

Managing healthy women at risk of breast cancer

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SYNOPSIS

Early detection with effective treatment has reduced mortality in some groups of women with breast cancer, however reducing the risk of breast cancer is clearly an important goal. Several risk factors for breast cancer have been identified. The most important of these are ageing and a positive family history. Models incorporating these risk parameters are available to help identify women who may benefit from the various risk reduction approaches. Optimal breast cancer prevention strategies in high-risk women are still to be determined and are the subject of ongoing clinical trials.

Index words: tamoxifen, raloxifene, mammography.

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Introduction

Approximately 1 in 13 (8%) Australian women will develop breast cancer by the age of 75 years. It is the commonest cause of death from cancer in Australian women. Although the cause of breast cancer is unknown there are numerous risk factors. Being female and ageing are the two main risk factors for developing the disease. The presence of a family history is also an important and well-established risk factor. Weaker risk factors include early age at menarche, nulliparity and age of menopause.

The majority of breast cancers are sporadic occurring in women without a family history. Only a small proportion (5-10%) of all breast cancers occur in women with a very strong family history and a proportion of these are attributable to germline mutations in single highly penetrant cancer susceptibility genes, such as BRCA1 or BRCA2. Some 'familial clusters' of breast cancer may result from interactions of multiple genes and environmental factors or single low penetrance cancer susceptibility genes. Importantly, most women with a family history of breast cancer do not carry germline mutations in single highly penetrant cancer susceptibility genes.

Breast cancer risk management strategies

Several important medical decisions, particularly risk reduction strategies, may be affected by a woman's underlying risk of breast cancer. Management in this situation should involve comprehensive quantitative risk assessment, counselling appropriate to the individual's risk, the opportunity for genetic testing where appropriate, and advice regarding specific management strategies.

Quantifying breast cancer risk

Many of the known risk factors for breast cancer may interact, so evaluating the risk conferred by combinations of risk factors is challenging. Several risk prediction models are available and provide an epidemiological basis for counselling women with a family history.^{1,2} The Gail model, developed in the USA, incorporates family history, reproductive factors, and history of benign breast disease. A software program of this assessment tool is available from the National Cancer Institute web site*. Little Australian data exist on which to base familial risk assessments. Care needs to be taken in using tables based on American data as the underlying breast cancer rate is one-third higher in the USA.

The Australian National Breast Cancer Centre (NBCC) has established a set of easily understood criteria to define those at increased risk based on family history†. Assessing family history in detail helps estimate a woman's risk of developing breast cancer as well as the probability of inheriting a mutation in a known cancer-predisposing gene. There are three NBCC criteria.

Category 1

These women have no family history or a weak family history (for example, one first-degree relative diagnosed with breast cancer at 50 years or older). This group covers 95% of the population and their lifetime risk of developing breast cancer is between 8 and 12% (compared to 8% for the general population).

Category 2

These women have a moderately increased risk. There may be one or two first-degree relatives diagnosed with breast cancer before the age of 50, or two or more distant relatives on the same side of the family with breast or ovarian cancer. Fewer than 4% of all women are at moderately increased risk and their lifetime risk for developing the disease is 12-25%.

Category 3

Less than 1% of the female population are at potentially high risk. They usually have several (three or more) closely affected relatives with breast cancer occurring at relatively young ages. There may also be bilateral or multifocal breast cancer, and the occurrence of ovarian cancer in the family. Inherited

* <http://bcra.nci.nih.gov/brc>

† <http://www.nbcc.org.au/pages/info/resource/nbccpubs/advice.htm>

predisposition in these families is possible and may be the result of a mutation in an autosomal dominant breast cancer susceptibility gene such as BRCA1 or BRCA2. For women who carry mutations in these genes the lifetime risk of breast cancer may be as high as 40–80%, and of ovarian cancer 10–60%. These families should be referred to cancer genetic clinics for genetic counselling and consideration of genetic testing.

Breast cancer prevention strategies

Chemoprevention

Tamoxifen can prevent second primary breast cancers. There are also extensive molecular, cellular and animal data to show that it acts as an effective oestrogen antagonist in the breast. Tamoxifen has therefore been studied in several randomised trials for the primary prevention of breast cancer.

The Breast Cancer Prevention Trial was a randomised placebo-controlled trial involving over 13 000 women at high risk of developing breast cancer.³ After a mean follow-up period of four years, tamoxifen had reduced the incidence of breast cancer by 49%. However, this beneficial effect was confined to oestrogen receptor positive tumours and there were more serious adverse events, including endometrial cancer, vascular events (stroke, pulmonary embolism, deep vein thrombosis) and cataracts, in the tamoxifen group. Despite these problems the trial led to the Food and Drug Administration in the USA approving tamoxifen for the reduction of breast cancer risk in women whose risk of developing breast cancer is equal to the minimum eligibility criteria for the trial. These women were at least 35 years of age with a five year predicted risk of breast cancer development of at least 1.66% (calculated by the Gail model).

The preliminary results of the International Breast Cancer Intervention Study (IBIS)⁴ also suggest that tamoxifen has some effect in preventing breast cancer, but not on overall mortality. This trial involved 7139 women aged 35–70 years including Australian women. All the women had risk factors for breast cancer indicating at least a two-fold relative risk for ages 45–70, a four-fold relative risk for ages 40–44, and an approximately 10-fold relative risk for ages 35–39. After a mean follow-up of 50 months, there was a 32% (8–50%) reduction in breast cancer incidence associated with tamoxifen (69 versus 101, $p = 0.013$). Endometrial cancer was increased about two-fold (11 versus five), but this was not significant ($p = 0.2$). Thromboembolic events were significantly increased (43 versus 17, odds ratio = 2.5 (1.5–4.4), $p = 0.001$) and the effect was particularly apparent following surgery (20 versus 5 events, $p = 0.004$). There was a non-significant increase in deaths from cancers other than breast, thromboembolic events, and cardiovascular causes, giving rise overall to a significant excess of deaths in the tamoxifen arm (25 versus 11, $p = 0.028$).

