

Chapter VI: Breast Cancer

Risk Factors³⁻¹²

- o Breast cancer risk factors analysis allows the identification of women at high risk for the future development of breast cancer.
- o High risk factors (3-fold or more increase):
 - Female gender.
 - Age (older than 40 years).
 - Women with previous breast cancer specially if it occurred before menopause.
 - A family history of breast cancer at a young age in a first-degree relative.
 - Women with atypical hyperplasia on breast biopsy.
 - Nulliparity.
 - Late age at first pregnancy (after the age of 31 years)
 - Lobular carcinoma in situ carries a 30% risk of invasive cancer.
 - Previous exposure to therapeutic irradiation.
- o Intermediate risk factors (1.2 to 1.5-fold increase):
 - Menstruation history :
 - Early menarche.
 - Late menopause.
 - Diet:
 - Diet high in fat.
 - Use of alcoholic beverages.
 - Oral contraceptives (long-term use in young women).
 - Long-term oestrogen replacement therapy.
 - Obesity.
 - History of cancer ovary, uterine fundus or colon.
 - Diabetes mellitus.

Burden

- o Approximately 32% of all new malignant neoplasms in women are cancers of the breast, the most common neoplasm in women.
- o Breast cancer is the leading contributor to cancer mortality in women aged 15-54.

Screening tests

o The three screening tests usually considered for early detection of breast cancer are :

- Breast self-examination (BSE).
- Clinical breast examination (CBE).
- X-ray mammography.

Recommendations for prevention

o Routine screening for breast cancer every 1-2 years, with mammography alone or mammography and annual clinical breast examination (CBE), is recommended for women aged 50-69 .

o There is insufficient evidence to recommend for or against routine mammography or CBE for women aged 40-49 or aged 70 and older, although recommendations for high-risk women aged 40-49 and healthy women aged 70 may be made on other grounds (see Clinical Intervention).

o There is insufficient evidence to recommend for or against the use of screening CBE alone or the teaching of breast self-examination (BSE).

o The primary care team should encourage women to attend breast screening and be aware of women's concerns about the procedure.

o Women should be encouraged to become aware of their breasts and report any change from what is normal.

Burden of Suffering

- o Approximately 32% of all new malignant neoplasms in women are cancers of the breast, the most common neoplasm in women.¹
- o For women, the estimated lifetime risk of dying from breast cancer is 3.6%.²
- o Breast cancer is the leading contributor to cancer mortality in women aged 15-54,¹ although 48% of new breast cancer cases and 56% of breast cancer deaths occur in women age 65 and over.²
- o As the large number of women in the "baby boom" generation age, the number of breast cancer cases and deaths will increase substantially unless age-specific incidence and mortality rates decline.

Accuracy of Screening Tests

- o The three screening tests usually considered for early detection of breast cancer are:
 - Breast self-examination (BSE),
 - Clinical breast examination (CBE), and
 - X-ray mammography.
- o Estimates of the sensitivity and specificity of these maneuvers depend on a number of factors, including:
 - The size of the lesion,
 - The characteristics of the breast being examined,
 - The age of the patient,
 - The extent of follow-up to identify false negatives,
 - The skill and experience of the examiner or radiographic interpreter, and
 - The quality of the mammogram (in the case of mammography).

Breast self-examination (BSE)³⁸

- o Breast self-examination (BSE) is a very important part of every adult woman's personal health regimen.
- o BSE should be performed once each month beginning at age 20 and should continue each month throughout a woman's lifetime.
- o In addition to BSE, adult women should receive regular physician-performed clinical breast exams.
- o The Importance of BSE:
 - Regularly examining her own breasts allows a woman to become familiar with how her breasts normally look and feel and can help her more readily detect any changes that may occur.
 - Many women naturally have some lumpiness and asymmetry (differences between the right and left breast). The key to the breast self-exam is to learn how to find changes in the breasts that persist over time.
 - While some women may be aware of monthly breast self-examination, many still do not know how to perform it properly.
 - Performing BSE incorrectly can be almost as bad as not doing the exam at all since it can give women a false sense of security. Women should discuss any questions they might have about BSE techniques with their physicians and ask them to

