Breast Cancer: A Review of Risk Factors, Screening and Treatment

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ABSTRACT
Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer-related death in women after lung cancer.1 This is despite the fact that breast cancer mortality rates are currently at a 25 year low. This decrease in mortality has been attributed to more aggressive screening and improved treatment outcomes. The purpose of this review is to briefly summarize the known risk factors, currently recommended screening strategies, and evolving treatment strategies for breast cancer.

EPIDEMIOLOGY
Breast cancer is the most common cancer in women in Canada and the second most common cause of cancer-related death in women after lung cancer.1 It is estimated that 21,600 Canadian women will be diagnosed with breast cancer in the year 2005 and that 5,300 will die of the disease.1 Furthermore, 2005 data estimate that the lifetime probability of developing breast cancer is one in every nine women.1 Despite the fact that incidence rates have been slowly increasing, attributed mostly to the increased use of mammography, breast cancer mortality rates are currently at the lowest levels measured over the past 25 years.1 This decrease in the mortality rates is attributed to more aggressive screening programs and improved post-surgical adjuvant therapy.1-4

There are different geographic patterns in the incidence of breast cancer, with the highest incidence in North America and the lowest in Africa and Asia.5 However, these patterns are dynamic as demonstrated by the increase in incidence rates in urban Asia which is thought to be associated with societal changes stemming from industrialization.6 In addition, studies of migration patterns to the United States suggest that environmental and lifestyle factors are important determinants of breast cancer risk.6 Interestingly, positive family history is associated with less than 10 percent of breast cancers.7 Documented genes with a strong correlation to breast cancer include the tumor suppressors BRCA1 and BRCA2.8,9 Several hundred mutations associated with an increased risk of breast cancer have been found on these genes.10

RISK FACTORS
Many factors are associated with an increased risk of breast cancer (Table 1).

Breast cancer incidence increases with age and 50% of women with breast cancer are over the age of 60.1 Family history is an important risk factor even though known genetic mutations account for a small minority of cases.7 In one report, compared to a woman without affected relatives, the risk ratio of breast cancer for a woman with one affected first degree relative was 1.80, which further increased to 3.90 when 3 or more first degree relatives were involved.7 Risk ratios were highest for women with affected premenopausal relatives. Women with mutations in either the BRCA1 or BRCA2 genes have a 60% – 85% lifetime risk of developing breast cancer.11,12

The risk of breast cancer is also increased by prolonged exposure to, and higher concentrations of, endogenous estrogen. Exposure to estrogens can be indirectly measured by age at menarche, age at menopause and age at first live birth.13 As a result, younger age at menarche, older age at menopause, nulliparity and first live birth at an older age have all been associated with higher incidence of breast cancer. Higher socioeconomic status and urban living are associated with these reproductive patterns and partly explain the increased incidence of breast cancer in these populations. Full term pregnancy, a high estrogen state, is itself associated with increased breast cancer risk and its protective effects are not seen for many years after delivery.14 On the other hand, abortions do not confer any protection against breast cancer.15 Some evidence suggests that multiparity and breastfeeding may reduce breast cancer risk.16,17

Obese postmenopausal women have higher estrogen levels due to conversion of adrenal androgens to estrogens in adipose tissue, and are at an increased risk of breast cancer.18 Two recent studies have shown that oral contraceptives do not increase breast cancer risk.19,20 However, there is evidence
that hormone replacement therapy in postmenopausal women increases risk. Invasive breast cancer is associated with an increased risk of 0.5 – 1% per year of developing breast cancer in the contralateral breast. Some studies have linked diets low in calories and fat to decreased breast cancer risk. Increased breast density, moderate alcohol intake, previous radiation to breast and antibiotic use are also associated with a higher incidence of breast cancer.

### SCREENING AND DIAGNOSIS

The classic presentation of breast cancer is a palpable, painless breast lump. In a recent study, however, breast cancer was found in only eleven percent of women presenting with a lump, and the majority of cases were later confirmed to be benign fibroadenomas or cysts. Other features at presentation may include breast pain, nipple discharge, an axillary lump, skin changes over the breast, and mammographic abnormalities.

