinoma in situ (DCIS) presented as breast mass nipple discharge or paget's disease which is seen in 3-4% of symptomatic patient. It may be detected on screening program (17%) with microcalcification either localized or widespread in breast tissue of variable sizes and density.[23,24] Histologically, DCIS

is classified into comedo, and non comedo which include cribriform, solid, papillary and micropapillary types. Nuclear cytology of DCIS is classified into high grade, intermediate grade and low grade features.[25] The histological pattern of DCIS may contain necrosis, however, the term comedo necrosis indicates solid growth pattern with central necrosis, and highnuclear grade cytology of the cells. It is important to recognize micropapillary pattern as in its pure form is associated with extensive disease multi focal and multi centric. Therefore, subsequent management will be different.

Invasive carcinoma.[11,22,25] In the past, pathologist were diagnosing carcinomas confidently as of the size of the mass usually more than 3 cm, felt by medical examination or by patient, and usually there is a lot of tissue material for examination. Currently, in the mammographic era, smaller lesions are discovered commonly, and benign lesions that can mimic carcinoma should be considered. Few definitions of smaller size cancer are present in the literature such as micro invasive cancer and minimally invasive cancer, and they should be differentiated. Micro invasive carcinoma is a term used to describe invasive lesion of 0.1 cm or less in greatest diameter, this term is used if tangential cut of a duct contain CIS is excluded. Immuno stain for basement membrane or myoepithelial cells are helpful in resolving this problem.[23] Micro invasion is usually associated with high grade and comedo DCIS, but it may also occur in other types of DCIS. Minimally, invasive carcinoma as defined by the National Cancer Institute and American Cancer Society working group as invasive carcinoma less than 1.0 cm in diameter. Seventy-five percent of these cancer are infiltrating duct carcinoma not otherwise specified, and few contain specialized types such as colloid carcinoma (3%), medullary carcinoma (19%), tubular carcinoma (10%), and infiltrating lobular carcinoma (11%).[26] Invasive mammary carcinoma of breast exhibit large variety of histological patterns. There are specific histological subtypes that have a useful clinical correlation and better prognostic implication. There are 3 groups of invasive mammary carcinoma based on prognosis; the first group with excellent prognosis are tubular carcinoma and mucinous carcinoma. This group has 90-95% 5-years survival rate.[27] Medullary and lobular carcinoma have an intermediate prognosis with 70-80% 5-years survival. The last group with 60% or less 5-years survival is the most common type of breast cancer; for example invasive ductal carcinoma not otherwise specified or no special type. The first group of special type cancer are commonly detected in breast cancer screening programs.[28] Sometimes breast carcinomas exhibit more than one type, therefore, each type present in the tumor and its percentage should be recorded.

Ductal carcinoma not otherwise specified (DCNOS). Ductal carcinoma not otherwise specified is the diagnosis of choice if 50-90% of the tumor is of this type, however, if other carcinoma is present, it has to be specified.[22] The tumor cells are present in small or large cohesive gland or irregular shapes of glands with occasional central lumina, solid single infiltrating strands are also seen. They exhibit large nuclei with variable degree of pleomorphism; mitosis is variable. Invasion of the breast stroma is present; vascular invasion has to be documented. There are different grading systems of breast carcinoma. The most widely used and accepted one is Modified Nottingham grading of Bloom and Richardson (BR).[28] The component of the grading system is tubular formation, nuclear pleomorphism and mitotic rate, each of this categories are score from 1-3. To obtain the overall tumor grade, the sum of the scores are calculated, 3-5 points are grade I - well differentiated, 6-7 points are grade II - moderately differentiated and 8 - 9 points are grade III - poorly differentiated.[29]

