Clinical review

Recent developments

Breast cancer

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As our understanding of the biology of breast cancer continues to improve, treatment of the disease continues to change. Although the ultimate goal of treatment remains improved survival, increasing emphasis is now put on less morbid treatments and improving quality of life. Prevention remains a major focus, particularly in women at high risk of developing breast cancer because of mutations in susceptibility genes. In this article, we review the current prevention strategies in carriers of BRCA1 and BRCA2 mutations, data on sentinel node biopsy for axillary staging, and trials of new endocrine treatments for advanced breast cancer.

Methods

We selected topics on the basis of their current or likely future impact on practice, with an emphasis on areas in which significant changes in our knowledge base have occurred in the past three to five years. We did English language Medline searches, giving priority to prospective randomised trials or large prospective multi-institutional studies when available. We also reviewed abstracts from meetings on breast cancer in the past three years.

Management of risk in carriers of BRCA1 and BRCA2 mutations

Mutations of the breast cancer susceptibility genes BRCA1 and BRCA2 are responsible for approximately 10% of breast cancers, and women with these mutations have a cumulative risk of developing breast cancer up to age 70 of 55-85%.^{1 2} The appropriate strategies for surveillance in these women and the efficacy of chemoprevention with tamoxifen and of prophylactic mastectomy are all controversial. Several recent studies provide new information that helps to clarify the outcomes of these approaches.

Chemoprevention

The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 prevention trial, which compared tamoxifen with placebo over five years, found that tamoxifen reduced the incidence of breast cancer by 49% in women at high risk.³ To assess the effect of tamoxifen in carriers of BRCA1 and BRCA2 mutations, DNA sequencing was performed on 288 of the 315 women who developed invasive breast

Recent developments

Prophylactic mastectomy reduces the risk of breast cancer by approximately 90% in women at high risk; short term follow up suggests similar benefits in carriers of BRCA1 and BRCA2 mutations

Reducing exposure to oestrogen by oophorectomy or tamoxifen also seems to reduce risk in this population

Women at risk should be the major decision makers in the selection of a strategy for reduction of risk

A sentinel node can be identified in more than 90% of patients with breast cancer; the false negative rate of sentinel node biopsy is less than 5%, but the long term rate of axillary recurrence is unknown

Anastrozole and letrozole are appropriate choices for first line treatment of hormone receptor positive, metastatic breast cancer in postmenopausal women

Fulvestrant is a new endocrine agent with a distinct mechanism of action that has antitumour activity equivalent to anastrozole

Non-steroidal and steroidal aromatase inhibitors are under evaluation as adjuvant treatment in patients with early stage breast cancer

cancer.⁴ Only 19 (6.6%) had mutations, eight in BRCA1 and 11 in BRCA2. The risk ratios for tamoxifen versus placebo were 1.67 (95% confidence interval 0.41 to 8.00) for BRCA1 and 0.38 (0.06 to 1.56) for BRCA2. The small number of cases and the wide confidence intervals do not allow any conclusions to be drawn from these data. Narod et al performed a case-control study of 593 carriers of BRCA1 and BRCA2 mutations with bilateral (cases) or unilateral (controls) breast carcinoma.⁵ The odds ratio for contralateral breast cancer in women taking tamoxifen was 0.50 (0.28 to 0.89). Benefit was seen for

An extra table and
two figures appear
on bmj.com

Table 1 Strategies for managing women carrying mutations of BRCA1 or BRCA2

Intervention	Benefits	Risks
Surveillance: mammography, clinical breast examination, breast self examination	Non-invasive; promising early data on magnetic resonance imaging in this population	Does not reduce cancer incidence; sensitivity of mammography lower in younger women; evidence of reduction in mortality in this population is lacking
Tamoxifen	50% reduction in cancer incidence in women at high risk; case-control evidence of benefit in gene carriers; absence of major toxicity in premenopausal women	Effect on oestrogen receptor positive tumours only; duration of benefit uncertain; increased risk of thrombosis and endometrial cancer in postmenopausal women
Prophylactic oophorectomy	50% reduction in cancer incidence in carriers of BRCA1 mutation	Long term sequelae of early menopause with increased risk of osteoporosis, cardiovascular disease, and reduced quality of life
Prophylactic mastectomy	90% reduction in cancer incidence; preliminary data in carriers of BRCA1 or BRCA2 mutations similar	Major surgery, chest wall anaesthesia, need for multiple operations with reconstructive procedures; psychological sequelae