While most breast masses are benign, the possibility of underlying breast cancer must be considered. In a premenopausal woman, a small breast mass can be a normal component of the menstrual cycle and can be observed for a period of 1-2 weeks for post-menses resolution. If the mass persists, further testing is required. In post-menopausal women, all breast masses require investigation.

Annual mammography screening of women between the ages of 40 to 74 reduces mortality by up to 30%. For women presenting with a lump, mammography allows for its evaluation and the identification of clinically occult lesions. Increased density, spiculations, irregular margins and clustered microcalcifications are mammographic features that suggest malignancy (Figure 1a,b). The sensitivity and specificity of mammography in women with a non palpable lesion is 82.3% and 91.2% respectively, while in women with a palpable mass, it is 87.3% and 84.5%. As a result, 10 – 20% of clinically palpable breast cancers are missed by mammogram screening. Thus, a negative mammogram should not prevent further investigations if a lump is thought to be suspicious. Mammography is not clinically beneficial for women under the age of 35 because of associated increased breast density, and is only reserved for instances of high cancer suspicion.

Ultrasound can be used to determine whether a breast mass is cystic or solid in nature. There has been some debate as to how to best use ultrasonography in breast cancer screening. Some authors recommend using ultrasound in conjunction with mammography, while others believe that women should undergo fine needle aspiration biopsy of the lump instead of ultrasound following a suspicious mammogram. Canadian practice guidelines consider either approach as adequate. The negative predictive value of ultrasound in the setting of a patient with a palpable breast mass and non-suspicious mammogram is over 97-99%. Fine needle aspiration biopsy (FNAB) allows for the direct sampling of the breast lump. When bloody fluid is drained from a cyst, it is positive for breast cancer in 7% of cases and should be sent for cytological analysis. Clear drained fluid need not be sent for analysis. Lack of fluid or a persistent mass could indicate a solid tumor and cytology can be performed to rule out cancer. Fine needle aspiration is operator-dependent with a sensitivity and specificity ranging between 65 – 98 and 34 – 100 percent respectively.

Needle core biopsy (NCB) is an option similar to FNAB. Unlike FNAB, NCB uses a large bore needle to obtain a core of tissue, preserving the architecture of the tumor. Pathology review of the tumor core can identify if the tumor is malignant, and more importantly, whether it has invasive features. The

### Table 1. Risk factors for breast cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Low Risk Group</th>
<th>High Risk Group</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>150.0</td>
</tr>
<tr>
<td>First degree relative with breast cancer</td>
<td>No</td>
<td>Yes</td>
<td>2.6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30-34</td>
<td>70-74</td>
<td>17.0</td>
</tr>
<tr>
<td>Age at menarche (yr)</td>
<td>&gt;14</td>
<td>&lt;12</td>
<td>1.5</td>
</tr>
<tr>
<td>Age at menopause (yr)</td>
<td>&lt;45</td>
<td>≥55</td>
<td>2.0</td>
</tr>
<tr>
<td>Age at birth of first child (yr)</td>
<td>&lt;20</td>
<td>≥30</td>
<td>1.9 – 3.5</td>
</tr>
<tr>
<td>Breast-feeding (mo)</td>
<td>≥16</td>
<td>0</td>
<td>1.37</td>
</tr>
<tr>
<td>Parity</td>
<td>≥5</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>Use of birth control pill</td>
<td>Never</td>
<td>Previous or current</td>
<td>1.07 – 1.2</td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td>Never</td>
<td>Current</td>
<td>1.2 – 1.4</td>
</tr>
<tr>
<td>Postmenopausal BMI</td>
<td>&lt;22.9</td>
<td>&gt;30.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Serum estradiol concentration</td>
<td>Lowest quartile</td>
<td>Highest quartile</td>
<td>1.8 – 5.0</td>
</tr>
<tr>
<td>Breast density on mammography</td>
<td>0</td>
<td>≥75</td>
<td>6.0</td>
</tr>
<tr>
<td>Bone density</td>
<td>Lowest quartile</td>
<td>Highest quartile</td>
<td>2.7 – 3.5</td>
</tr>
</tbody>
</table>

pathologic classification of breast malignancies can be seen in Table 2. In one study, the specificity and sensitivity of NCB for the diagnosis of cancer was 100% and 90% respectively, while that of FNAB was 100% and 97.5%.41 Canadian practice guidelines recommend the use of NCB when ultrasound or FNAB fail to quell high level of suspicion.35

