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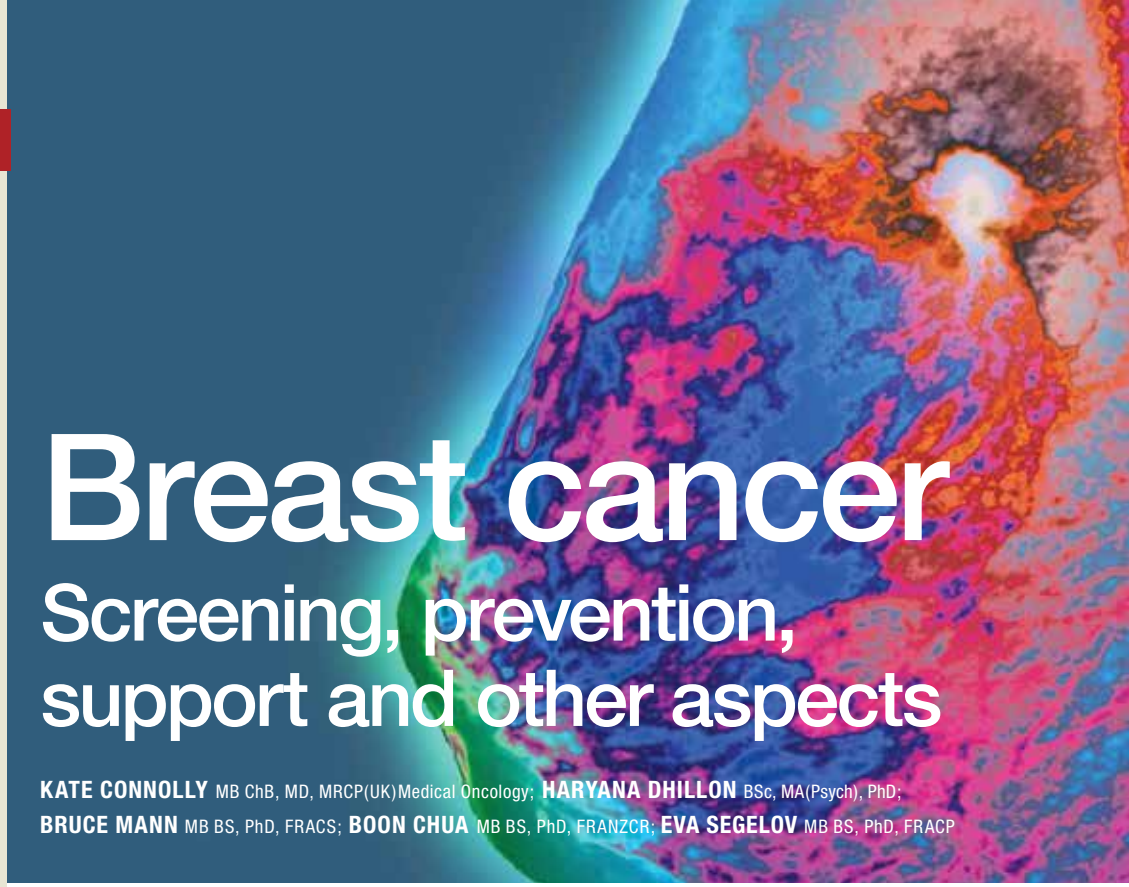

Breast cancer

Screening, prevention, support and other aspects

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Key points

- Over the past 25 years breast cancer survival has increased; however, indigenous Australian women and women living in remote areas have a lower survival rate compared with other subgroups.
- Women aged 50 to 74 years are specifically encouraged to attend BreastScreen Australia for screening mammography every two years.
- The triple test of clinical, radiological and cytological/histological assessments is an essential diagnostic approach to breast complaints.
- Women with early breast cancer should engage in a healthy diet and regular physical activity, which promotes wellbeing and may improve survival.
- Menopausal symptoms and psychological side effects of breast cancer treatment should be actively managed.

Breast cancer survival has increased and this probably reflects the detection of earlier stage cancers through screening and the wider use of adjuvant systemic therapy. Modification of lifestyle and other risk factors reduces cancer and cardiovascular risk and promotes wellbeing. This is the last article in a three-part series on breast cancer.

