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Title: Early Breast cancer: more than one disease

Abstract

Breast cancer is the most common female cancer and globally remains a major public health concern. The diagnosis and treatment of breast cancer continues to develop. Diagnosis is now more precise, surgery is less mutilating and women now have the option of breast conserving therapy with better cosmesis without sacrificing survival. Radiotherapy is more targeted and the selection of patients for adjuvant chemotherapy is based not only on prognostic and predictive factors but also on newer molecular profiling which will ensure that chemotherapy is given to the patients who need and respond to it. These developments all provide a more tailored approach to the treatment of breast cancer. The management of breast cancer today involves multidisciplinary team approach in order to provide the highest standard of care for patients throughout their cancer journey from diagnosis through treatment and into follow up care.

Introduction:

Breast cancer is a major public health issue worldwide (Benson et al, 2009). In the United Kingdom breast cancer is the most common cancer in women accounting for 31% of all female cancers. In 2008 there were 48,034 new cases of breast cancer diagnosed 47,693(99%) in women and 341(less than 1%) in men, and 12,122 (16%) deaths from breast cancer (Ferlay et al, 2008).

Mortality rates have improved in European countries where screening mammography has been introduced, centralized breast cancer services are available, and modern multidisciplinary management is in place (Benson et al, 2009). Interestingly, some of the lowest European incidences are to be found in eastern European countries where screening programs are not yet established (Autier et al, 2010).

Causes of breast cancer

There are many risk factors associated with the development of breast cancer. These include age, gender, reproductive history, hormonal factors and family history. Lifestyle issues may also increase a woman's risk; including obesity, alcohol intake, and absence of breastfeeding. Women from higher socioeconomic groups are more at risk, however women from lower socioeconomic group usually present with more advanced disease (Bradley et al, 2002). Reproductive factors are associated with the length of unopposed oestrogen which the woman is exposed to and includes long menstrual history, nulliparty, hormone replacement therapy and late age at first birth (Nelson et al, 2012). The absence or short duration of breast feeding also contributes to the risk of breast cancer. There is an increased risk of breast cancer in women who use oral contraceptives (Nelson et al, 2012). Hormone replacement therapy can also increase a woman risk by 35% after 10 years of use (Benson et al, 2009; Li et al, 2009). Oestrogen receptor negative tumours tend to occur in younger women whereas oestrogen receptor positive tumours are more common in women over the age of 50 (Fouilkes et al, 2010).

Regarding lifestyle issues, regular strenuous physical activity, maintenance of healthy weight and adaptation of a healthy lifestyle have all been shown to reduce breast

cancer risk (Benson et al, 2009; Li et al, 2009). Alcohol consumption also increases the risk of breast cancer (Jermal et al, 2011). Less than 10% of breast cancers are associated with germ line mutations. The two most common of these genes are BRCA1 and BRCA2 and mutations in these genes account for three quarters of hereditary breast cancers. Women who carry these genetic mutations have an estimated life time risk of breast cancer of 40% (Li et al, 2009).

Diagnosis and staging

In developed countries, most breast cancers are now diagnosed through symptomatic mammogram assessment. The diagnosis of breast cancer involves triple assessment in breast cancer centres. This assessment integrates the components of the clinical examination, radiological imaging and tissue diagnosis. Dedicated breast imaging includes mammogram, ultrasound of the breast and in some incidences, breast MRI.

Mammography remains the most important diagnostic tool in detecting cancer for women with breast tissue that is not too dense, usually seen in women after the menopause. Approximately 10% of breast cancers are not seen on mammogram (Benson et al, 2009).   In women with dense breasts, ultrasound is a very useful diagnostic test. Ultrasound is also used to measure the size of the tumour and allows assessment of the lymph nodes in the axilla (Kelly et al, 2010). MRI is used to screen high risk BRCA positive women and may also be utilised when conventional diagnostic methods fail or when clarification is needed to establish if the patient is a candidate for breast conserving surgery (Veronesi et al, 2005).