both BRCA1 and BRCA2 carriers, independent of age. The protective effect increased with duration of use of tamoxifen up to four years.

Oophorectomy

Narod et al also noted a benefit for oophorectomy in women diagnosed with their first breast cancer before age 50.⁵ These findings are consistent with the observations of Rebbeck et al that oophorectomy reduces risk of breast cancer by approximately 50% in BRCA1 carriers,⁶ and with observations that a reduction in exposure to endogenous oestrogen, the number of ovulatory cycles, or both is protective. These findings indicate that a reduction in exposure to oestrogen by oophorectomy or tamoxifen is an alternative approach to managing risk in gene carriers who do not want prophylactic mastectomy.

Prophylactic mastectomy

Hartmann et al identified 6039 women with a family history of breast cancer who underwent prophylactic mastectomy.⁷ The reduction in adjusted cancer incidence, compared with the sisters of study participants, ranged from 90% to 94%, and the reduction in death from breast cancer ranged from 81% to 94%. Among a subset of 110 women with very strong family histories of breast cancer, 18 had deleterious mutations of BRCA1 and BRCA2. After a median follow up of 16 years, none of these women had developed breast cancer.⁸ Meijers-Heijboer et al prospectively studied 139 mutation carriers without a personal history of breast cancer.⁹ Seventy six underwent prophylactic mastectomy, and after a mean follow up of 2.9 years no cases of breast cancer were observed, compared with eight cancers in the surveillance group. Decision analysis has also been used to assess the survival benefits of prophylactic mastectomy in a theoretical cohort of 30 year old women carrying mutations.^{10 11} With lifetime risks of breast cancer ranging from 40% to 85%, survival was increased by 2.8 to 3.4 years. Minimal survival gains were seen for women having surgery after age 60.¹⁰

Attitudes towards prophylactic mastectomy vary widely, with some women and their physicians considering this an unacceptable intervention, and major variations in acceptance are seen around the world. However, psychological and social functioning in women who choose to have the procedure seem to be well maintained.¹²

Advising patients about risk reduction

As with any preventive interventions, the role of the physician is to inform women at high risk about the risks and benefits of prophylactic surgery (table 1). The

decision to undertake a risk reducing strategy, whether prophylactic mastectomy, oophorectomy, or tamoxifen, ultimately rests with the woman at risk.

Sentinel lymphadenectomy for breast cancer

Axillary dissection is considered a standard part of treatment for breast cancer. It provides prognostic information, maintains local control in the axilla, and in a minority of cases determines the need for adjuvant systemic treatment. The therapeutic value is controversial but would be limited to patients with nodal metastases. Lymphatic mapping and sentinel node biopsy is a new minimally invasive technique to identify patients with axillary node involvement. The sentinel node is defined as the first node to receive drainage from a tumour and is identified by injecting a vital blue dye, a radiocolloid, or both around the area of the primary tumour. A small incision is made in the axilla, and a hand held gamma probe or direct visual inspection is used to identify a radioactive node or blue stained lymphatic channels leading to a blue lymph node.

Individual investigators have reported identification of the sentinel lymph node in more than 95% of breast cancer patients, with false negative rates for prediction of axillary nodal metastases of less than 5%.¹³ Table 2 summarises the results of three large multi-institutional trials.¹⁴⁻¹⁶ The false negative rates were established by completing the axillary dissection after sentinel node biopsy. In all three studies, patient age over 50 was associated with a significant decrease in the ability to identify a sentinel node.¹⁴⁻¹⁶ There was no agreement on factors influencing the false negative rate.

