Management of breast cancer—Part I

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Breast cancer remains the second most common cause of cancer related death in women in the United Kingdom, with over 12 000 deaths a year. However, substantial progress is being made: deaths from breast cancer in the Western world have fallen by over 25% in the past two decades,¹ reflecting substantial improvements in management (fig 1). Incidence in Great Britain has risen by 50% over the past three decades, reflecting not only changes in population demographics and environmental factors but also an increase in diagnosis as a result of screening. Over a similar time period mortality has fallen.

We review here the recent advances in the prevention, screening, and treatment of breast cancer and the recent efforts to individualise treatment. The review is published in two parts; in the second part we will review advances in the systemic treatment of breast cancer and how an increasing understanding of the biology of breast cancer is beginning to change the way we treat the disease.

Primary prevention

What risk factors may be avoidable?

Progress in primary prevention has come from improved understanding of the causes of breast cancer; identification of modifiable risk factors such as avoidance of post-menopausal obesity, increased exercise, reducing alcohol intake; and encouragement to breast feed (see www.breakthrough.org.uk and www.cancer.gov, which review these issues comprehensively). No conclusive evidence exists of risk from specific dietary components,² such as dairy products and fat, other than that mediated through the link with obesity. Similarly, randomised studies examining reduced dietary fat in secondary prevention, after treatment for early breast cancer, have found no consistent effect on recurrence of breast cancer.^{3,4}

Prolonged exposure to exogenous oestrogen has now been confirmed as a risk factor for post-menopausal women. The women's health initiative, followed by the million women study, confirmed that hormone replacement therapy with combined oestrogen and progestogen doubled the risk of breast cancer,⁵ whereas oestrogen-only therapy increased the risk by 30%.⁵ The use of combined therapy represents a potentially key modifiable factor, and in the United

States the incidence of breast cancer fell significantly after many women stopped taking long term hormone replacement therapy.⁶

Interest has been expressed in the interaction between environmental risk factors and genetic predisposition.⁷ Some risk factors probably have a higher impact in some genetic backgrounds than in others. Large cohort studies are under way that will help identify these interactions, including the UK breakthrough generations study (www.breakthroughgenerations.org.uk).

Can drugs be used to prevent breast cancer?

On the basis of the evidence linking cumulative oestrogen exposure to breast cancer, randomised studies of chemoprevention were started over 20 years ago, initially with tamoxifen, a selective oestrogen receptor modulator. These studies recruited women considered to be at higher risk of developing breast cancer because of their family history or their Gail risk score (a score of risk of breast cancer). They found that tamoxifen taken for five to eight years reduced the risk of developing invasive breast cancer by 38%.⁸ Whether this would also apply to women without risk factors is less clear. Another selective oestrogen receptor modulator, raloxifene, was noted to reduce the risk of breast cancer in women not selected for breast cancer risk, in a study of osteoporosis treatment.⁹ A subsequent randomised trial of nearly 20 000 post-menopausal women at risk of breast cancer found that the preventive effect of raloxifene was similar to that of tamoxifen.¹⁰

Despite the reduction in breast cancer incidence with tamoxifen and raloxifene, there has been no improvement in breast cancer specific mortality or in overall survival,^{8,10} although these studies were not powered to detect a small effect on mortality.⁸ Tamoxifen was associated with side effects with a small increase in the incidence of endometrial cancer, venous thromboembolism, stroke, and cataracts; however, these were less frequent with raloxifene¹⁰ and are uncommon in younger women. The failure to improve survival may reflect the types of cancer prevented by selective oestrogen receptor modulators (only the less aggressive oestrogen receptor positive breast cancers,⁸ many of which would have been cured on presentation).

SOURCES AND SELECTION CRITERIA

We obtained references from PubMed after searching with the term "breast cancer" and limiting our search to clinical trials. All reductions in risk are quoted as relative risk reductions unless otherwise stated.

TIPS FOR
NON-SPECIALISTS

- All patients with a possible presentation of breast cancer should be referred urgently for rapid assessment in a specialist clinic. In the UK all patients referred with a breast problem should be seen by a specialist within two weeks
- Patients with a strong family history of breast and/or ovarian cancer should be referred to specialist clinics for risk and cancer genetics assessment. Local guidelines will determine referral practice

These limited benefits with selective oestrogen receptor modulators have led to their approval for breast cancer prevention in the United States but not in Europe. The preventive effects of aromatase inhibitors are currently being examined in the second international breast cancer intervention study (IBIS II).