- demonstrate how to perform BSE during the clinical breast exam portion of the physical exam.
- o The best time to perform breast self-exam:
 - Menstruating women:
 - Hormonal changes due to the menstrual cycle may make the breasts more lumpy or swollen.
 - Women who are menstruating should perform breast self-exam 5 days after the end of the menstrual cycle, when breasts are usually less tender or swollen.
 - Women who are no longer menstruating:
 - They should do their BSE on the same day every month.
 - They should try to pick a day that is easy to remember, such as the first or fifteenth of every month, and make that the day each month for breast self-exam.
 - Women using oral contraceptives:
 - They are encouraged to do their BSE each month on the day they begin a new package of pills.
 - o Breast changes and warning signs to watch for with breast self-exam:
 - Any new lump found in the breast or armpit.
 - Any lump or thickening that does not shrink or lessen after the next period.
 - Any change in the size, shape or symmetry of the breast.
 - A thickening or swelling of the breast.
 - Any dimpling, puckering or indentation in the breast.
 - Dimpling, skin irritation or other change in the breast skin or nipple.
 - Redness or scaliness of the nipple or breast skin.
 - Nipple discharge (fluid coming from the nipples other than breast milk), particularly if the discharge is bloody, clear and sticky, dark or occurs without squeezing the nipple.
 - Nipple tenderness or pain.
 - Nipple retraction: turning or drawing inward or pointing in a new direction
 - Any breast change that may be cause for concern.
 - o Data regarding the accuracy of BSE are extremely limited. One report calculated an upper limit of sensitivity ranging from 12 to 25%.¹⁵
 - o Estimated BSE sensitivity decreased with age, from 41% for women aged 35-39 to 21% for women aged 60-74.²² Thus, as currently practiced, BSE appears to be a less sensitive form of screening than is CBE or mammography, and its specificity remains uncertain.
 - o The sensitivity of BSE can be improved by training, as measured by the proportion of benign lumps²³ detected on human models and artificial lumps²⁴ on silicone breast models, although whether this improved detection on models translates into improved personal BSE performance is unknown.

Clinical breast examination (CBE)³⁹

- o A clinical breast examination (CBE) is a physical examination of the breasts by a physician every 3 years for women between 20-40 years of age and annually for women older than 40 years of age.
- o CBE includes inspection (looking) and palpation (feeling) of the entire breast/chest area including the lymph node areas above and below the collarbone and under each arm.

- o A small percentage of breast cancers are not detected by mammography but can be felt during a clinical breast examination. Therefore it is important that a woman have both her mammogram and clinical breast exam done in the same month.
- o The earliest sign of breast cancer is usually an abnormality that shows up on an annual mammogram before a woman or her health care provider can feel it.
- o Mammography can often detect very small cancers up to two years before it can be discovered by physical exam.
- o The effectiveness of CBE alone has not been evaluated directly, but comparisons of the sensitivity and specificity of this maneuver to that of mammography can be considered.
- o Assessing the incremental value of mammography above a careful, thorough (5-10 minutes) CBE^{19,20} shows no incremental benefit highlighted the fact that higher sensitivity (88% for mammography plus CBE vs. 63% for CBE alone)¹⁵ may not guarantee improved effectiveness.
 - Specificity was comparable or slightly better for CBE alone.
- o Sensitivity of CBE for women aged 40-49 was about 10% lower at initial screen compared to the estimate for women aged 50-59.²¹
 - Specificity estimates were similarly lower for younger women.