**Table 2. Pathological classification of invasive breast carcinoma**

<table>
<thead>
<tr>
<th>Pathological classification</th>
<th>% Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrating ductal</td>
<td>70 - 80</td>
</tr>
<tr>
<td>Invasive lobular</td>
<td>5 - 10</td>
</tr>
<tr>
<td>Tubular</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Medullary</td>
<td>5 - 10</td>
</tr>
<tr>
<td>Mucinous (colloid)</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Micropapillary, metaplastic, and others</td>
<td>1 - 2</td>
</tr>
</tbody>
</table>


**STAGING AND PROGNOSIS**

The staging of breast cancer is based on tumor size, lymph node involvement and presence of metastasis (TNM system; Table 3a). The size of the tumor is determined by pathologic review of the gross tumor after surgical excision (Figure 1c-f). The pathologist also determines nodal involvement by analyzing dissected axillary nodes (see below). The staging of breast cancer is important for two reasons. First, the TNM classification allows for the determination of the patient’s prognosis as the two most important prognostic factors for invasive carcinoma are tumor size and nodal involvement (b). Second, the approach to disease management is dependent on the TNM stage.

In addition to TMN staging, the histologic grade of the tumour is important for prognosis. A histological score is given by the pathologist representing the degree of cellular differentiation and integrity of nuclear architecture. High grade lesions are associated with increased likelihood for metastasis. Lymphovascular infiltration is associated with increased risk of metastasis and is another important prognostic factor.

**Table 3a. TNM classification of breast cancer**

<table>
<thead>
<tr>
<th>Tumor Size (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

**Table 3b. Staging of breast cancer and associated 5-year relative survival rate**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>% 5-year survival</th>
<th>Stage</th>
<th>TNM</th>
<th>% 5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
<td>100</td>
<td>I</td>
<td>T1 N0 M0</td>
<td>98</td>
</tr>
<tr>
<td>I</td>
<td>T1 N1 M0</td>
<td>95</td>
<td>II A</td>
<td>T0 N1 M0; T2 N0 M0</td>
<td>88</td>
</tr>
<tr>
<td>II A</td>
<td>T1 N1 M0</td>
<td>95</td>
<td>IV</td>
<td>Any T Any N M1</td>
<td>16</td>
</tr>
<tr>
<td>IIB</td>
<td>T2 N1 M0; T3 N0 M0</td>
<td>76</td>
<td>II A</td>
<td>T0 N2 M0; T1 N2 M0; T2 N2 M0; T3 N0 M0</td>
<td>56</td>
</tr>
</tbody>
</table>

# data for stage IIIC is unavailable as it is a relatively recent stage designation. 5-year survival data from the American Cancer Society.
Figure 1. Radiologic and pathologic evidence of breast cancer
(a) Mammogram showing adenocarcinoma of the right breast and (b) a normal contralateral breast. Note spiculated density near the centre of the panel (a). (c) Normal breast tissue under microscopy. (d,e) Infiltrating ductal carcinoma. (f) Lymph node involvement by breast cancer. Blue and pink (arrow) stained cells represent lymph node tissue and malignant tissue respectively.
Secondary prognostic factors include the relative presence of estrogen and progesterone receptor (ER/PR) and her2/neu receptor on the surface of malignant cells. Their presence are also key parameters for disease management (see below).

**TREATMENT**

Management of breast cancer utilizes a multidisciplinary approach that typically includes surgery, radiotherapy and systemic therapy.