Infiltrating lobular carcinoma (ILC).[11,22,25] Infiltrating lobular carcinoma account for 2-4% of breast carcinoma, it may be reach 14% in some series.[22] Grossly, it may appear as a well defined scirrhous mass or poorly defined area of induration. Histologically, it composed of rounded cells with hyperchromatic nuclei, increase nuclear cytoplasmic ratio and cytoplasmic vacuoles. The tumor cells infiltrates the stroma in single files or strands. There are variable patterns of ILC including classical variant 90% solid, alveolar, mixed and pleomorphic variant. The classical variant usually of low grade according to the (BR) scoring system. The prognostic implication of ILC is high incidence of bilaterality especially seen in the mixed or pleomorphic type.[30]

Medullary carcinoma (MC)[11,22,25] Medullary carcinoma represent 6-10% of all infiltrating mammary carcinoma. In its typical form medullary carcinoma characterize by proliferation of high nuclear grade tumor infiltrating loose stroma with dense lymphoplasmocystic infiltrate throughout the majority of the tumor. The tumor cells are forming irregular syncytial islands without sharp edges. It pushes the adjacent stroma rather than infiltrating it, within the tumor there is loose connective tissue stroma with dense lymphocytes and plasma cell infiltration. When the previous criteria are followed in diagnosing medullary carcinoma, usually those cases have no lymph node invasion, and predict good prognosis.[29] Medullary carcinoma found more commonly in patient with hereditary cancer syndrome associated with mutations in the BRCA 1 gene.[31]

Mucinous carcinoma (MuC). Pure mucinous carcinoma comprise 2-4% of invasive mammary carcinoma. It is more common in females older than 60-years of age. The tumor classically composed of an island of tumor cells, floating in pools of mucin, having either smooth irregular contour or sharp circumscribed tumor by connective tissue. The cells lack bizarre nuclei and with mild nuclear atypia. The cells are present in groups which may mimic cribriform or papillary pattern, tumor necrosis and lymphatic invasion are regularly absent.[11,22]

Tubular carcinoma. This type of cancer comprises 1-7% of invasive mammary carcinoma in the USA series. It has higher incidence in Japan.[9,22] Majority of these lesions are small one cm in greatest diameter. Histologically the tumor composed of tubular structure; oval or rounded angulated spaces lined by single layer of orderly epithelium. The stroma is fibrotic or may be dense hyalinized, particularly in the center of the tumor. Infiltration of breast parenchyma and adjacent fat does not elicite desmoplastic reaction. The cells are regular, rounded with apical snouts, no nucleoli or atypia. Areas of CIS commonly cribriform or micropapillary pattern is present intermingled with the invasive tumor. The differential diagnosis from other benign lesion such as sclerosing adenosis and CSL can be very difficult. I think we cannot conclude this paper if we do not present the currently used biological markers that is present in breast tumors, and it has great impact on the subsequent clinical management. The status of ER and PR in invasive carcinoma is an integral component in management. It could be detected by either biochemical analysis of the receptors on fresh tissue, or the most recent method which show great acceptance and accuracy is by immunohistochemistry (IHC) stains for estrogen and progesterone on paraffin sections. The later method is widely used as interpretation of estrogen and progesterone is in the context of histopathology especially for smaller size carcinoma. Several studies have shown IHC for ER has a predictive value on survival.[32,33]

Measurement of cell proliferation activity (CPA). This is very useful in determining prognosis of a tumor. There are several methods of measuring it, the simplest one is by counting number of mitosis in tumor sections, and this method is reflecting on the grading system that is previously discussed. Other immunological markers of CPA is by detecting the cell proliferation antigen Ki67 by MIB-1 antibodies in paraffin embedded material by using IHC.[34,35] There are several studies emphasis upon genetic changes in breast carcinoma including over expression of oncogenes such as ras[36,37] and HER-2/neu (HER2)[38,39] and detection of tumor suppressor gene such as p53.[40] HER 2 over expression can be detected by IHC in 25% of human breast cancer.[38] Over expression is seen as positive in the cell membrane of breast cancer and it carries a significant increase relative risk for relaps.[41] P53 mutation can be detected by IHC as positive nuclear staining, and it is seen in invasive carcinoma of breast and in high nuclear grade DCIS.[42,43]