X-ray mammography⁴⁰

- o Mammography is a special type of x-ray imaging used to create detailed images of the breast. It detects 85% of breast cancers.
- o Mammography uses low dose x-ray; high contrast, high-resolution film; and an x-ray system designed specifically for imaging the breasts.
- o Mammography can show changes in the breast well before a woman or her physician can feel them. 45% of breast cancers can be seen on mammography before they are palpable.
- o Once a lump is discovered, mammography can be key in evaluating the lump to determine if it is cancerous.
- o If a breast abnormality is found or confirmed with mammography, additional breast imaging tests such as ultrasound (sonography) or a breast biopsy may be performed.
- o A biopsy involves taking a sample(s) of breast tissue and examining it under a microscope to determine whether it contains cancer cells.
 - Many times, mammography or ultrasound is used to help the radiologist or surgeon guide the needle to the correct area in the breast during biopsy.
- o There are two types of mammography exams, screening and diagnostic:
 - Screening mammography:
 - It is an x-ray examination of the breasts in a woman who is asymptomatic (has no complaints or symptoms of breast cancer).
 - The goal of screening mammography is to detect cancer when it is still too small to be felt by a woman or her physician.
 - Early detection of small breast cancers by screening mammography greatly improves a woman's chances for successful treatment.
 - Diagnostic mammography:

- It is an x-ray examination of the breast in a woman who either has a breast complaint (for example, a breast lump or nipple discharge is found during self-exam) or has had an abnormality found during screening mammography.
 - Diagnostic mammography is more involved and time-consuming than screening mammography and is used to determine exact size and location of breast abnormalities and to image the surrounding tissue and lymph nodes.
 - Typically, several additional views of the breast are imaged and interpreted during diagnostic mammography. Thus, diagnostic mammography is more expensive than screening mammography.
 - Women with breast implants or a personal history of breast cancer will usually require the additional views used in diagnostic mammography.
- o Sensitivity of mammography is about 75%, while estimates for mammography combined with CBE ranges from 75% to 88%.
 - Sensitivity estimates for mammography alone and for combined screening with CBE have generally been 10-15% lower for women aged 40-49 compared with women greater than age 50.^{13,15-17}
 - Sensitivity of mammography improved, especially for women in their forties, with current mammographic techniques.¹⁸
 - Specificity for mammography estimates ranges from 83% to 98.5%.
 - o Annual mammograms have been demonstrated to reduce breast cancer mortality in women older than 50 years of age.
 - o The American Cancer Society (ACS) recommends a mammogram as a baseline for women 35 to 39 years old, mammograms every 1 to 2 years for women 40 to 49 years old and mammograms yearly for women 50 years of age and older.
 - o The national cancer institute makes no recommendations for mammographic screening before 50 years of age but does recommend annual mammography after 50 years of age.
 - o Mammographic signs of malignancy
 - Calcium deposits, unless in a mulberry (fibroadenoma) or curvilinear (cystic disease) pattern.
 - Mammary duct distortion or asymmetry.
 - Skin or nipple thickening.
 - Speculated breast mass.

Adverse effects of screening tests

- o False- positive tests, resulting from the effort to maximize disease detection, may have negative consequences including unnecessary diagnostic tests.
- o Mammographic screening may also adversely affect psychological well- being. Increased anxiety about breast cancer after a false-positive mammogram has been reported.^{25,26}
- o Women who underwent a surgical biopsy as a result of a false- positive screening mammogram were more likely to report their workup as a stressful experience than were those who did not have a biopsy.²⁵
- o Excess breast cancers in populations that received doses of ionizing radiation significantly greater than currently delivered by mammography, such as survivors from atomic bombing in Japan²⁷ and patients with benign breast disease,²⁸ have raised

concerns about the potential radiation risk from screening mammograms, and exposure of 1 cGy is expected to increase the risk for breast cancer by 6 cases per 1 million population.

- There is no direct evidence of an increased risk of breast cancer from mammographic screening.
 - Using film screen equipment exposed the breast to 0.02 cGy for a two view study.
- o Fewer data are available regarding adverse effects associated with CBE and BSE.