**Surgery**

Initial attempts at breast cancer surgery were associated with such poor outcomes that in 1894, Halsted suggested that an extensive resection of tissue may be required to improve local control and mortality.42,43 The suggested procedure required complete removal of the breast, pectoralis major and minor, and extensive removal of axillary lymph nodes. While this procedure greatly decreased the rate of local recurrence and was readily adopted, survival remained poor.44 Years later, it was suggested that less extensive surgery, the modified radical mastectomy (MRM), may lead to similar outcomes. This procedure entailed the removal of the breast, the fascia of the pectoralis major and some but not all of the axillary nodes. Indeed, randomized clinical trials found equivalent survival rates between the two procedures, with the modified approach also resulting in less morbidity.45-47

One of these studies, the NSABP B-04 trial,45 provided critical momentum to the development of breast conservation surgery. In this trial, clinically node-negative women with breast cancer were randomized to receive a radical mastectomy, or a simple mastectomy (i.e. breast removal only) with local node radiation or a simple mastectomy with axillary node dissection. At 10 years follow-up, disease-free survival and overall survival were similar between the three treatment arms suggesting that variation in local control strategies did not ultimately influence survival, and that survival was more dependent on the systemic spread of disease.

Several clinical trials compared MRM to breast conservation therapy (BCT; lumpectomy plus breast irradiation and axillary dissection) and all showed equivalent overall survival with either approach.48-50 While BCT is now the standard of care, the presence of inadequate tumor margins after surgery, multifocal disease, prior chest wall irradiation and pregnancy are all absolute contraindications and mastectomy is preferred in these situations.51 Relative contraindications include connective tissue diseases, especially scleroderma,51 which would compromise the ability to deliver post-operative adjuvant radiation. Recently, a procedure known as skin sparing mastectomy has been gaining increased popularity. Preservation of the skin allows for better cosmetic results, and while studies have not shown an increased incidence of local recurrence with this procedure, long-term studies are lacking.52,53

**Radiation Therapy**

Radiation therapy (RT) is an integral component of breast conservation therapy (BCT) and may be used post mastectomy in some cases. In BCT, the addition of RT to lumpectomy is crucial as it is associated with large improvements in local control. Long-term follow-up from the NSABP B-06 trial revealed that lumpectomy plus RT had a recurrence rate of 14% versus 39% for lumpectomy alone at 20-years.49

Local recurrence post BCT has been shown to occur near the original excision site in the vast majority of cases. Several studies adding a radiation boost to the surgical bed have shown further reductions in local recurrence, especially in younger women, although no improvements on overall survival have been observed.54 It is now recommended that women 50 or younger undergoing BCT receive a radiation boost to the lumpectomy surgical bed.54,55

Studies thus far comparing lumpectomy with or without RT have not shown an overall survival advantage. However, a recent pooled analysis of 13 randomized controlled trials, showed an increased relative risk (RR) of mortality for the no RT group (RR 1.086, 95% CI = 1.003 to 1.175).56 This corresponded to an 8.6% relative excess mortality for the non-irradiated group. Since RT can be a burden to patients and resources due to its daily scheduling, often urban location, and cost, some have investigated whether certain groups of women may forego RT post lumpectomy. Based on the results of such studies, which included women with favorable breast cancer features, no subgroup of women undergoing BCT has been found to have a low enough risk to justify foregoing RT post lumpectomy.57-59 One possible exception is postmenopausal women receiving adjuvant hormonal therapy as the calculated benefit from RT has been determined to be low (1% versus 4% recurrence).60

Although survival outcomes are equivalent between mastectomy and BCT, some recent studies indicate that adding RT to mastectomy in women at high risk of local relapse may improve survival. In a meta-analysis of 18 trials published between 1967 and 1999, radiation therapy to the chest wall and loco-regional lymph nodes post-MRM in women with node-positive (N+) disease led to decreased risk of local recurrence (odds ratio 0.25, 95% CI, 0.19 to 0.34) and mortality (odds ratio, 0.83; 95% CI, 0.74 to 0.94).61 In a trial from British Columbia, RT to N+ women treated with MRM and CMF chemotherapy was associated with increased overall survival (OS of 52% vs. 43%) compared to no radiation.62,63 Despite these findings, superior survival in N+ women receiving radiation therapy post mastectomy remains controversial and definite answers await ongoing clinical trials. Canadian practice guidelines currently suggest post-mastectomy irradiation be considered for women with 4 or more positive lymph nodes, or for T3/T4 tumors.64 In addition, premenopausal women with positive margins may benefit from post-mastectomy irradiation.65

Since the vast majority of local recurrences occur near the original tumor excision site, some have questioned whether local radiation to the surgical bed has a similar recurrence profile as whole breast RT. This strategy, known as partial breast irradiation (PBI), involves either placement of a radiation source in close proximity to the surgical bed, or more precisely...
planned external beam radiation. As radiation doses can be intensified to the smaller breast volume, treatments are typically less time consuming than with whole breast RT. In one study, at 5 year follow-up, PBI showed similar outcomes than lumpectomy plus RT.66 Larger clinical trials to validate PBI over whole breast radiation are beginning to recruit patients.