The epidemiology of breast cancer, breast cancer screening programs and long-term supportive care issues are the focus of this last article of a three-part series on advances in the diagnosis and management of breast cancer. Reflecting a growing area of interest and research, lifestyle and other risk factor modifications are considered. The approach to diagnosis, the follow up of patients with early breast cancer, the management of the consequences of ovarian failure after chemotherapy and male breast cancer are discussed (see the box on page 30).

The first and second articles in the series covered early breast cancer and locally advanced and metastatic breast cancer, respectively (published in the June and July issues of *Medicine Today*).[1,2]

EPIDEMIOLOGY

In 2008, more than 13,500 cases of new invasive breast cancers were diagnosed in Australia. The number of new breast cancers more than doubled between 1982 and 2008, with the sharp increase between 1990 and 1995 most likely due to the introduction of the national breast cancer screening program.[3]

In 2007, breast cancer was the second most

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BREAST CANCER: ADVANCES IN DIAGNOSIS, SCREENING, PREVENTION, LIFESTYLE AND SUPPORTIVE CARE

- Detection of earlier stage cancers through breast screening and wider use of adjuvant systemic therapy have improved survival after breast cancer
- Funding for the BreastScreen Australia program now covers women aged 50 to 74 years (previously it was women aged 50 to 69 years). Comorbidities and life expectancy should be taken into account when recommending screening mammography for older women
- Lifestyle modification – weight management, limiting of alcohol consumption and increased physical activity – reduces cancer and cardiovascular risk and promotes wellbeing
- Online resources are available for long-term supportive care of patients with breast cancer, see the Cancer Australia and the Cancer Council Australia websites
- Rehabilitation approaches to the cognitive effects of cancer and its treatments are being investigated in clinical trials
- Sleep problems associated with breast cancer are being studied
- Models for breast cancer survivorship care are continually evolving

common cause of cancer death in females. The breast cancer mortality rate was 22 per 100,000, accounting for 16% of female deaths from cancer. Between the periods 1982 to 1987 and 2006 to 2010, the five-year relative survival from breast cancer increased from 72% to 89%, probably reflecting the detection of earlier stage cancers through screening and the wider use of adjuvant systemic therapy (Figure 1).[3,4] However, some patient subgroups have lower survival than others, such as women living in remote areas and Aboriginal and Torres Strait Islander women.

AETIOLOGY

Being female and increasing age are the strongest risk factors for breast cancer, with about 75% of breast cancers being diagnosed after the age of 50 years. The risk for women aged in their 30s is approximately one in 250, rising to one in 30 for women aged in their 70s.

Women diagnosed with invasive breast cancer or ductal carcinoma in situ (DCIS) have an increased risk of developing a new cancer in the other breast or in another part of the same breast after conservative surgery. Several benign proliferative lesions (e.g. atypical hyperplasia, radial scar and some types of papilloma) and high breast density are associated with a slightly increased risk of breast cancer development.

A family history of the condition is a well-established risk factor for breast cancer. Women at increased risk include those with:

- three or more first-degree relatives affected
- relatives diagnosed under 40 years of age
- male relatives with breast cancer
- relatives with bilateral breast cancer or ovarian cancer.

Deleterious mutations in *BRCA1* and *BRCA2* genes are present in less than 1% of the population but are associated with a lifetime risk of breast cancer in the order of 50 to 80%. Referral to a genetics clinic for consideration of mutation testing is important in those who seem to be at high risk. If high risk is confirmed, a risk management plan should be implemented, potentially including a combination of enhanced surveillance, medical prevention using tamoxifen or raloxifene and prophylactic breast or ovarian surgery. Certain ethnicities, such as Ashkenazi Jews, have a higher incidence of specific *BRCA* mutations. An online tool, Familial Risk Assessment – Breast and Ovarian Cancer, is available to help assess familial risk (http://canceraustralia.nbocc.org.au/health-professionals/clinical-best-practice/assessing-family-risk).

Nulliparity and later age at first birth are associated with a modestly increased risk of breast cancer, whereas breastfeeding is modestly protective. Factors affecting hormonal status, such as early menarche, late menopause and use of combined oestrogen/progesterone hormone replacement therapy, are also associated with an increased risk. It is unclear if the use of the oral contraceptive pill is associated with an increased risk. Women with a history of exposure to ionising radiation to the thorax, especially before 20 years of age, also have an increased risk; this is relevant to survivors of childhood and young adult cancers treated with high doses of radiotherapy many years ago.