Tissue diagnosis is usually obtained by core biopsy. The invasive carcinomas consist of several histological subtypes with invasive ductal carcinoma the most common type (Veronesi et al, 2005) (Table 1).

The TNM staging system defines the extent of the disease. Newer classification of breast cancer encompasses the molecular subtype of the cancer which takes into consideration other prognostic factors including hormone receptor status, Her 2 neu status, and tumour grade and lymphovascular invasion. All newly diagnosed breast cancers are tested for oestrogen, progesterone receptors status and Her 2 neu overexpression (Benson et al, 2009).

Treatment options

Surgery

The treatment of early stage breast cancer includes surgery, radiotherapy, chemotherapy, endocrine therapy and biotherapies. Breast conserving surgery is now the standard of care for early breast cancer which provides patients with better cosmetic results without comprising survival (Jones et al, 2009). Many cancers are now diagnosed earlier due to the introduction of screening, and many large tumours are treated with neo adjuvant therapy to reduce their size thus allowing for breast conservation surgery. However, careful selection of patients for breast conservation is paramount as adequate surgical margins are essential to reduce the risk of ipsilateral breast tumour recurrences which may affect cosmetic results (Park et al, 2000).

Mastectomy is still indicated when there is multicentric invasive cancer, extensive intraductal carcinomas, inflammatory carcinoma, large primary tumours not reduced by neoadjuvant therapy and patient preference (Benson et al, 2009). The majority of patients following mastectomy are now offered immediate reconstruction. There are various different surgical options to choose from including tissue expander (Benson et al, 2009). However, the need for post mastectomy radiotherapy will affect which reconstruction method is utilised. Skin sparing mastectomies followed by reconstruction is now one of the most popular forms of reconstruction (Benson et al, 2009). A meta-analysis, by the Early Breast Cancer Trialists' Collaborative Group, of nine trials comparing mastectomy versus breast conserving surgery and radiotherapy found that there was no difference in survival between the two groups (Abe et al, 1995).

The status of the axillary lymph nodes is an important prognostic factor in early stage breast cancer. Axillary lymph node dissection remains the standard of care for patients with clinically palpable or positive histological confirmed lymph nodes (Benson et al, 2009). Newer technologies have advanced the management of the axilla, the most important of these being the sentinel lymph node biopsy. Sentinel lymph biopsy (SLNB) is based on the observation that tumour cell migrate from the primary to one or a few lymph nodes before progressing to other lymph nodes (Langer et al, 2007). In patients with a negative lymph node biopsy further axillary

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lymph node dissection (ALND) is not required thus reducing the risk of lymphoedema, nerve injury and shoulder dysfunction which are associated with the more extensive surgery (Kwan et al, 2002). Sentinel lymph node biopsy has now become the standard of care (ASCO and NCCN guidelines) (Burstein et al, 2010; NCCN, 2012). The false negative rates associated with sentinel lymph node biopsy range from 5-10% however many studies have found that recurrence rates in the axilla after sentinel lymph node biopsy alone range from 0-4.5% (e.g. Veronesi et al, 2010; Andersson et al, 2012).

Radiotherapy

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in their meta-analysis in 2011 found that the addition of radiotherapy after breast conserving surgery reduced by half the 10 year risk of recurrence and reduced by 20% breast cancer deaths over 15 years (Darby et al, 2011). Current debates are centred on identifying the subgroup of patients who do not require radiotherapy following breast conserving surgery and also different radiation treatment schedules. Numerous trials have been undertaken in an effort to identify a subgroup of patients with a low enough risk of recurrence after surgery to justify eliminating radiotherapy (e.g. Lim et al, 2006). However, to date no specific group of patient has been defined for which radiotherapy can be omitted and radiotherapy after breast conserving surgery remains the standard treatment (Lim et al, 2006).