Effectiveness of Early Detection

- o Screening for breast cancer in women by either mammography alone or combined with CBE for women aged 50-69 years compared to no periodic screening showed a reduction in breast cancer mortality of 20-30%.^{14,29-35}
- o There are few data regarding the optimal periodicity of screening in this age group. Although an annual interval has been recommended by many groups, data suggests that biennial screening intervals are as effective as annual intervals.^{29,30,35}
- o There is limited and conflicting evidence regarding the benefit of screening women aged 70-74.^{14,36}
- o No clinical trials have evaluated screening in women over 74 years of age at enrollment.
- o Although there is a benefit of screening among women who are 40-74 years,^{14,29-35} there is uncertainty about the effectiveness of screening women between the ages of 40 and 49.
- o Thorough CBE may be as effective as mammography for screening in the age group 50-59.¹⁹
- o Evidence for effectiveness of BSE alone is limited, but women who practice BSE before their illness may be less likely to have a tumor of 2.0 cm or more in diameter or to have evidence of extension to lymph nodes.³⁷

Clinical intervention

Screening

- o Screening for breast cancer every 1-2 years, with mammography alone or mammography and annual clinical breast examination (CBE), is recommended for women aged 50-69.
- o Clinicians should refer patients to mammographers who use low-dose equipment and adhere to high standards of quality control.
- o There is insufficient evidence to recommend annual CBE alone for women aged 50-69.
- o For women aged 40-49, there is conflicting evidence of fair to good quality regarding clinical benefit from mammography with or without CBE, and insufficient evidence regarding benefit from CBE alone; therefore, recommendations for or against routine mammography or CBE cannot be made based on the current evidence.
- o There is no evidence specifically evaluating mammography or CBE in high-risk women under age 50; recommendations for screening such women may be made on other grounds, including:
 - Patient preference,
 - High burden of suffering, and
 - The higher positive predictive value of screening, which would lead to fewer false positives than are likely to occur from screening women of average risk in this age group.
- o There is limited and conflicting evidence regarding clinical benefit of mammography or CBE for women aged 70-74 and no evidence regarding benefit for women over age 75; however, recommendations for screening women aged 70 and over who have a reasonable life expectancy may be made based on other grounds, such as:
 - The high burden of suffering in this age group, and
 - The lack of evidence of differences in mammogram test characteristics in older women versus those aged 50-69.
- o There is insufficient evidence to recommend for or against teaching BSE in the periodic health examination.

Management⁴¹

Symptoms and Referral

Conditions that can be initially managed in general practice:

- Young women < 35 with tender, lumpy breasts and older women with symmetrical nodularity, provided no localised abnormality.
- Women with minor and moderate degrees of breast pain who do not have a discrete palpable lesion.
- Women < 50 with nipple discharge from more than one duct or intermittent discharge which is not bloodstained.

Conditions that require referral to a breast specialist include:

Lump

- Any new discrete lump.
- New lump in pre-existing nodularity.
- Asymmetrical nodularity persisting after menstruation.
- Abscess or breast inflammation not settling after one course of antibiotics.
- Cyst persistently refilling or recurrent cyst (if the patient has recurrent multiple cysts and the GP has the necessary skills, then aspiration is acceptable).

Pain

- If associated with a lump.
- Intractable pain that interferes with a patient's lifestyle or sleep and does not respond to reassurance, simple measures such as wearing a well-supporting bra, or common drugs.
- Unilateral persistent pain in post-menopausal women.

Nipple discharge

- All women aged 50 and over
- Women under 50 with:
 - bloodstained discharge;
 - bilateral discharge sufficient to stain clothes; or
 - persistent single duct discharge.