Excess weight after menopause, alcohol consumption and low physical activity are other known personal and lifestyle risk factors for the condition.

PRIMARY PREVENTION

Lifestyle modification

There is convincing evidence that alcohol use increases the risk of breast cancer and hence the Cancer Council Australia recommends limiting alcohol consumption to no more than two standard drinks on any day, in line with the NHMRC alcohol guidelines.[5,6] General advice to increase physical activity and manage weight is also recommended, as these are relevant to cancer and cardiovascular risk.

Chemoprevention

Clinical trials have shown that five years' use of tamoxifen or an aromatase inhibitor (in postmenopausal women) in high-risk individuals is associated with about a 40% reduction in breast cancer incidence. Mortality reductions are smaller, possibly because the cancers prevented tend to be

hormone receptor-positive and associated with a more favourable prognosis.

Tamoxifen may be considered for prevention of breast cancer as it is low cost; PBS reimbursement for this use is currently under review.

BREAST SCREENING

The BreastScreen Australia program aims to reduce illness and death from breast cancer through population-based two-yearly screening mammography to detect unsuspected cancers and enable early intervention. The target population is women aged 50 to 74 years, funding recently having been extended from age 69 to age 74 years. In older women, comorbidities and life expectancy should be taken into account when recommending screening. Screening mammography is less effective in women under 50 years of age because of the lower incidence of breast cancer in these women and their higher breast density making mammograms less sensitive.

The program aims to achieve a participation rate of 70%.[7] At the present time only about 56% of women aged 50 to 69 years in Australia participate in breast screening. Participation varies by area of residence, with the highest participation recorded in inner and outer regional areas and the lowest in very remote areas. There is minimal variation by socioeconomic status; however, the participation rate is significantly lower for indigenous women (32%).

Population-based mammographic screening has been the subject of debate, with some arguing that the harms caused by the anxiety of false-positive recalls and the 'overdiagnosis' of clinically insignificant lesions outweigh the benefits. However, a recent review of BreastScreen Australia suggests that there is a 16% reduction in breast cancer mortality in a screened population.[7] In addition, a review of the UK screening program indicates that one life is saved for every 180 women screened but three women are diagnosed and treated for a cancer that would not otherwise have become apparent in their lifetime.[8]

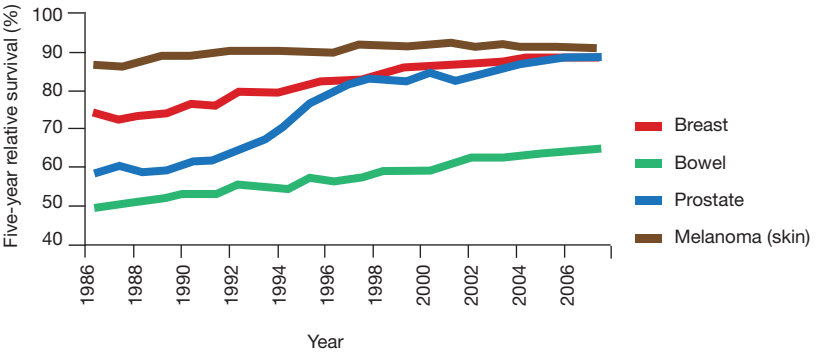

Figure 1. Five-year relative survival (%) of the four most prevalent tumour types in Australia from 1986 to 2007. Adapted from Cancer in Australia: an overview 2012.[4]

It is important to appreciate that screening applies only to asymptomatic women and involves only two standard mammographic views and no ultrasound (unless an abnormality is detected). Therefore symptomatic women (for example, a patient presenting with a breast lump) should NOT be referred to a screening service but should undergo a full diagnostic workup as noted below.

DIAGNOSIS

About 30% of invasive breast cancers and most cases of DCIS in Australia are diagnosed through screening; the majority of cancers are symptomatic at presentation.

Patients presenting with a breast complaint are often anxious about the possibility of cancer. Exclusion of cancer is a major part of breast care delivered by GPs and breast surgeons. The triple test for breast cancer (clinical examination, imaging and biopsy) is an essential concept in the approach to a breast complaint. If a change or finding is clinically, radiologically and cytologically or histologically benign, it is almost certainly benign and no further investigation is required to exclude breast cancer.