References

1. Shapiro S, Venet W, Strax P, Roeser R. Method of tumor detection, follow-up, and analysis in the Health Insurance Plan study: A randomized trial with breast cancer screening. ***Natl Cancer Inst Monogr*** 1985; 67: 64-74.
2. Cancer Care Ontario - Interim Cancer Report, April 24, 1998.
3. National Cancer Registry, Kingdom of Saudi Arabia, Ministry of Health, Cancer incidence report 1988-1997, 20-21.
4. Shapiro S. Evidence on screening for breast cancer from a randomised trial. ***Cancer*** 1977; 39: 2772-2782.
5. Shapiro S, Venet W, Strax P, Vent L, Roser R. Ten to fourteen year effect of screening on breast cancer mortality. ***J Nat'l Cancer Inst*** 1982; 69: 349-355.
6. Verbeek ALM, Hendricks JHCL, Holland R. Reduction in Breast cancer mortality through mass screening with modern mammography (First results of the Nijmegen Project 1975-81). ***Lancet*** 1984; I: 1222-1224.
7. Tabar L, Fagerberg CJ, Gad A, Holmberg LH, Grontoft O, Ljungquist U et al. Reduction in mortality from breast cancer after mass screening with mammography. ***Lancet*** 1985; i: 829-832.
8. Elston CW, Ellis IO. Pathology of breast screening. ***Histopathology*** 1990; 16: 109-118.
9. Forrest APM. Breast cancer Screening. Report to the health Ministers of England, Wales, Scotland and Northern Ireland. London (UK): HMSO; 1986.
10. Blanks RG, Moss SM, Wallis MG. Use of two view mammography compared with one view in the detection of small invasive cancers: further results from the National Health Service breast screening programme. ***J Med Screen*** 1997; 4: 98-101.
11. Pathology Reporting in Breast Cancer Screening. Royal College of Pathologists Working Group. ***J Clin Path*** 1991; 44: 710-725.
12. Schnitt SJ, Conolly JL. Processing and Evaluation of Breast Excision Specimens, a clinical oriented approach. Review Article Anatomic Pathology. AJCP 1992; 13: 125-137.
13. Oberman HA, A Modest Proposal. ***Am J Surg Pathol*** 1992 16: 69-70.
14. Schmidt-Ullrich R, Wazer DE, Tercilla O, Safaii H, Marchant DJ, Smith J et al. Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. ***Int J Radiat Oncol Biol Phys*** 1989; 17: 733-738.
15. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. ***Cancer*** 1986; 57: 1717-1724.
16. Bartelink H, Borger JH, van Dongen JA, Peterse JL. The impact of tumor size and histology on local control after breast-conserving therapy. ***Radiother Oncol*** 1988; 11: 297-303.
17. Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D et al. Risk factors for breast recurrence in premenopausal and postmenopausal patients with ductal cancers treated by conservation therapy. ***Cancer*** 1990; 65: 1867-1878.
18. Veronesi U, Volterrani F, Luini A, Saccozzi R, Del Vecchio M, Zucali R et al. Quadrantectomy versus lumpectomy for small size breast cancer. ***Eur J Cancer*** 1990; 26: 671-673.