A variety of radiotherapy techniques have been developed in recent years, including rapid fractionation, partial breast irradiation and intraoperative radiotherapy. More than three quarters of local recurrences arise near the primary tumour location (Veronesi et al, 2005; Benson et al, 2009). This has led to the development of partial breast irradiation which can be delivered using brachytherapy, intraoperative radiotherapy or Mammosite. However, the complexity of brachytherapy and the facilities required for intraoperative radiotherapy have precluded their widespread use. An alternative to brachytherapy is provided via a double lumen catheter attached to a soft Mammosite balloon placed within the surgical cavity, which delivers a total dose of 34Gy in ten fractions. 5 year recurrence rates show local recurrence rates of 0-6% with good cosmetic result in the majority of the patients treated. Extended long term

follow up is awaited to determine the full efficacy of this treatment modality (Benson et al, 2009; Benitez et al, 2007).

Systemic treatments

Historically the management of breast cancer depended on conventional prognostic and predictive factors. However, these parameters alone did not take into account the heterogeneous and phenotypically diversity of breast cancer which resulted in many patients being over treated with conventional chemotherapy (Rakha et al, 2008; Hayes, 2012). The development in recent years of gene expression profiling has identified distinct biological classes of tumour that can help to predict breast cancer outcome and response to treatment based on gene expression patterns and DNA copy number alterations. Three prognostic tests have been approved for clinical use; Oncotype DX, Mammaprint and H/I (Reis-Filho and Pusztai, 2011). These tests are used to predict the risk of recurrence in patients with newly diagnosed node negative oestrogen positive breast cancer and to select those patients most likely to benefit from adjuvant systemic chemotherapy (Benson et al, 2009). A low recurrence score indicates that patients are more likely to benefit from endocrine therapy and would not need adjuvant chemotherapy. A high recurrence score indicates that these patients would require the addition of adjuvant systemic chemotherapy to endocrine therapy. In Ireland the Oncotype DX is available to node negative breast cancer patients under the public health system. Internationally in the United States the test is covered by Medicare and private insurances. In the United Kingdom recent draft NICE guidance stated that more evidence is needed on these tests before they can be recommended for use in the NHS (NICE, 2012).

Knowing the subtypes of breast cancer therefore provides clinicians with valuable information that informs systemic treatment decisions. Distinct molecular subtypes of breast cancer are evident (Table 2). This designation of molecular subtypes illustrates a range of cancers, some of which are highly endocrine dependent and relatively resistant to chemotherapy (Luminal A) to highly endocrine independent and highly sensitive to chemotherapy (Basal- like) (Hayes, 2012). Of all the subtypes, Luminal A breast cancer has the best prognosis. Traditionally Her 2 neu and Basal–like cancers were considered to have the worse prognosis but the prognosis of Her 2 neu cancer

have improved dramatically with the introduction of HER 2 neu directed therapies, such as trastuzumab (Bonilla et al, 2010; Slamon et al, 2011).

Adjuvant chemotherapy

Adjuvant systemic therapies consist of chemotherapy, endocrine therapy and human epidermal growth factor receptor 2 directed therapies. Adjuvant chemotherapy is administered to eradicate micro metastases and aims to reduce relapse rates and increase overall survival. Many studies have demonstrated the benefits of adjuvant chemotherapy however controversies with it do exist. For example, many commentators still advocate adjuvant chemotherapy for breast cancer patients with node positive disease even if they fall into the Luminal A subcategory of breast cancer where benefits from chemotherapy are low (Reis-Filho and Pusztai, 2011). Many patients do not need or will not respond to chemotherapy and the new molecular testing will help in predicting benefit for these patients.

The anthracycline and taxane chemotherapies are considered to be the two most effective chemotherapies in the adjuvant setting particularly for patients in the triple negative group (Table 2) for whom endocrine therapy or trastuzumab are not an option (Fouilkes et al, 2010). The addition of taxanes to the tradition combination of doxorubicin/cyclophosphamide (A/C) showed improved survival. The use of taxanes is NICE approved in England and Wales for all node positive breast cancers (NICE 2009).