Benign findings on clinical assessment include:

- a 'possible lump' that is not well defined and varies over one or two menstrual cycles
- a smooth, mobile and firm (but not hard) 'breast mouse' in a young woman, consistent with a benign fibroadenoma
- a classical cyst that fits the clinical criteria of benignity.

Mammography is critical for the diagnosis of breast cancer, and ultrasound has a key role in the assessment of breast conditions (Figure 2). In women who have benign ultrasound findings (category 1 or 2 in the Breast Imaging-Reporting and Data System, or BI-RADS; i.e. 'Negative' or 'Benign') and no clinical finding, no further investigation is required, particularly when the presenting complaint is breast pain or asymmetry. For patients with benign clinical findings, a biopsy for cytological or histological confirmation provides definite proof that the lesion is benign and no further action is required.

When the ultrasound finding is equivocal (category 3; i.e. 'Probably benign'), the lesion is usually benign but requires histological confirmation using ultrasound-guided core biopsy, as some lesions with imaging findings resembling an atypical fibroadenoma are in fact cancers. If the histology is unequivocally benign and concordant with the ultrasound finding, no further action is required. On occasions, follow-up imaging in three to six months to confirm stability is sufficient to exclude serious pathology

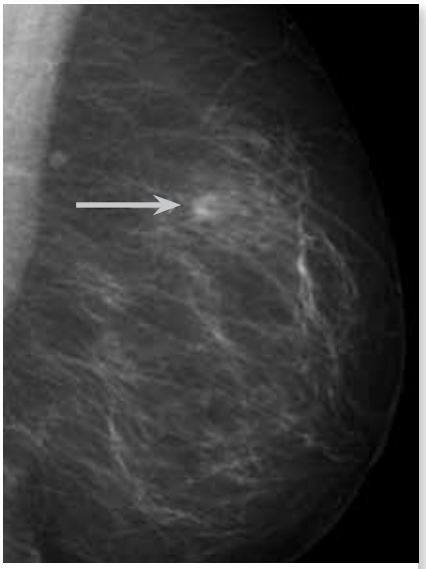

Figure 2. Mammogram showing a breast cancer (arrow).

without the need for a core biopsy.

A suspicious (category 4; i.e. 'Suspicious abnormality') imaging finding does not confirm the diagnosis of cancer but indicates that percutaneous biopsy is indicated. Malignant (category 5; i.e. 'Highly suggestive of malignancy') findings are almost always malignant, and warrant surgical excision after preoperative core biopsy.

Histology is required to confirm a definite diagnosis of breast cancer, most often through a preoperative percutaneous core biopsy and occasionally by excisional biopsy. In addition, bilateral mammography to exclude synchronous cancers and axillary ultrasound with fine needle aspiration of any suspicious lymph nodes is standard. These measures enable undertaking of the most appropriate definitive cancer surgery at the first operation.

Extensive staging tests are not recommended for patients diagnosed with early breast cancer. Unless there is evidence of extensive nodal involvement, the chance that a CT scan or bone scan would identify asymptomatic metastatic disease is minimal, and ordering such tests should be left to the treating multidisciplinary team.

SECONDARY PREVENTION

Lifestyle modifications

Modifications of lifestyle (as described earlier under 'Primary prevention') should be considered part of the medical treatment of patients with breast cancer and actively facilitated by all members of the health care team. The GP is particularly influential and helpful in this regard.

Women with early breast cancer should engage in a healthy diet and regular physical activity, which promote wellbeing and may improve survival, as shown in epidemiological studies.[9-13] Randomised trials have demonstrated the positive effect of increased physical activity on a range of outcomes for women, including quality of life, depression, body image and self-efficacy (an individual's perception of their ability to effect behavioural change themselves).

Women should aim to meet the Australian physical activity guidelines for adults of 30 minutes of moderate intensity activity on most or all days of the week.[14] Moderate intensity physical activity should make most people sweat and puff (not able to comfortably talk while exercising) and moderately raise their pulse.

