Breast cancer

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Breast cancer remains a public-health issue on a global scale. We report new information about the disease from the past 5 years. Early age at first birth, increasing parity, and tamoxifen use are related to long-term lifetime reduction in breast-cancer risk. Ductal carcinomas in situ has been suggested to be renamed ductal intraepithelial neoplasia to emphasise its non-life-threatening nature. An alternative approach, the progenitor/stem cell theory, predicts that only some tumour cells cause cancer progression and that these should be targeted by treatment. Mammography and ultrasonography are still the most effective for women with non-dense and dense breast tissues, respectively. Additionally, MRI, lymphatic mapping, the nipple-sparing mastectomy, partial breast irradiation, neoadjuvant systemic therapy, and adjuvant treatments are promising for subgroups of breast-cancer patients. Although tamoxifen can be offered for endocrine-responsive disease, aromatase inhibitors are increasingly used. Assessment of potential molecular targets is now important in primary diagnosis. Tyrosine-kinase inhibitors and other drugs with anti-angiogenesis properties are currently undergoing preclinical investigations.

Breast cancer is a major public-health issue worldwide. According to estimates in 2002, there were 1 151 298 new cases of breast cancer diagnosed, 410 712 deaths caused by breast cancer, and more than 4·4 million women living with breast cancer worldwide.[1] In developed countries, there were 636 128 incident cases compared with 514 072 in developing countries, which translates to 189 765 and 220 648 breast-cancer deaths, respectively. In Europe, 2004 estimates indicated 371 000 new cases of breast cancer diagnosed and 129 900 breast-cancer-related deaths.[2]

Mortality rates rose from 1951 to about 1990 but fell afterwards in most European countries, noticeably in the UK (figure 1A). However, mortality rates in central and eastern European countries have been rising (figure 1B). Although rates in Hong Kong and Japan have been lower than those in Europe, they have also been increasing (figure 1B). Rates in North and South America have been similar to those in western Europe (figure 1C).

Reasons for the decline in mortality rates in western Europe, Australia, and the Americas include widespread mammographic screening, precise diagnosis, and increased numbers of women receiving the best treatment for their conditions—including, notably, the extensive use of tamoxifen.[3] The effect of reduction due to early diagnosis of breast cancer has been outlined with patients' data by the Surveillance, Epidemiology, and End Results (SEER) programme in a competing-risk

Search strategy and selection criteria

We searched the Cochrane Library (data range) and MEDLINE (data range), using the search term "breast cancer". We mainly selected publications in the past 5 years, but did not exclude older reports that were commonly referenced and highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged as relevant. Several review articles or book chapters were included because they provided comprehensive overviews that were beyond the scope of this Seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

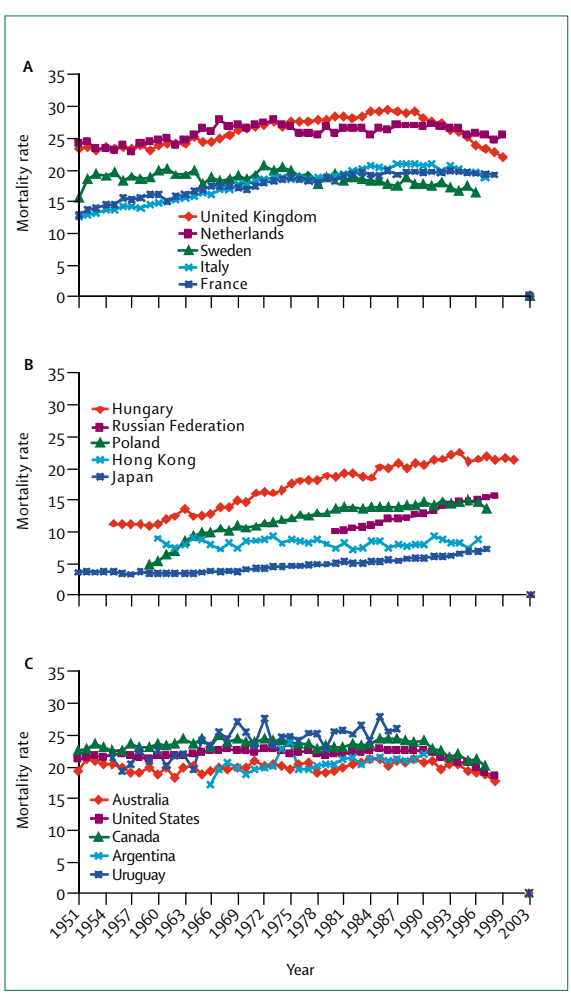


Figure 1: **Breast-cancer mortality in women, 1951–2000**
Data are for all ages, with age-standardised rates per 100 000 people. Selected countries are grouped in broad geographical regions.

	Relative risk	High-risk group
Age	>10	Elderly individuals
Geographical location	5	Developed countries
Breast density	>5	Extensive dense breast tissue visible on mammogram
Age at menarche	3	Before age 11 years
Age at menopause	2	After age 54 years
Age at first full pregnancy	3	First child after age 40 years
Family history	⩾2	Breast cancer in first-degree relative
Previous benign breast disease	4–5	Atypical hyperplasia
Cancer in other breast	>4	Previous breast cancer
Socioeconomic group	2	Groups I and II*
Body-mass index		
Premenopause	0·7	High body-mass index
Postmenopause	2	High body-mass index
Alcohol consumption	1·07	7% increase with every daily drink
Exposure to ionising radiation	3	Abnormal exposure to young girls after age 10 years
Breastfeeding and parity	Relative risk falls by 4·3% for every 12 months of breastfeeding in addition to a 7% reduction for every birth	Women who do not breastfeed
Use of exogenous hormones		
Oral contraceptives	1·2	Current users
Hormone-replacement therapy	1·66	Current users
Diethylstilbestrol	2	Use during pregnancy

Source: references 7–11. *I and II represent high and low socioeconomic status, respectively.