19. Solin LJ, Fowble BL, Schultz DJ, Goodman RL. The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. ***Int J Radiat Oncol Biol Phys*** 1991; 21: 279-287.
20. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. ***N Engl J Med*** 1985; 312: 146-151.
21. Hutter RVP. Consensus meeting. "Is fibrocystic disease of the breast precancerous" ***Arch Pathol Lab Med*** 1986; 110: 146-151.
22. Page DL, Anderson TJ. Diagnostic histopathology of the breast. Churchill Livingstone; 1987. p. 51-61, 89-103, 104-119, 120-156, 146-151, 157-252.
23. Page DL, Steel CM, Dixon JM. Carcinoma in situ and patients at high risk of breast cancer. ***BMJ*** 1995; 310: 39-42.
24. American Cancer Society, Concensus conference on the classification of Ductal Carcinoma in situ. ***Hum Pathol*** 1997; 28: 1221-1225.
25. Rosen PP. Rosen's breast pathology. 2nd ed. Baltimore (MD): Lippincott William Wilkins; p. 303-356.
26. Summary report of the Working Group to review the national nacer Institute - American cancer Society of breast cancer detection demonstration projects, Section III Pathology review of Minimal Breast Cancer detection in BCDDP. ***J Nat'l Cancer Inst*** 1979; 62: 673-684.
27. Gallager HS. Pathologic types of breast cancer; their prognosis. ***Cancer*** 1984; 53: 623-629.
28. Anderson TJ, Alexander F, Chettyll U, Forrest AP, Kirk Patrick A, Muir B et al. Comparative pathology of prevalent and incident cancers detected by breast screening. ***Lancet*** 1986; 1: 519-522.
29. Page DL, Jensen RA, Simpson JF. Routinely available indicators of prognosis in breast cancer. ***Breast Cancer Res Treat*** 1998; 51: 195-208.
30. Dixon JM, Anderson TJ, Page DL, Lec D, Duffy SW, Stewart HJ. Infiltrating lobular carcinoma of the breast: An evaluation of the incidence and consequence of bilateral disease. ***Br J Surg*** 1983; 70: 513-516.
31. Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P et al. Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. ***Cancer*** 1996; 77: 697-709.
32. Esteban JM, Ahn C, Battifora H, Felder B. Predictive Value of estrogen receptors evaluated by quantitative immunohistochemical analysis in breast cancer. ***Am J Clin Pathol*** 1988; 19: 960-966.
33. Esteban JM, Ahn C, Battifora H, Felder B. Quantitative immunohistochemical assay for hormonal receptors: technical aspects and biological significance. ***J Cell Biochem*** 1994; 19: S138-145.
34. Connor AJM, Pinder SE, Elston CW, Bell JA, Wencyk P, Robertson JFR et al. Intratumoral heterogeneity of proliferation in invasive breast cancer evaluated with MIBI antibody. ***The Breast*** 1997; 6: 171-176.
35. Keshgegian AA, Cnaan A. Proliferation markers in breast carcinoma: Mitotic figure count, S phase fraction, proliferation cell nuclear antigen Ki-67 and MIB-1. ***Am J Clin Pathol*** 1995; 104: 42-49.
36. Kumar R, Sukumar S, Barbacid M. Activation of ras oncogenes preceding the onset of neoplasia. ***Science*** 1990; 248: 1101-1104.
37. Ohuchi N, Thor A, Page DL, Hand PH, Halter SA, Schlom J. Expression of the 21,000 molecular weight res protein in a spectrum of benign and malignant human mammary tissues. ***Cancer Res*** 1986; 46: 2511-2519.
38. Lodato RF, Maguire HS Jr, Greene MI, Weiner DB, LiVolsi VA. Immunohistochemical evaluation of c-erbB-2 oncogene expression in ductal carcinoma in situ and atypical ductal hyperplasia of the breast. ***Mod Pathol***1990; 3: 449-454.
39. Allred DC, Clark GM, Molina R, Tandon AK, Schnitt SJ, Gilchrist KW et al. Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. ***Hum Pathol*** 1992; 23: 974-979.
40. Seth A, Palli D, Mariano JM, Metcalf R, Venanzoni MC, Bianchi S et al. p53 gene mutations in women with breast cancer and a previous history of benign breast disease. ***Eur J Cancer*** 1994; 30A: 808-812.
41. Mark DP, Gottfried K, Dennis JS. Use of HER2 for Predicting Response to Breast Cancer Therapy. Diseases of the Breast, Updates. No. 4; 1999. p. 1-10.
42. O' Mally FP, Unencak-Jones CL, Dupont WD. P53 mutations are confined to the comedo type ductal carcinoma in situ of the breast. Immunohistochemical and sequencing data. ***Lab Invest*** 1994; 7: 67-72.
43. Moriya T, Sakamotok, Sasano H, Kawanaka M, Sonoo H, Manabe T et al. Immunohistochemistry analysis of Ki67, p53, p21 and p27 in benign and malignant apocrine lesions of the breast, its correlation to histologic findings in 43 cases. ***Mod Pathol*** 2000; 13: 838-841.