Complications of radiation therapy to the breast and loco-regional lymph nodes, although rare, include arm lymphedema, pneumonitis, brachial plexopathy, cardiac toxicity and secondary malignancies (RR 1.15) such as contralateral breast cancer, sarcomas, leukemias and lung cancer.

**Axillary Lymph Node Dissection**

Axillary lymph node dissection (ALND) has classically accompanied mastectomy for breast cancer treatment and has been associated with decreased axillary recurrence,45 a small survival improvement67,68 and is critical for disease staging. In ALND, the number of lymph nodes resected is inversely proportional to local recurrence.69,70 In addition, a larger sample of axillary nodes is associated with more accurate staging but increased morbidity.71 It has been estimated that the adequate number of resected lymph nodes is ten.72,73 Following ALND, axillary lymph nodes may be irradiated when risk of recurrence is high.

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**Figure 2.** Approach to the systemic therapy for breast cancer. Treatment decisions are made on the basis of menopausal status, ER/PR status and nodal involvement. Postmenopausal, but not premenopausal, women with ER/PR+ and N- disease may receive tamoxifen alone. Tumors in premenopausal women are generally more aggressive and need additional adjuvant chemotherapy. Tamoxifen and AI’s are used in ER/PR+ disease. N+ disease is more advanced and may warrant the addition of a taxane.
is high.\textsuperscript{74} Complications associated with ALND include infection, seroma formation, and arm and shoulder morbidity (stiffness, paresthesias and lymphedema).\textsuperscript{75}

Sentinel lymph node biopsy is a relatively new procedural option to ALND that is associated with less morbidity.\textsuperscript{76} It is based on the hypothesis that tumor metastases initially spread to a few axillary lymph nodes before dissemination to other nodes. Peritumoral application of a colored or radioactive dye helps identify these sentinel nodes at the time of surgery. Absence of micrometastasis in sentinel nodes likely indicates that other axillary lymph nodes are not involved. On the other hand, micrometastasis in sentinel nodes requires further axillary node dissection. The superiority of sentinel node biopsy over axillary node dissection has not yet been determined and definitive answers await ongoing clinical trials. One disadvantage of sentinel node biopsy is its operator dependence and a certain level of expertise is required to perform the procedure satisfactorily. Finally, positron emission tomography (PET) imaging and ultrasound guided FNA are also being evaluated as a tool to examine the axilla and may play an important role in the future.

Systemic Therapy

Some of the key systemic therapy data comes from the Early Breast Cancer Trialists’ Collaboratory Group (EBCTCG). In an EBCTCG review of all trials prior to 1990, which included 18,000 women in 47 trials treated with or without chemotherapy, it was determined that chemotherapy is associated with decreased disease recurrence and superior survival outcomes, especially in younger women.\textsuperscript{77} In women under 50 years of age, chemotherapy was associated with an increase in 10-year survival from 71\% to 78\% in node-negative (N-) women and 42\% to 53\% in N+ women. In women between 51 and 69 years of age, chemotherapy was associated with an increase in 10-year survival from 67 to 69\% in N- women and from 46 to 49\% in N+ women. Superior chemotherapy outcomes in younger women may be related to the induction of ovarian failure in premenopausal women. Supporting this hypothesis is the observation that treatment-induced amenorrhea in premenopausal women was associated with improved survival.\textsuperscript{78,79} Younger women also have a higher likelihood of developing ER negative tumors,\textsuperscript{80} which respond better to chemotherapy\textsuperscript{77} (see Figure 2 for a summary of adjuvant systemic therapy for breast cancer).