Anthracyclines have been used in the treatment of breast cancer for over 25 years and their benefit is well established. Studies have shown that antracyclines reduce annual breast cancer deaths by approximately 38% in premenopausal women and by approximately 20% in post menopausal women (Gianni et al, 2009). However, their use is currently being debated in early stage breast cancer due in part to associated cardio toxicity with anthracyclines (Slamon et al, 2011). Nevertheless, many authors still advocate the use of anthracycline based therapy particularly in high risk patients and Her 2 neu positive patients until results from other randomised trials become available (Gianni et al, 2009; Burstein et al, 2012). In addition, for patients with Her 2 neu positive disease the addition of trastuzumab to adjuvant chemotherapy and

maintenance therapy with trastuzumab for 1 year significantly improves disease free survival and overall survival in this cohort of patients and is now the recommended standard of care (Gianni et al, 2009; Slamon et al, 2011).

Hormone manipulation

Breast cancers with oestrogen positive and /or progesterone positive disease (Table 2) provide a unique therapeutic treatment option. Tamoxifen has been the drug of choice for many years and is used in both pre and post menopausal women (Benson et al, 2009). This antioestrogen has been shown to benefit patients with oestrogen positive disease but no benefit has been shown seen in oestrogen negative disease (EBCTCG, 2011). The standard duration of therapy is 5 years and this is associated with a reduction in mortality of 26% and up to 47% reduction in local recurrence at 10 year follow up (EBCTCG, 2011).

Newer agents, aromatase inhibitors (AIs), when compared to Tamoxifen have shown improved disease free survival among post menopausal women, improved survival after initial treatment with Tamoxifen and reduced risk of recurrence especially at distant sites (Darby et al, 2011). AIs are not used in pre menopausal women, as oestrogen is produced in the ovaries until menopause and by the adrenal glands after menopause. AIs target the adrenal gland induced oestrogens so would have no benefit pre menopause. The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) now recommend that aromatase inhibitors are used in postmenopausal women in the adjuvant setting either as upfront therapy or as a sequential treatment after Tamoxifen (Burstein et al, 2010; NCCN 2012). Oestrogen receptor positive patients remain at a chronic risk of relapse. Patients currently receive 5 years of adjuvant endocrine therapy however the optimal duration of therapy is still not established but studies are ongoing (Mouridan et al, 2009; EBCTCG 2011).

Survivorship

Breast cancer survival rates are improving with the introduction of breast screening and adjuvant therapies (Rock et al, 2002; Berry et al, 2005) and breast cancer survivors are the most numerous of all cancer survivors (Mayer et al, 2012).

Breast cancer survivors require ongoing medical care, psychological support, monitoring for recurrences and late side effects from treatment. These late effects include weight gain and physical inactivity which can have major medical health consequences, cognitive dysfunction, infertility, premature menopause, second malignancies, osteoporosis, sexual dysfunction, lymphoedema and cardiomyopathy (Jones et al, 2009; Mayer et al, 2012; Howard-Anderson et al, 2012). The greatest challenge is how best to provide long term care and this raises issues regarding who will carry out surveillance, what duration should follow-up be and what tests should be performed. The American Society of Clinical Oncology have published guidelines on post treatment surveillance and testing (Khatcheressian et al, 2006). The guidelines recommend that the basics of breast cancer follow up should include regular follow up with history and physical examination and regular scheduled mammograms. The routine performing of blood tests and scans is not recommended (Khatcheressian et al, 2006).

Most surveillance is concentrated in the first 5 years after the initial diagnosis when most recurrences are likely to occur. However some subgroups of breast cancer patients, especially oestrogen receptor positive patients (Table 2), have a risk of recurrence that can persist for 20 years or longer. Surveillance with these patients therefore, needs to be individualised to their specific needs.