Many cancer survivors are anxious about commencing physical activity and may benefit from the support of an experienced exercise physiologist; GPs may refer women to these allied healthcare providers through the Chronic Disease Management items on Medicare. Despite many women being anxious about commencing resistance training and its potential negative effects on arm and shoulder symptoms, particularly lymphoedema and limb cellulitis, there is good evidence that physical activity can improve these symptoms and reduce their severity. Seeking guidance from a physiotherapist experienced in arm and shoulder rehabilitation is advisable.

Data from pilot studies and a randomised trial supports the benefit of women exercising before and during their chemotherapy. Studies have shown that women who maintained some regular physical activity during adjuvant chemotherapy reported less fatigue and fewer and less severe side effects of chemotherapy.[15]

Chemoprevention

Hormone therapy with tamoxifen or an aromatase inhibitor given as part of the treatment of an oestrogen receptor (ER) and/or progesterone receptor (PR)-positive breast cancer also reduces the risk of a new hormone receptor-positive cancer by 50%.

There is interest in assessing the potential benefit of low dose aspirin in preventing recurrence in women following standard treatment for early breast cancer.[16] Clinical trials are also examining the role of agents such as metformin, bisphosphonates and celecoxib.

FOLLOW UP AFTER TREATMENT FOR EARLY BREAST CANCER

Of the patients treated for early breast cancer, 80% will achieve long-term survival, and many subgroups will have higher survival rates. Follow up should be tailored to the needs of the individual patient, and the GP is an important multidisciplinary team member in providing this care. In general, regular clinical assessments and yearly bilateral mammography to screen for local recurrence or a new primary in the same or contralateral breast are recommended. Routine CT or bone scan and blood tests in otherwise asymptomatic patients lack the sensitivity and specificity to detect recurrence at a stage that would alter survival, and are not recommended. In particular, the nonspecific serum tumour marker CA15-3 is not helpful in identifying early recurrence.

With the recognition that the various subgroups of early breast cancer behave differently biologically, the adage 'five years until cured' is no longer applicable. Basal phenotype cancers (ER-, PR- and human epidermal growth factor receptor 2 [HER2]-negative) tend to recur within three years after diagnosis, whereas a significant number of ER/PR-positive

FOLLOW UP OF WOMEN AFTER EARLY BREAST CANCER

- Encourage compliance with hormone therapy
- For patients taking aromatase inhibitors, assess bone density with dual energy x-ray absorptiometry (DXA, previously DEXA) every one to two years
- Ensure adequate intake of calcium and vitamin D
- Encourage normal weight and physical activity
- Address menopausal symptoms
- Manage psychological wellbeing, body image and sexual function – ongoing management required
- Recommend regular clinical assessments and yearly bilateral mammography to screen for local recurrence or a new primary in the same or contralateral breast

cancers recur after five to 10 years or longer. Relapse patterns among the breast cancer subtypes also differ. HER2-positive cancers tend to relapse more frequently in the central nervous system (i.e. brain metastases). It is unknown whether this is innate biology or the consequence of reduced systemic recurrence and undertreatment of the central nervous system due to the lack of penetration of trastuzumab through the blood–brain barrier.

A proportion of women will experience high levels of fear of cancer recurrence, manifesting as difficulties adjusting to the post-treatment period, intrusive thoughts about the cancer and high levels of anxiety. Psychological support may help women adjust to their post-cancer life and GP referral using mental health care plans could be considered. New psychological interventions to address fear of cancer recurrence are being trialled in Australia.

Key points in the follow up of women after early breast cancer are listed in the box above.

MANAGING OVARIAN FAILURE

Ovarian failure as a consequence of chemotherapy for breast cancer impacts both fertility and menopausal status, but may be beneficial in reducing recurrence and improving survival in premenopausal patients with ER-positive tumours. The effects of chemotherapy on ovarian function vary widely and are age, dose and drug-dependent.

Premature menopause

During chemotherapy, most premenopausal women develop amenorrhoea with high serum gonadotrophin levels; however menstrual function often returns months to several years later. These women should be prescribed tamoxifen, and not an aromatase inhibitor, as adjuvant hormone therapy. A switch to an aromatase inhibitor (anastrozole, letrozole and exemestane) on the basis of lack of return of menstruation should only be considered after two years of amenorrhoea. Measurement of serum hormone levels is not helpful as it reflects current physiology and does not predict future return of ovarian function.