Appendix 1
Questionnaire

Name: _____ Age: _____ Date of Birth: _____

Marital Status: Single Married Widow Separated

Nationality: _____ No of Children: _____

Age of Menarche: _____

Age of first pregnancy: _____ No. of pregnancy: _____ Menopause: _____

Breast feeding: _____ Age: _____ Total duration: _____

Contraceptive methods: Pills: _____ Duration: _____ Others: _____

Family history of:
Breast Cancer: _____ Mother: _____ Sister: _____ Others: _____

Past History:
Proliferative breast disease : _____ Other breast lesions: _____

Other health problems: _____ Type: _____

Other malignancy: _____ Site: _____ Type: _____

Diet History:

Type of fat: Animal fat: _____ Vegetable oil: _____

Type of food consumed: Vegetables: _____ large amount >3 portions small amount <2 portions

Animal meat: Goat Beef Others
Portions: Small Large

Seafood portions: Fish Shrimps Others
Portions: Small Large

Drinks:
Coffee: ____ Amount cups/day ____ Tea: ____ Amount cups/day ____ Other drinks: _____

Arabic Green Others
American Black
Turkish
Others

Appendix 2
Breast Screening Histopathology

Family Name: First Name: Date of Birth:
Screening No: Hospital No: Report No:

Side: Right Left Histological Calcification: Absent Benign Malignant

Specimen radiograph seen? Yes No Mammographic abnormality present in specimen? Yes No Unsure

Specimen type: Location biopsy Open biopsy Segmental excision Mastectomy Wide bore needle core

Specimen size (excluding mastectomies and needle core biopsy): x x cm

HISTOLOGICAL DIAGNOSIS: NORMAL BENIGN MALIGNANT

For BENIGN lesions please tick the lesions present:

Fibroadenoma
Papilloma
Single
Multiple
"Fibrocystic change"
Solitary cyst
Periductal mastitis/duct ectasia
Complex sclerosis lesion/radial scar
sclerosing adenosis
Other (please specify) .....

EPITHELIAL PROLIFERATION

Not present
Present without atypia
Present with atypia ('ductal')
Present with atypia ('lobular')

For MALIGNANT lesions please tick any of the following present:

NON-INVASIVE Ductal Subtype -Comedo -Micropapillary -Solid -Cribriform -Papillary Lobular Paget's disease

Size
EXCISION Reaches Margin Does not reach margin (Distance): ..... mm Uncertain

MICROINVASION Not present Possible Present

INVASIVE 'Ductal'not otherwise specified) Tubular or cribriform carcinoma
Medullary carcinoma Mucoid carcinoma

Lobular carcinoma
Other primary carcinoma (specify) .....
Other malignant tumor (specify) .....

MAXIMUM DIAMETER (Invasive component) ..... mm (In situ) ..... mm
AXILLARY NODES Not present Number positive: ..... Total Number .....
OTHER NODES site ..... Not present Number positive: ..... Total Number .....
Excision Reaches margin Does not reach margin Distance: ..... mm Unsure

GRADE I II III Not assessable

DISEASE EXTENT Localized Diffuse single quadrant Multiquadrant Not assessable

VASCULAR INVASION Present Not seen COMMENTS/ADDITIONAL INFORMATION

Site (Optional)
ULQ
LLQ
UIQ
LIQ

IMMUNO HISTOCHEMISTRY

Estrogen receptors Progesterone receptors Tumor suppressor gene (P-53) Onco-protein (C-erb B-2)

PATHOLOGIST Case for review? Yes No

Date: .....