Nipple retraction or distortion, nipple eczema

Change in skin contour

General Principles of Care

- Patients should be managed by a multidisciplinary team in a designated breast unit.
- Patients should be fully informed of the different treatment options and be involved in decision-making to the extent they wish.
- All women should have access to a breast care nurse at all stages of their illness.
- All professionals should be alert to psychological and psychiatric problems in patients and family members at all stages of the disease.
- Patients should be entered into clinical trials where possible.

Information and Support

- All staff involved in the care of patients with breast cancer should be encouraged to develop communication skills.
- Patients should be given appropriate information over a period of time, since what they wish or need to know may vary over time.

Assessment and Investigation

- All patients with a localised abnormality should undergo triple assessment:
 - Clinical examination.
 - Two view mammography.
 - Fine needle aspiration cytology or core biopsy.
- All patients should be investigated for asymptomatic metastases because the presence or absence would influence management.
- All patients should be staged using the TNM system (see below).

TNM Staging

T: Primary tumour	N: Regional lymph nodes	M: Distant metastasis
<ul style="list-style-type: none"> • <u>T0</u>: No evidence of primary tumour. • <u>T1</u>: Tumour ≤ 2 cm in greatest dimension. • <u>T2</u>: Tumour >2 cm and ≤ 5 cm. • <u>T3</u>: Tumour >5 cm. • <u>T4</u>: Tumour of any size with extension to chest wall or skin or inflammatory carcinoma. 	<ul style="list-style-type: none"> • <u>N0</u>: No regional lymph node metastasis. • <u>N1</u>: Metastasis to movable ipsilateral axillary lymph node(s). • <u>N2</u>: Metastasis to: <ol style="list-style-type: none"> 1. Ipsilateral axillary lymph node(s) fixed to one another or to other structures. 2. Ipsilateral internal mammary lymph node(s). • <u>N3</u>: Metastasis to: <ol style="list-style-type: none"> 1. Ipsilateral infraclavicular lymph node(s). 2. Ipsilateral internal mammary lymph node(s) + axillary lymph node(s). 3. Ipsilateral supraclavicular lymph node(s). 	<ul style="list-style-type: none"> • <u>M0</u>: No distant metastasis • <u>M1</u>: Distant metastasis

Management by Stage

• T1-3, N0 or 1, M0:	○ Consider primary surgery.
• Larger T2 (>3cm) or T3, N0 or 1, M0:	○ Consider primary systemic therapy (neoadjuvant) prior to surgery.
• T4:	○ Mostly inoperable, but may become operable after a course of primary systemic therapy or radiotherapy.

- Elderly fit patients with potentially operable tumours should be managed as younger women, rather than giving tamoxifen as sole therapy.

Surgery

Locoregional treatment

- For women with stage I and stage II breast cancer, mastectomy with axillary lymph nodes dissection OR breast-conserving therapy with lumpectomy, axillary dissection and breast irradiation are medically equivalent primary treatment options.
- The decision to recommend mastectomy or breast-conserving therapy depends on:
 - Tumour more than 5 cm in diameter.
 - The ratio of the size of the tumour to the size of the breast.
 - The pathological features of the tumour:
 - Multicentric cancer.
 - Paget's disease.
 - Very extensive intraductal carcinoma in situ (a high rate of recurrence after radiotherapy).
 - Disease with positive or uncertain margins.
 - Worrisome mammographic abnormalities:
 - Diffuse indeterminate-type calcifications.
 - Residual disease on postoperative mammogram.
 - Situations in which there are difficulties with radiotherapy.
 - Large pendulous breast.
 - Pregnancy (1st or 2nd trimester).
 - Collagen vascular disease, particularly scleroderma or systemic lupus.

- The possibility of breast reconstruction should be discussed with all patients prior to mastectomy.

- The decision to recommend mastectomy or breast conservation depends on:
 - The ratio of the size of the tumour to the size of the breast.
 - The pathological features of the tumour
(*disease \leq 1 mm from the excision margins and multicentric disease are associated with increased risk of local recurrence*).
 - Age of patient (patients aged < 35 are at increased risk of local recurrence).
 - Fitness for surgery and/or radiotherapy.