Under investigation is whether or not young patients with ER-positive cancers whose menstruation returns after a period of amenorrhoea should be offered artificial ovarian ablation with luteinising hormone-releasing hormone (LH-RH) agonists or oophorectomy as part of adjuvant hormone therapy.

Fertility issues

Chemotherapy affects the numbers of maturing follicles in the ovary rather than the oocytes. In vitro fertilisation (IVF) or oocyte preservation (a viable option but not as reliable as IVF) should be offered to women who wish to preserve fertility. Modern oocyte stimulating regimens using letrozole and gonadotropin-releasing hormone (GnRH) give peak oestradiol levels similar to those of a natural menstrual cycle. No increase in risk of breast cancer recurrence or death has been demonstrated with these regimens but further investigation is warranted.

Recommended options for contraception in women with premature menopause include barrier methods and the copper intrauterine devices. Hormonal contraception is not recommended. Use of the levonorgestrel-releasing intrauterine device is controversial because of a potential increased risk of cancer recurrence despite the low systemic hormone levels.

Most studies indicate that subsequent pregnancy in women with a history of breast cancer does not compromise survival regardless of the oestrogen receptor status of the tumour. In fact, many series show a survival benefit for women who have children after ER-positive breast cancer, with no difference in timing of the subsequent pregnancy. There is no evidence for increased rates of congenital abnormalities or developmental impacts in offspring.

Women in whom breast cancer is diagnosed during pregnancy should be managed in a specialised centre. Chemotherapy, but not trastuzumab, may be safely administered during the second and third trimesters with minimal risk to the fetus, and does not appear to affect the normal development of the offspring.

Menopausal symptoms

About three-quarters of women going through menopause will experience hot flushes, which can be exacerbated by adjuvant hormone therapy with either tamoxifen or aromatase inhibitors. Early menopause resulting from cancer treatment requires proactive management.

Most clinical trials of complementary therapies to treat hot flushes have not shown a benefit compared with placebo, probably due to eventual subsidence without intervention, as placebo alone reduces the incidence by 25%. Lifestyle changes aimed at keeping the core body temperature cool, such as light layers of clothing in natural fibres and regular exercise, are recommended. Vitamin E, at a dose of 800 IU daily, has shown a small but significant benefit in controlled trials,

is inexpensive and has minimal side effects.[17]

If the symptoms are particularly troublesome, antidepressants (venlafaxine; off-label use) and gabapentin (off-label use) have some limited benefit. Megestrol acetate and medroxyprogesterone acetate (off-label uses) are highly effective but their initiation should be discussed with the treating team.

Hormone replacement therapy (HRT) is not recommended in women with a history of breast cancer. A randomised trial showed a higher incidence of breast cancer events in women who received two years of HRT and the HRT substitute drug tibolone.[18,19]

Changes in sexual function and intimacy may occur as a consequence of menopausal symptoms and altered body image after breast surgery, and may lead to changes in libido and strain on relationships. Intercourse may be painful due to vaginal dryness (exacerbated by the aromatase inhibitors). Gynaecological review (to exclude other pathology), the use of water-soluble lubricants and/or vaginal dilators, and counselling may be helpful. Psychological or sexual rehabilitation support may reduce the impact of changes in sexual function. Whether the use of vaginal oestrogen cream may slightly increase the risk of cancer recurrence is controversial. Further information about sexual wellbeing is available to download from the Breast Cancer Network Australia website (http://www.bcna.org.au/living-breast-cancer/sexual-wellbeing).

LONG TERM SUPPORTIVE CARE ISSUES

Psychosocial and emotional support

Breast cancer is a confronting diagnosis that significantly impacts women and families. Breast care nurses, psychologists and social workers specialising in cancer care are valuable in providing psychosocial and emotional support.

Information tailored to the needs of women is available through the Cancer Australia and Cancer Council Australia websites (http://canceraustralia.gov.au and http://www.cancer.org.au). There are services linking newly diagnosed women with trained patients who have had similar experiences (e.g. the Cancer Council Australia's Cancer Connect program). In addition, decision aids are available to assist with decision-making around preservation of fertility and genetic testing (e.g. *Fertility-Related Choices: a Decision Aid for Younger Women with Early Breast Cancer* available at http://www.bcna.org.au/sites/default/files/fertility_decision_aid_20120117_0.pdf and *Understanding Genetic Tests for Breast and Ovarian Cancer that Runs in the Family: Information and Decision Aid* available at http://www.genetics.edu.au/Publications%20and%20Resources/PublicationsBrochuresandPamphlets/Understanding%20Genetic%20Tests%20for%20Breast%20and%20Ovarian%20Cancer%20that%20runs%20in%20the%20Family/at_download/file).