What evidence exists for prevention in high risk groups?

Women with germline mutations in the genes *BRCA1* and *BRCA2* have a lifetime risk of developing breast cancer of up to 80%, and advances in breast cancer genetics have led to the recent identification of several new predisposition genes.¹¹ In addition, women who received thoracic irradiation for Hodgkin's disease after menarche and before age 30 have a substantial increased risk of breast cancer.¹² Whether the preventive strategies discussed above reduce risk for high risk groups (especially those with different genetic backgrounds) is uncertain.

Preventive strategies that have been investigated specifically in women with mutations of the genes *BRCA1* and *BRCA2* include:

- Tamoxifen: insufficient women with *BRCA1* and *BRCA2* mutations were included in the tamoxifen studies for meaningful conclusions to be drawn.¹³ No data have been reported with raloxifene
- Bilateral oophorectomy, as well as reducing risk of ovarian cancer by up to 85% reduces the risk of breast cancer by 50%¹⁴
- Bilateral risk reducing mastectomy cuts the risk of breast cancer by 90%¹⁵ (some breast tissue is left behind after mastectomy).

Recently the uptake of these strategies has been reported in a study of over 2600 women with *BRCA1* and *BRCA2* mutations from nine different countries at a median of 3.9 years after genetic testing: 57% of women had a prophylactic oophorectomy, 18% had a risk reducing mastectomy, and 9% (who had not had a risk reducing mastectomy) had hormonal chemoprevention.¹⁶ Just under half of women with known *BRCA1* and *BRCA2* mutations had not taken up a preventive strategy and relied on radiological screening alone.

Screening

How beneficial is mammography?

A Cochrane review concluded that mammographic screening reduces the risk of dying of breast cancer by about 15%,¹⁷ at the expense of a 30% increase in diagnosis. About 2000 women need to be screened for 10 years to prevent a single death from breast cancer.¹⁷ Over the same period 10 women will be diagnosed with breast cancer that would otherwise have remained clinically occult, never to be diagnosed. However, no consensus exists over the benefit of mammographic screening, and other analyses have concluded that mammography is more effective than the Cochrane review suggested, and these quote reductions in mortality of up to 35%.¹⁸ Across Europe and the

United States no consensus exists on the age for starting screening or on frequency.

Is magnetic resonance imaging an advance on mammography?

Contrast enhanced magnetic resonance imaging has been shown to be more sensitive than mammography in detecting invasive breast cancers in high risk populations.¹⁴ In the UK MARIBS study of women with a strong family history of breast cancer, the sensitivity of annual mammography was estimated at 40%, compared with 77% for magnetic resonance imaging and 94% for combined magnetic resonance imaging and mammography.¹⁹ Concerns have been expressed about the specificity of magnetic resonance imaging (83% alone and 77% for combined, compared with 93% for mammography).¹⁹ Magnetic resonance imaging is also more sensitive at identifying the non-invasive early stages of breast cancer (ductal carcinoma in situ); in one study it detected 92% of cases before surgery whereas mammography detected 56%.²⁰

In the UK, the National Institute for Health and Clinical Excellence (NICE) has advised annual screening with magnetic resonance imaging for high risk women from age 30 (or age 20 with germline P53 mutations).¹⁴ Magnetic resonance imaging for breast screening, however, presents substantial financial and resource concerns, which have yet to be fully resolved in the UK. Moreover, the impact on breast cancer mortality of screening with magnetic resonance imaging is unknown.

Local treatment of early stage disease

The diagnosis of breast cancer by triple assessment (clinical, radiological, and pathological, increasingly with core biopsy) is established in the context of multidisciplinary management. Magnetic resonance imaging is useful in selected cases to define tumour extent, especially in invasive lobular breast cancer, and to detect multifocal disease before surgery and assess the contralateral breast (fig 2). Functional imaging with positron emission tomography using fluorodeoxyglucose (FDG-PET) is accepted in the staging of many cancers but is not routinely used in breast cancer at diagnosis.

Fig 1 | Age standardised (European) incidence and mortality rates of breast cancer in women in Great Britain, 1975-2005. Adapted from Cancer Research UK (<http://info.cancerresearchuk.org/cancerstats/types/breast/>)

Fig 2 | Contrast enhanced magnetic resonance scan of the breast. Left: At presentation from a 39 year old woman with a 3 cm breast cancer in the right upper outer quadrant (large arrow) with two involved lymph nodes (small arrows). Right: Same woman after neoadjuvant chemotherapy. Surgical pathology tests confirmed a pathologically complete remission

How is surgery for breast cancer advancing?