Ductal carcinoma in situ (dcis)

- Mastectomy should be performed in patients with extensive DCIS (> 4 cm) or disease affecting more than one quadrant.
- Localised areas should be excised both widely and completely pathologically.
- Surgical staging of the axilla is not required.
- After adequate local excision of DCIS, patients should be considered for radiotherapy to the breast.

Surgery to the axilla

- All patients with clinical stage I or stage II breast cancer requires pathologic assessment of axillary lymph nodes status (at least 10 lymph nodes should be provided to accurately stage the axilla with the level I and level II dissection).
- N.B.: Dissection should be extended to include level III nodes only if gross disease is apparent in level I or II nodes.

Adjuvant radiotherapy

- After wide local excision or quadrantectomy radiotherapy should normally be given to the breast.
- After mastectomy, radiotherapy should be given to the chest wall only in patients at high risk of local recurrence (tumour more than 5 cm or positive surgical margins).
- After axillary sampling the axilla should only be irradiated if node positive (more than 3 lymph nodes) or inadequately sampled (less than 10 lymph nodes) or capsule ruptured.
- After adequate axillary clearance, the axilla should not normally be irradiated.

Definitions of risk

- Low risk disease: mostly T1-2, tumour < 3 cm, node negative, grade I, positive ER.
- Intermediate or high risk disease: node positive or negative with grade 3, tumour > 3cm, negative ER and PR, angiolymphatic invasion, HER-2 over expression.

Adjuvant systemic therapy

- All women with invasive breast cancer should be considered for adjuvant systemic therapy.
- Adjuvant therapy should be determined by:
 - An assessment of the risk of recurrence (based primarily on node status, histological grade, tumour size and hormonal receptors),
 - Oestrogen receptor (ER),
 - Status of the primary tumour, and
 - Patient's menopausal status.

Pre- or peri-menopausal women

- For low risk disease consider tamoxifen if ER positive.
- For intermediate or high risk disease, ER positive tumours, offer chemotherapy (tamoxifen) or ovarian ablation for women younger than 50 yrs (through surgery, radiation or treatment with LH-RH agonists).
- For intermediate or high risk disease, ER negative tumours, offer adjuvant chemotherapy.

Post-menopausal women

- For low risk disease consider tamoxifen if ER positive.
- For intermediate or high risk disease, ER positive tumours, consider tamoxifen and CMF chemotherapy.
- For fit women with intermediate or high risk disease, ER negative tumours, consider CMF chemotherapy.

Locally advanced tumours

Definition: Locally advanced cancers are usually defined as stage III breast cancer, normally patients presenting with T3-4, N0-2, M0 tumours.

- Primary radical radiotherapy is not recommended as sole treatment for local control of advanced tumours.
- Patients with locally advanced breast cancer should be treated with systemic induction chemotherapy (3-4 months), usually followed by surgery and/or radiotherapy. Systemic treatment is resumed with chemotherapy and hormonal therapy for positive ER or PR tumors.
- Inflammatory breast cancer should be treated with multimodality treatment.
- Patients unfit for surgery should be offered tamoxifen as initial therapy.

Metastatic disease

- Currently, patients with distant metastases are incurable.
- The aim of treatment is therefore to maintain the highest quality of life and to relieve symptoms.
- Referral to a specialist palliative care unit should be considered.
- All patients with metastatic disease should be considered for systemic treatment.

Surveillance and follow up

- Performed by members of the treatment team.
- Regular physical examination & mammography.
- In patients undergoing breast conserving therapy, first mammography should be done 6 months after completion of radiotherapy.
- Routine tumor markers for breast cancer & bone scans in asymptomatic patients are not recommended.
- The performance of routine yearly transvaginal ultrasound is recommended, and rapid evaluation of any vaginal spotting in patients who are taking tamoxifen.

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