The chemotherapeutic agents most commonly used today are CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and anthracycline-based regimens such as AC (doxorubicin, cyclophosphamide), CAF (cyclophosphamide, doxorubicin and 5-fluorouracil) and CEF (doxorubicin, epirubicin and 5-fluorouracil). Whether one regimen is superior to the other remains somewhat controversial. In the aforementioned EBCTCG analysis,\textsuperscript{77} review of the data on 6000 women in 11 trials comparing anthracycline-containing regimens to CMF revealed that anthracycline-based regimens were somewhat superior to CMF in terms of recurrence (40.5\% versus 43.2\%) and mortality (28.8\% versus 30.5\%). Other data published after the EBCTCG review have reported either supportive or contradictory evidence to this effect. In the INT 0102 trial,\textsuperscript{81} CAF was shown to be moderately superior to oral CMF in terms of recurrence-free survival (85\% versus 82\%) and overall survival (92\% versus 90\%). In addition, in a NCIC-CTG study, CEF was associated with improved recurrence-free survival (63\% versus 53\%) and overall survival (77\% versus 70\%) compared to oral CMF.\textsuperscript{82} On the other hand, both the NSABP B-15 and B-23 trials showed that AC chemotherapy was equivalent to oral CMF.\textsuperscript{83,84} Some have suggested that since AC chemotherapy (4 cycles for a total of 12 weeks) is shorter than oral CMF chemotherapy (6 cycles for a total of 6 months), prolonging AC treatment with the addition of 5-fluorouracil (i.e. CAF or CEF for 6 cycles) may increase survival.\textsuperscript{81,82} This hypothesis is supported by INT 0102 and NCIC-CTG studies above, and Canadian practice guidelines recognize anthracycline-based regimens as superior.\textsuperscript{85}

Anthracycline-containing chemotherapy does appear to have a clearer superiority over CMF in treating her2/neu positive tumors.\textsuperscript{86-88} The American Society of Clinical Oncology (ASCO) currently recommends the prescription of anthracycline chemotherapy for her2/neu overexpressing tumors.\textsuperscript{89} However, patients should not be denied CMF should there be a contraindication to anthracyclines, and the lack of her2/neu expression does not preclude the prescription of anthracycline-based regimens.

Recent clinical trials have compared the use of anthracycline-based chemotherapy with or without taxanes in N+ women. In both CALGB 9344 and BCIRG 001 trials, the use of taxanes in addition to anthracycline-based chemotherapy was associated with increased disease-free and overall survival.\textsuperscript{90,91} Results from other trials have not been as optimistic.\textsuperscript{92-94} Despite the latter trials, data has been sufficiently encouraging that docetaxel in combination with AC chemotherapy has been approved for the treatment of N+ women in the United States. The use of taxanes in women with N- disease has not been validated by clinical trials. Taxanes remain an active topic in breast cancer research.

Trastuzumab, a monoclonal antibody to her2/neu has been shown to be effective in the treatment of metastatic breast cancer.\textsuperscript{95,96} Concurrent use with anthracyclines has been associated with cardiomyopathy. Ongoing clinical trials involving the sequential use of trastuzumab with chemotherapy and its role in non-metastatic disease remain to be evaluated.

Women receiving BCT can delay radiation therapy up to 6 months post-lumpectomy to receive chemotherapy, without any adverse effect.\textsuperscript{97} Radiation therapy and anthracycline-based regimens can interact leading to high treatment toxicity.\textsuperscript{98} For this reason, concurrent treatment using anthracyclines and RT is not advised. Women over 70 have not been included in many breast cancer clinical trials.\textsuperscript{99} It is likely that women 70 or older may also benefit from chemotherapy, although patient comorbidity may preclude prescription.\textsuperscript{99,100} The use of good clinical judgment is very important in these situations.
Hormonal Therapy