Contraindications to sentinel node biopsy include suspicious palpable axillary adenopathy, pregnancy, and multicentric carcinoma. Few data exist on the accuracy of the procedure for patients with tumours larger than 5 cm, with features of locally advanced breast cancer, or who have received preoperative chemotherapy, and sentinel node biopsy should be considered investigational in these circumstances. How

Table 2 Outcome of sentinel node biopsy in multi-institutional trials

Author	No of surgeons	No of procedures	Technique	Sentinel node identified (%)	False negatives (%)
Krag et al ¹⁴	11	443	Radiocolloid	91	11.4
Tafra et al ¹⁵	48	535	Blue dye plus radiocolloid	87	13.0
McMasters et al ¹⁶ :					
1-20 cases per surgeon	226	1817	Surgeon choice	91.7	9.0
>20 cases per surgeon	28	331	Surgeon choice	96.7	1.9

Table 3 Comparison of aromatase inhibitors and megestrol acetate (MA)²⁴⁻²⁶

	Anastrozole 1 mg v MA	Letrozole 2.5 mg v MA	Exemestane 25 mg v MA
No of patients	263 v 253	174 v 189	366 v 403
Response rate*	AN=MA	LET>MA	EXE=MA
Duration of response	Not reported	LET>MA	EXE=MA
Time to progression	AN=MA	LET>MA	EXE>MA
Overall survival	AN>MA	LET=MA	EXE>MA

*Objective response rate=complete response plus partial response.

many cases of sentinel node biopsy followed by axillary dissection must be done before a surgeon is competent to perform axillary staging with sentinel node biopsy alone is uncertain. Simmons, in a review of this subject, suggested that an 85% rate of identification and a false negative rate of 5% are achieved after 10-20 cases on average.¹⁷

Sentinel node biopsy has several advantages over axillary dissection. It is a brief outpatient procedure requiring no drains and allowing a return to full activity in 2-3 days. In the first prospective comparison of sentinel node biopsy and axillary dissection, 3% of 67 patients having sentinel node biopsy experienced complications compared with 35% of 57 patients undergoing axillary dissection.¹⁸ In addition to decreasing morbidity, sentinel node biopsy may improve staging. It has been known for many years that lymph nodes found to be free of tumour cells by standard sectioning and haematoxylin and eosin staining will have microscopic tumour deposits identified in 10-25% of cases if multiple sections of the node are examined or immunohistochemical staining techniques are used.¹⁹ However, the reported impact of these micrometastases on survival is variable, and their detection in an entire axillary dissection specimen is time consuming and expensive. With the sentinel node technique, the pathologist is presented with a small number of nodes to which serial sections and immunohistochemical staining can be readily applied. Two large prospective trials are assessing the prognostic significance of micrometastases in the sentinel node (see table on bmj.com). Additional questions that will be answered by ongoing trials include the incidence of axillary recurrence after a negative sentinel node biopsy and the benefit of completion axillary dissection in patients staged as node positive with sentinel node biopsy.

Treatment of metastatic breast cancer in postmenopausal women

The goals of therapy for metastatic carcinoma are the prolongation of life and improvement of symptoms with low toxicity due to treatment. New endocrine treatments that meet these goals are now approved for clinical use.

Aromatase inhibitors

Tamoxifen was until recently the standard first line treatment of hormone receptor positive, metastatic breast cancer. In the past year randomised clinical trials have provided data supporting the use of the newer selective aromatase inhibitors as first line treatment of hormone receptor positive, metastatic breast cancer in postmenopausal women.²⁰⁻²²