Recent advances in surgery have focused on reducing morbidity. Breast conserving surgery by wide local excision is the preferred option, with mastectomy predominantly reserved for tumours not suitable for wide local excision and for patients who request it. In selected cases where breast conserving surgery is not possible, neoadjuvant chemotherapy or hormone therapy may be used to “downstage” the tumour, thus potentially allowing conservative surgery (fig 2).

Sentinel lymph node biopsy

At surgery the axillary nodes are dissected to provide prognostic information that will guide adjuvant therapy and to achieve local control. Biopsy of the sentinel lymph node is accepted as the standard of care in early breast cancer, with removal of the first lymph node or nodes that drain the tumour. The decision to proceed to a full axillary clearance can potentially be made during surgery with touch imprint cytology, fresh frozen section histology, or with molecular polymerase chain reaction assays such as the GeneSearch BLN Assay (Veridex, USA).²¹ Sentinel lymph node biopsy is safe, with a false negative rate of less than 10% and reduced arm morbidity and hospital stay compared with full axillary clearance.²² Current research is evaluating the role of complete axillary clearance versus radiotherapy after a positive sentinel lymph node biopsy. In addition, uncertainty remains over the correct management of micrometastases (metastases less than 2 mm) and isolated tumour cells in the biopsy, which by themselves do not alter prognosis.

Endoscopic assisted surgery

Endoscopic removal of axillary nodes and endoscopic mastectomy have been examined in small series with encouraging reports of improved morbidity.²³ Currently the evidence is insufficiently robust to advocate widespread use of these techniques outside clinical trials or specialist centres. Nipple endoscopy is finding a role in the investigation of nipple discharge.

Minimally invasive techniques

Percutaneous ablation of small (generally less than 3 cm) breast tumours has been examined with

radiofrequency ablation, laser therapy, and cryotherapy. Insufficient evidence exists of the effectiveness of these techniques for use outside a research setting.

Oncoplastic surgery

Reconstruction of the breast with better implants and reconstructive surgical techniques continues to improve the cosmetic results of mastectomy. Immediate reconstruction is often feasible, although many centres prefer to delay reconstruction until after adjuvant radiotherapy if that is required. The overlying skin and nipple can be spared in selected cases of ductal carcinoma in situ and small cancers.²⁴ In addition, there are several new approaches to performing oncoplastic procedures after breast conserving surgery.

Improvements in adjuvant radiotherapy

After breast conserving surgery all women require breast radiotherapy, which reduces local recurrence rates from 26% to 7%.²⁵ Until recently, radiotherapy was given over five weeks, but long term follow-up of randomised trials has shown that accelerated hypofractionated radiotherapy (for example, 40 Gy in 15 fractions over three weeks) produces equivalent low rates of local recurrence^{26 27} without prejudicing cosmesis or late effects. Accelerated radiotherapy requires fewer visits for the patient and has substantial cost savings.

Meta-analysis of randomised trials has shown that radiotherapy after mastectomy improves survival in women with axillary node metastases,²⁸ and it is generally accepted that women with four or more involved nodes benefit from radiotherapy. However, since many of these trials were conducted, the risk of local recurrence has improved substantially, owing to better surgery and systemic adjuvant therapy, as well as to stage migration. The relevance, therefore, of the meta-analysis to women with one to three node involvement is less clear and is subject to ongoing randomised trials.

ONGOING RESEARCH

- Large cohort studies are recruiting participants to identify new risk factors for breast cancer and to examine links between environmental factors and genetics
- Aromatase inhibitors and other agents in the prevention of breast cancer
- Appropriate management of patients after biopsy of the sentinel lymph node
- Safety and side effects of techniques for partial breast irradiation

SUMMARY POINTS

Breast cancer mortality is falling in the Western world as a result of advances in treatment, but it remains a leading cause of death owing to the high and increasing incidence

Several risk factors may present opportunities to lower risk, such as prolonged use of combined hormone replacement therapy and lifestyle factors

Tamoxifen or raloxifene taken for five years prevents a third of breast cancers, but with no evidence of a reduction in deaths from breast cancer

For women at high risk of breast cancer, screening with magnetic resonance imaging is significantly more sensitive than mammography