Cognitive effects of cancer and its treatments

Women commonly report physical and psychological side effects during adjuvant treatment, some of which are long-lasting and distressing. Cognitive effects of cancer and its treatment, commonly called 'chemofog', are measurable on classical neuropsychological assessments in about 30% of women after diagnosis and before chemotherapy, suggesting cancer itself may cause some of the changes. These effects could be exacerbated by the stress of diagnosis. By the end of chemotherapy, estimates of impairment range from 30 to 70%, which may be related to the type and intensity of chemotherapy.

Some women report cognitive impairment impacts their ability to return to work, daily activities, role function and relationships. It is important to screen these women for depression, anxiety and fatigue, thyroid dysfunction and menopausal symptoms, and to treat appropriately as these symptoms are likely contributors to cognitive impairment. Clinical trials that address cognitive rehabilitation approaches are in progress.

Sleep problems

Sleep disturbance is a common problem experienced by women with breast cancer, and may be related to hot flushes. For some women, cognitive behaviour therapy may minimise sleep problems. Sleep apnoea, often associated with weight gain in this population, is under study and sleep studies should be considered in women with persistent sleep disturbance.

Depression

Development of depression should prompt a review of whether this is temporally related to either tamoxifen or aromatase inhibitor therapy, as both can induce mood changes. Choice of selective serotonin reuptake inhibitor antidepressants for patients taking tamoxifen is recommended to be restricted to low inducers of cytochrome P450 2D6 to ensure minimal interference with tamoxifen metabolism.

Breast cancer survivorship care

Multidisciplinary long-term breast cancer survivorship care of women after completion of adjuvant therapy is important, with GPs and allied health professionals being integral members in a shared care arrangement. Although the optimal model of survivorship care is evolving, the need to fully assess and manage long-term symptoms and concerns of breast cancer survivors has been recognised. The symptoms and concerns of women after breast cancer are changeable, and it is recommended that patients' needs are regularly assessed so that care can be adjusted appropriately.

MALE BREAST CANCER

Breast cancer in men is about 100 times less common than breast cancer in women, with a prevalence of one per 10,000 men. The five-year survival estimate is similar to that in women but the 10-year survival is significantly lower, 76%

compared with 83%.[3] This is thought to be due to diagnosis at a later stage in men, with larger tumours and more frequent lymph node involvement.

Many of the risk factors for male breast cancer are the same as in women. Importantly, all men with breast cancer should be considered for genetic counselling for *BRCA* mutation testing through a family cancer clinic. The diagnosis, staging and treatment of male breast cancer parallel those for women.

SUMMARY

Breast cancer survival has increased and this probably reflects the detection of earlier stage cancers through screening and wider use of adjuvant systemic therapy. However, indigenous Australian women and women living in remote areas have a lower survival rate. Screening mammography is recommended every two years and is funded for women aged 50 to 74 years, the upper age limit having been recently increased from 69 years. The triple test of clinical, radiological and cytological/histological assessments remains the essential diagnostic approach to breast complaints.

Modification of lifestyle risk factors such as weight, alcohol use and physical activity has become an area of interest recently in the primary and secondary prevention of breast cancer. Epidemiological studies have shown that engagement in a healthy lifestyle and regular physical activity promotes wellbeing and may improve survival.

Follow up of patients treated for early breast cancer, about 80% of whom will achieve long-term survival, should be tailored to the needs of the individual patient. Regular clinical assessments and yearly bilateral mammography to screen for local recurrence or a new primary in the same or contralateral breast are generally recommended.

Breast cancer treatments have physical and psychological side effects, some of which are long lasting and distressing. Ovarian failure as a consequence of chemotherapy impacts both fertility and menopausal status, but may reduce recurrence and improve survival in premenopausal patients with ER-positive tumours. Menopausal symptoms and psychological side effects of the various breast cancer treatments should be actively managed. MT

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A list of references is included in the website version (http://www.medicinetoday.com.au) and the iPad app version of this article.

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