The hormone estrogen is responsible for driving the growth of breast cancer cells that express ER/PR on their surface. Current pharmacological strategies exploit this relationship between estrogen and breast cancer cells. Tamoxifen, a selective estrogen receptor modulator (SERM), works at the level of the ER to inhibit estrogen binding and is the most well studied hormonal therapy agent. In 1998, the EBCTCG reviewed all randomized controlled trials of adjuvant tamoxifen versus no hormonal therapy started before 1990. At 10-year follow-up, it was found that 5 years of adjuvant tamoxifen compared to no hormonal therapy was associated with a proportional decrease of recurrence by 47% and a proportional reduction of mortality by 26% in ER/PR-positive women. In addition, tamoxifen was associated with a 30% decrease in the risk of contralateral breast cancer. No benefits were observed in ER/PR-negative women. Studies have also looked at the appropriate treatment duration with tamoxifen. These trials have found that optimal treatment duration was 5 years and that longer therapy may be of benefit to N+ women. Ongoing clinical trials will address the possibility of longer treatment duration in N+ women. Currently, the standard duration of tamoxifen treatment is 5 years. The side effect profile of tamoxifen includes hot flashes, vaginal discharge, and increased risk of thromboembolism and endometrial cancer.

The enzyme aromatase is involved in the conversion of androgens to estrogen in adipose tissue. This source of estrogen is important in driving the proliferation of breast cancer cells in postmenopausal women. Drugs that inhibit the activity of aromatase are currently being studied and data thus far have been encouraging. In the ATAC trial, mostly ER+ postmenopausal women were randomized to 5 years of anastrozole alone, tamoxifen alone or combined therapy. At 68-month follow-up, compared to tamoxifen alone, the aromatase alone treatment arm was associated with improved disease-free survival (hazard ratio 0.87, 95% CI 0.78-0.97), but no difference in overall survival. Compared to tamoxifen, anastrozole was also associated with a reduction in the proportional risk of contralateral breast cancer by 42%. No advantage to combined therapy was found. Tamoxifen remains a common first line adjuvant hormonal therapy as long-term studies with aromatase inhibitors (AIs) are lacking and the long-term side effect profile is unknown.

While results for concurrent therapy have been disappointing, data for sequential use of tamoxifen with AIs have shown improved outcomes. In the NCIC-CTG MA 17 trial, women who were postmenopausal over the age of 50 at the start of treatment with 5 years of tamoxifen were randomized to 5 years of letrozole or placebo after tamoxifen. The trial was stopped early after 2.4 year follow-up data showed improved disease-free survival at 4 years (93% versus 87%). No statistically significant improvements in overall survival were observed. In addition, two other trials showed improved disease-free survival but no change in overall survival with sequential use of exemestane or anastrozole after 2 to 3 years of tamoxifen for a total of 5 years. In these studies, sequential therapy with AIs was associated with a decreased incidence of contralateral breast cancer compared to tamoxifen alone. These data present a strong argument for sequential treatment with tamoxifen followed by an AI. Appropriate length of treatment and long-term side effect profile await ongoing randomized clinical trials. Side effect profile of AIs includes osteoporosis, hot flashes, vaginal discharge and musculoskeletal pain.

LHRH agonists can inhibit the synthesis of ovarian estrogen and have also been used to treat breast cancer. The data for LHRH agonists (i.e. goserelin) have been scant. There is some indication that premenopausal women may benefit from goserelin in addition to tamoxifen plus chemotherapy. Furthermore, some studies have found goserelin plus tamoxifen to be at least equivalent to IV CMF and perhaps oral CMF or AC. The potential role goserelin may play in the treatment of premenopausal women with breast cancer awaits future studies.

CONCLUSION

Many clinical trials over the last few decades have led to substantial advances in our understanding of breast cancer risk factors and genetics, screening protocols and strategies, and optimal treatment modalities. Results from completed trials have resulted in the routine use of breast preservation strategies. In addition, more treatment options have become available and greater improvements in survival have been seen. Ongoing trials may confirm the role of sentinel node dissections and PET scans to further reduce the morbidity currently associated with axillary surgery. Radiation therapy trials are evaluating more targeted treatment approaches. Cell-targeted biologicals such as trastuzumab are showing great promise. SERMs and AIs may be used in the future to prevent breast cancer in high risk women and their use in patients with disease continues to evolve. Many important clinical questions remain and the need for patients to be involved in ongoing clinical trials has never been greater.

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REFERENCES


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