The overall risk:benefit ratio for the use of tamoxifen in prevention is still unclear, and continued follow-up of the patients in the current trials is essential. In Australia at this time primary chemoprevention is not an approved indication for tamoxifen use.

Raloxifene acts on oestrogen receptors and antagonises the effects of oestrogen in the breast and uterus. Preliminary reports (albeit from studies with osteoporosis as the major end-point) suggest that raloxifene may be associated with a reduced risk of developing breast cancer in postmenopausal women (at average or below average risk).⁵ This suggestion is based on a relatively small number of breast cancers. It is therefore premature to recommend raloxifene to lower the risk of developing breast cancer outside of a clinical trial. There is currently no evidence to conclude that raloxifene will reduce the risk of dying from breast cancer for women who do not have breast cancer. Currently, a large number of postmenopausal women are entering, or are continuing to be followed in, randomised clinical trials evaluating raloxifene's effect on a wide range of clinical end-points. Results from such studies may influence future recommendations regarding raloxifene use.

Prophylactic surgery

Bilateral prophylactic mastectomy is a controversial clinical option for women who are at increased risk of breast cancer. High-risk women, including women with a very strong family history of breast cancer (NBCC category 3) and BRCA 1/2 mutation carriers, must make a decision with the primary focus on risk reduction or early detection.

Prophylactic mastectomy may significantly reduce, but does not completely eliminate the risk of breast cancer. There are no randomised clinical trials to ascertain efficacy in preventing disease or reducing mortality. The trade-offs of prophylactic mastectomy are substantial. It is an irreversible procedure with potential physical and psychological sequelae. Furthermore the reduction in breast cancer risk achieved by prophylactic mastectomy is likely to depend on a woman's underlying risk of the disease. A decision analysis involving women who were carriers of BRCA1 or BRCA2 mutations found that the benefit of prophylactic mastectomy differed substantially according to the breast cancer risk conferred by the mutations.⁶ For women with an estimated lifetime risk of 40% (approximately four times the population risk), prophylactic mastectomy would add almost three years of life, whereas for women with an estimated lifetime risk of 85% the procedure would add more than five years.

Breast cancer screening

The preventive options currently available for Australian women at increased risk for breast cancer are limited. Early detection (screening) strategies are an important consideration. There is general agreement that screening mammography reduces breast cancer mortality for women older than 50 years.^{7,8} Its value for women younger than 50, regardless of risk status, remains controversial. The National Program for the Early Detection of Breast Cancer's current policy is to offer mammograms to asymptomatic women aged over 40 years at their request. The program provides women aged 40–49 years with advice of the limited evidence for the benefits of screening in women of their age. They are also given information on the possible adverse effects of screening,

such as over-diagnosis, radiation exposure and false positive results. The women may then make an informed decision on whether to participate in the program.

If screening women before 50 years of age does reduce breast cancer mortality, the women who stand most to benefit from beginning screening then are those at higher risk of the disease, particularly the 15–20% of women who have a family history of breast cancer. Thus a policy of offering early screening to these high-risk women seems reasonable. A number of promising early detection options are being evaluated. They include digital mammography, magnetic resonance imaging and ductal lavage and may prove to be more sensitive tests in this group of women.

Conclusion

Studies suggest that many women overestimate their breast cancer risk, however the great majority of Australian women can be reassured that they are at, or at most only slightly above, population risk.⁹ This means that most will not develop breast cancer in their lifetime. Breast cancer is a serious disease and an important cause of premature mortality and morbidity. It is important to encourage women to participate in mammographic screening programs. At present risk reduction strategies for women at high risk are limited and require further investigation in the context of clinical trials.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 151)

5. Most women with breast cancer have a strong family history of the disease.
6. Tamoxifen can reduce the risk of breast cancer but can increase the risk of endometrial cancer.

Book review

Therapeutic Guidelines: Neurology. Version 2. Melbourne: Therapeutic Guidelines Limited; 2002. 191 pages.

Price: \$33, students \$25.30, plus postage.*

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The 2002 edition of Neurology, the red book in the series, is another fine example of the art of therapeutic review. The guide is a highly readable, highly practical document. For a busy general practitioner the topics are pertinent and thoroughly explored, the topic headings guide you to relevant information with ease and the Therapeutic Guidelines' format of italicising

the drug gives you the quickest opportunity for reviewing a favourite section.

A very good section is the headache section; there is nothing like a good review of evidence for helping to make some clarity of a problem that in my practice seems less than clear. Likewise the sections on facial pain and neuropathic pain are highly relevant for my practice. The sections on epilepsy and stroke, involuntary movements and central nervous system infections are not so commonly needed in my 'part time' world, but I feel confident that I could call on the relevant and up to date information quickly and easily. Another highlight of the 2002 version is the pictorial exposition of some of the manoeuvres for vertigo and motion sickness.

In summary: a very good and workable guideline for the busy general practitioner.

* For more information contact Therapeutic Guidelines Limited – 1800 061 260 or sales@tg.com.au