Advances in surgery continue to decrease morbidity through use of sentinel lymph node biopsy and oncoplastic surgery

Adjuvant radiotherapy for many women can now be given over shorter periods, with similar efficacy and side effects

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

- See *Journal of Oncology* 2008;26:5 (<http://jco.ascopubs.org/content/vol26/issue5/>). A review issue devoted to in-depth discussions on the current issues of breast cancer

Resources for patients

- Breakthrough (www.breakthrough.org.uk)—Charity tackling breast cancer through research, campaigning, and education
- CancerHelp UK (www.cancerhelp.org.uk/)—The patient information website of Cancer Research UK. It provides a free information service about cancer and cancer care for people with cancer and their families
- US National Cancer Institute (www.cancer.gov/)—Provides comprehensive information about cancer for patients

Current radiotherapy research is examining techniques to decrease toxicity and further accelerate treatment, with partial breast irradiation after wide local excision. Examples include:

- Intraoperative radiotherapy. Delivery of a single dose of radiotherapy during surgery to the breast cavity. Early results suggest encouragingly low recurrence rates, and large randomised studies are examining this further²⁹
- Brachytherapy, most commonly with MammoSite (Hologic, USA). Delivery of a radioactive seed directly into the breast cavity via a catheter placed at surgery, typically with five to 10 days of brachytherapy. Recurrence rates are low in early clinical trials³⁰
- Three dimensional conformal radiotherapy.

The evidence base for partial breast irradiation is not as strong as for conventional external beam radiotherapy and should, in general, be given in the context of a clinical trial.

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- Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet* 2000;355:1822.
- Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB. Diet and breast cancer: a review of the prospective observational studies. *Cancer* 2007;109(suppl):2712-49.
- Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the women's intervention nutrition study. *J Natl Cancer Inst* 2006;98:1767-76.
- Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the women's healthy eating and living (WHEL) randomized trial. *JAMA* 2007;298:289-98.
- Beral V. Breast cancer and hormone-replacement therapy in the million women study. *Lancet* 2003;362:419-27.
- Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008;299:1036-45.
- Brohet RM, Goldgar DE, Easton DF, Antoniou AC, Andrieu N, Chang-Claude J, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. *J Clin Oncol* 2007;25:3831-6.
- Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* 2003;361:296-300.
- Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282:637-45.
- Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. *JAMA* 2006;295:2727-41.
- Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. *Nat Genet* 2008;40(1):17-22.
- Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 2005;97:1428-37.
- King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: national surgical adjuvant breast and bowel project (NSABP-P1) breast cancer prevention trial. *JAMA* 2001;286:2251-6.
- Robson M, Offit K. Clinical practice. Management of an inherited predisposition to breast cancer. *N Engl J Med* 2007;357:154-62.
- Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menke-Pluymers MB, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001;345:159-64.
- Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, Gronwald J, Lynch H, Moller P, et al. International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. *Int J Cancer* 2008;122:2017-22.
- Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2006(4):CD001877.
- International Agency for Research on Cancer. *IARC Handbook of cancer prevention. Volume 7. Breast cancer screening*. Lyon, IARC, 2002.
- Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* 2005;365:1769-78.
- Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. *Lancet* 2007;370:485-92.
- Blumencranz P, Whitworth PW, Deck K, Rosenberg A, Reintgen D, Beitsch P, et al. Scientific impact recognition award. Sentinel node staging for breast cancer: intraoperative molecular pathology overcomes conventional histologic sampling errors. *Am J Surg* 2007;194:426-32.
- Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. *J Natl Cancer Inst* 2006;98:599-609.
- Lim SM, Lam FL. Laparoscopic-assisted axillary dissection in breast cancer surgery. *Am J Surg* 2005;190:641-3.
- Cunnick GH, Mokbel K. Skin-sparing mastectomy. *Am J Surg* 2004;188:78-84.
- Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087-106.
- Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143-50.
- The UK standardisation of breast radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371:1098-107.
- Gebski V, Lagle M, Keech A, Simes J, Langlands AO. Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. *J Natl Cancer Inst* 2006;98:26-38.
- Vaidya JS, Tobias JS, Baum M, Keshgar M, Joseph D, Wenz F, et al. Intraoperative radiotherapy for breast cancer. *Lancet Oncol* 2004;5:165-73.
- Benitez PR, Keisch ME, Vicini F, Stoler A, Scroggins T, Walker A, et al. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. *Am J Surg* 2007;194:456-62.