The rationale for the use of aromatase inhibitors is to decrease the levels of circulating and intratumoural

oestrogen by inhibiting the conversion of androstenedione and testosterone into oestrogen. Aromatase inhibitors are not effective in premenopausal women, as lower circulating levels of oestrogen result in increases in follicle stimulating hormone and luteinising hormone that stimulate the ovary to produce both androstenedione and the aromatase enzyme, resulting in maintenance of circulating oestrogen levels (see fig A on bmj.com). The primary source of oestrogen in postmenopausal women is the conversion of adrenal steroids (androstenedione and testosterone) into oestrogen by extra-ovarian sites of aromatase activity (liver, adipose tissue, muscle). Human breast tumours are also known to have aromatase activity.²³

The currently available, third generation aromatase inhibitors can be categorised as reversible, non-steroidal inhibitors (anastrozole and letrozole) or irreversible, steroidal inhibitors (exemestane).²³ The use of aromatase inhibitors as second line treatment for metastatic, hormone receptor positive breast cancer in postmenopausal women was established as a result of clinical trials comparing them with megestrol acetate. As summarised in table 3, the aromatase inhibitors were at least as effective as megestrol acetate and seemed to offer a survival advantage.²⁴⁻²⁶ The next step in assessing the role of the aromatase inhibitors was to evaluate them as first line treatment.

The US Food and Drug Administration has approved both anastrozole and letrozole as first line treatment for hormone receptor positive, metastatic breast cancer in postmenopausal women. Both agents have been directly compared with tamoxifen in prospective randomised studies that showed relatively small but significant improvements in outcome for patients treated with aromatase inhibitors.²⁰⁻²² No overall differences in toxicity were seen,²⁰⁻²² but fewer thromboembolic events occurred in the patients treated with aromatase inhibitors.²⁰⁻²¹ No association between the aromatase inhibitors and the risk of endometrial carcinoma has been found, but long term follow up is needed before definitive conclusions are drawn. A recently reported pilot study confirms the antitumour activity of exemestane in postmenopausal women with hormone receptor positive, metastatic breast cancer,²⁷ and a large randomised clinical trial is under way.

Data are also available to support the use of the aromatase inhibitors as primary treatment for postmenopausal patients with hormone receptor positive breast cancer who are not candidates for immediate surgery, because of either size of tumour or presence of comorbidity. In pilot trials with anastrozole²⁸ and exemestane²⁷ a significant proportion of patients who would have needed mastectomies were able to undergo breast conservation. In a larger trial (337 patients) comparing four months of tamoxifen (20 mg/day) with letrozole (2.5 mg/day) the rate of breast conservation was 45% for patients receiving letrozole and 35% for those receiving tamoxifen.²⁹ These results confirm that primary endocrine treatment is feasible in selected patients who are not candidates for surgery or may not be suitable for primary chemotherapy owing to refusal or comorbidity.

Several large randomised adjuvant clinical trials are now assessing whether the aromatase inhibitors add to the effects of tamoxifen or whether they are an alterna-

Sequence of treatment for postmenopausal women with hormone receptor positive, metastatic breast cancer. Antioestrogens are tamoxifen or toremifene. Non-steroidal aromatase inhibitors are anastrozole and letrozole. When fulvestrant is available for routine clinical use, it will also be a second line treatment

tive to tamoxifen in patients with early stage breast cancer.

Selective oestrogen receptor downregulators

Fulvestrant has properties distinct from those of tamoxifen and its analogues. These agents bind to the oestrogen receptor and block its activation, whereas the binding of fulvestrant to the oestrogen receptor results in rapid degradation and loss of oestrogen receptor protein (see fig B on bmj.com).³⁰⁻³² Two randomised trials comparing fulvestrant and anastrozole were recently reported.^{31, 32} In the European trial, 451 postmenopausal women with metastatic breast

cancer previously treated with tamoxifen in the adjuvant or metastatic setting were randomised to fulvestrant or anastrozole. Time to progression of disease, time to treatment failure, objective response rate, and rate of clinical benefit did not differ between the two treatment arms.³⁰ Both treatments were well tolerated. The North American trial was a randomised double blind trial in 400 postmenopausal women with metastatic disease recurring or progressing on tamoxifen.³¹ The time to disease progression, rate of clinical benefit, and duration of response all favoured patients who received fulvestrant.³¹

The results of these two trials establish fulvestrant as a treatment with equivalent activity to anastrozole in patients who have received tamoxifen. Data are now maturing from a completed clinical trial comparing fulvestrant with tamoxifen as first line endocrine treatment for patients with metastatic breast cancer.