Specialist breast care nurses play a role in treatment decision-making related to women and chemotherapy (Ballinger et al, 2012). Surveillance and follow-up of breast cancer patients is also an important nursing role. The provision of opportunities for breast cancer patients to discuss symptoms and concerns can offer reassurance regarding cancer recurrence (Clayton and Dudley, 2009). In addition, nurses need to be vigilant if patient concerns are not addressed in a short visit and arrange a second visit if necessary (Clayton and Dudley, 2009).

Survivorship models of care focus on management of ongoing side effects of treatments, prevention of late side effects or second cancers and health promotion to ensure the patient maintains optimum health. This approach is radically different from the traditional medical model of focusing on disease recurrence alone.

Oncology nurses play a key role in breast cancer survivorship. Internationally, oncology nursing societies have taken a lead role in the provision of follow up care. The importance of oncology trained specialist nurses and advanced nurse practitioners providing follow up care for patients is well documented (Offinger and McCabe 1996, Mayer et al, 2012). The majority of patients want to actively participate in their treatment decisions and care (Brown et al, 2012), and this provides an ideal opportunity for specialist nurses to provide quality specialist care in the area of management of treatment side effects, education, health promotion and lifestyle modifications (Rock et al, 2002; Oeffinger & McCabe, 2006; Li et al, 2009, Mayer et al, 2012). The benefits of adapting a healthy lifestyle, maintaining a healthy weight and participating in regular exercise in the reduction of breast cancer recurrence are well established (Rock et al, 2002). Internationally many specialist oncology nurses are now providing follow-up clinics to address survivorship needs (e.g. Cox and Wilson 2003, Kimman et al, 2011) and patients describe high levels of satisfaction with the care and support provided by specialist nurses when compared to follow up by oncologists (Koinberg et al, 2004).

Conclusion

The treatment of breast cancer is constantly evolving leading to better outcomes and ever increasing numbers of breast cancer survivors. The goal of cancer treatments must not only be to maximise cure rates but also to minimise long term effects of cancer treatments. Health promotion and education on disease preventing activities should be central to nurses' care of breast cancer patients in follow up and this is an ideal opportunity for specialist oncology nurses to take a lead role in this ever advancing area of cancer care.

Key Phrases

- Breast cancer remains the most common malignancy among women worldwide
- The introduction of screening mammography in postmenopausal women reduces breast cancer mortality by approximately 20%.
- Multidisciplinary expert team approaches to the care of breast cancer patients facilitates precise diagnosis and ensures that patients receive the best treatment and follow up care for their condition.
- Molecular profiling of breast cancer has allowed clinicians to character breast cancer tumours beyond conventional measures and to predict clinical outcome and response to therapy.
- Adopting a healthy lifestyle including regular physical exercise, healthy diet and maintaining a healthy weight can reduce the risk of breast cancer and for patients with breast cancer can reduce their risk of recurrence.
- Specialist oncology nurses play a key role in the follow-up of breast cancer survivors.

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Table 1. Histological subtypes prevalence of breast cancer (Li et al,2005)

Histological subtype	Percentage prevalence
Infiltrating ductal cancer	76%
Invasive lobular	8%
Ductal/lobular	7%
Mucinous	2.4%
Tubular	1.5%
Medullary	1.2%
Papillary	1%

Table 2: Main distinct molecular subtypes of breast cancer (Voduc et al, 2010).

Luminal A	Luminal B	Her 2 neu	Basal Like Cancers
40% of breast cancers	20% of breast cancers	10-15% of breast cancers	15-20% of breast cancers
ER/PR positive Her negative Low grade Low k67 Low oncotype DX	ER positive/PR negative Her negative High proliferation (k67, oncotype, grade)	Her 2 neu positive	Typically Triple Negative- ER,PR and Her-2 negative High proliferation