Treatment options

The introduction of new endocrine agents has increased treatment options for women with metastatic hormone sensitive breast cancer. The figure summarises the current treatment algorithm for these patients. As additional data emerge from clinical trials, the use of these agents may expand to the adjuvant, and possibly the prevention, setting.

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Additional resources

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Collected resources from BMJ.com

(www.bmj.com/cgi/collection/cancer%3Abreast?page=4)

The psychosocial impact of bilateral prophylactic mastectomy: prospective study using questionnaires and semi-structured interviews

How women with family history of breast cancer and their general practitioners act on genetic advice in general practice: prospective longitudinal study

General information on breast cancer on line

www.y-me.org

www.komen.org

www.cancer.org/cancifo.html

www.nci.nih.gov (Cancernet section)

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Two memorable patients Teaching myself lessons

In the 1950s we scaled and cleaned teeth mainly by hand—ultrasonic scalers and efficient aspirators of particulate matter and spray had yet to appear. We dislodged calculus and plaque from tooth surfaces manually and completed cleaning with paste, rotating brushes, and rubber cups. Operators sometimes impelled this bacteria-laden mixture into their own eyes, and after one such event my right eye became inflamed; it led to lesson one.

Salt eyebaths did not help, and, although a dentist who treats himself has a fool for a patient, I prescribed more radical care for myself. Thus, when everyone had gone home, I locked the doors in case the cleaners came early, drew the curtains, and injected penicillin into my left quadriceps. Repeating the process on following days cured the infection. Thereafter, I protected my own and my patients' eyes with spectacles.

Nowadays, seated dentists operate on recumbent patients. This multiplies hazards because, instead of facing the wall, patients now face the ceiling. Thus the bony surroundings of their eyes no longer protect them from falling objects and materials, but only their eyelids. These are poor barriers to hard particles of tooth or old fillings projected by high speed cutting tools and infective and irritant aerosols. Bodies such as the General Dental Council, Medical Protection Society, and British Dental Association all advise protective eyewear in operative procedures. Current advertisements and illustrations should therefore portray dental care with staff and patients wearing goggles—ideally to BS 2092—but they often do not. This is a pity because stereotypes of modern dentistry, if portrayed faithfully by the media, are important ways of advancing standards since they raise public awareness and encourage higher standards in the dental service itself.

A few months after the first lesson, I learnt a second. My partner, then in his late 50s (I was in my late 20s), needed a lower molar tooth extracting. His history of

dry sockets after extractions (a singularly painful outcome) suggested the need for penicillin as a prophylaxis. An hour or so before the operation, I therefore injected penicillin into his right buttock, and I was nonplussed when he immediately felt dizzy and became pale. Assuming syncope, I lowered him to the floor and raised his legs, but I was uneasy about his deep pallor and distress because he had been unperturbed by previous oral surgery. I called for our dental nurses, and we lifted him into a dental chair, where, recumbent and legs raised, he perspired and remained pale. He then reported that his tongue was starting to feel thick and his throat to swell. I (we), at last realised that this was acute anaphylaxis.

He needed adrenaline without delay, and I slowly injected about 1 ml of a 1 in 1000 solution subcutaneously into the forearm. His pallid complexion became slightly pink, and the thickened tongue and swollen throat did not advance. I therefore injected a little more, perhaps another 1 ml, the memory fails. He spent the night in hospital under observation and next day seemed none the worse.

Randomised controlled tests were not required as evidence for the first lesson, that eyes should be protected in dental operating procedures, nor for the second, that it is unwise in strict privacy to inject oneself with anything that might precipitate anaphylaxis.

D W Sarll *retired consultant in dental public health*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.