Table: **Risk factors in breast cancer**

analysis calculating probabilities of death from breast cancer and other causes according to stage, race, and age at diagnosis.[4]

Causes of disease

Nowadays, the identification of effective strategies and interventions to prevent breast cancer is still challenging. Although women who have first-degree relatives with a history of the disease are at increased risk, a major pooled analysis has revealed that they are unlikely to ever develop breast cancer, and most who do will be older than 50 years when diagnosed. In countries where breast cancer is common, the lifetime excess incidence of breast cancer is 5·5% for women with one affected first-degree relative and 13·3% for those with two. Eight of nine women who develop the disease do not have an affected mother, sister, or daughter.[5]

Pregnancy-related and hormone-related factors

The associations between breast-cancer risk with age at first birth and parity have been pioneered by MacMahon.[6] Currently, well-established evidence of breast-cancer risk has shown that: early age at first term birth is related to lifetime reduction in risk; increased parity is associated with a long-term risk reduction, even when age at first birth is controlled for; the additional, longlasting protective effect of young age at subsequent term pregnancies is not as strong as that for the first term pregnancy; a nulliparous woman has roughly the same risk as a woman with a first term birth aged about 30 years; risk is transiently increased after a term pregnancy; induced abortion and recognised spontaneous abortion are not associated with raised risk; and long duration of lactation has a small, additional reduction in risk after the age at pregnancy and number of term pregnancies are controlled for. Breast-cancer risk factors (table) have been comprehensively reviewed previously,[12] although there have been some advances in the understanding of breast-cancer causes and their contribution to potential strategies for prevention.

The absence or short-lifetime duration of breastfeeding that is typical of women in developed countries substantially contributes to the high incidence of breast cancer in these areas.[10] A collaborative analysis[10] estimated that risk of the disease was significantly reduced by breastfeeding in addition to the reduction for every birth. Breastfeeding practices can be modified and promoted usefully as a strategy to prevent breast cancer.

Two main conclusions seem to link breast-cancer risk with the use of oral contraceptives. First, women who take combined oral contraceptives and stop after 10 years have a small increase in the relative risk of being diagnosed with breast cancer. Second, there is no pronounced excess risk of diagnosis in women who stop using oral contraception after 10 or more years. The cancers diagnosed in women who had used combined oral contraceptives were less advanced clinically than those diagnosed in women who had never used these substances.[13] Further, the risk of a breast-cancer diagnosis is raised in women using hormone-replacement therapy and increases with extended duration of use.[9,14] This effect reduces after use of hormone-replacement therapy is stopped and largely (if not entirely) disappears after about 5 years, which should be considered with respect to the benefits and risks associated with this hormone treatment.

The hypothesis that an interrupted pregnancy might raise a woman's risk of breast cancer was examined in a prospective, population-based cohort study in Denmark.[15] After adjustment for known risk factors, induced abortion was not associated with an increased risk of breast cancer (relative risk 1·00, 95% CI 0·94–1·06). After this study, the Collaborative Group on Hormonal Factors in Breast Cancer brought together global epidemiological evidence on the possible relation between the disease and previous spontaneous and induced abortions.[16] Pregnancies that end as a spontaneous or induced abortion were recorded not to raise a woman's risk of developing breast cancer.

Anthropometric indices and physical activity

Anthropometric indices are clearly associated with the risk of breast cancer. With pooled data from seven prospective cohort studies (337 819 women and 4385 incident invasive breast-cancer cases in total) and after adjustment for reproductive, dietary, and other risk factors, the pooled relative risk of breast cancer per height increment of 5 cm was 1·02 (95% CI 0·96–1·10)

in premenopausal women and 1·07 (1·03–1·12) in postmenopausal women. Body-mass index showed substantial inverse and positive associations with the disease in premenopausal and postmenopausal women, respectively.[17] These findings indicate that height is an independent risk factor for breast cancer after menopause whereas the relation is not as clear in premenopausal women.[17]

In postmenopausal women not taking exogenous hormones, general obesity is an important predictor of breast cancer, yet abdominal fat assessed in waist-hip ratio or waist circumference has not shown to be related to excess risk after adjustment for body-mass index. In premenopausal women, weight and body-mass index showed non-significant inverse associations with breast cancer.[18]

Increased physical activity seems to be inversely related to the risk of breast cancer,[19] although some inconsistency in the findings are probably attributable to restrictions in methods used to assess physical activity. An analysis of the Nurses' Health Study II[20] showed no overall association between physical activity and risk of breast cancer in premenopausal women, but suggested that the effect of physical activity could be substantially modified by the underlying degree of adiposity. Physical activity and weight control are risk factors that are potentially modifiable and can be recommended at present,[21] although further research could highlight additional benefits.

Dietary factors

A pooled analysis[22] of eight prospective studies investigated whether intakes of specific types of fat were associated with breast-cancer risk independently of other types of fat. The pooled relative risks for an increment of 5% of energy were 1·09 (95% CI 1·00–1·19) for saturated fat, 0·93 (0·84–1·03) for monounsaturated fat, and 1·05 (0·96–1·16) for polyunsaturated fat, compared with equivalent energy intake from carbohydrates. For a 5% of energy increment, the relative risks were 1·18 (0·99–1·42) for substitution of saturated fat for monounsaturated fat, 0·98 (0·85–1·12) for substitution of saturated fat for polyunsaturated fat, and 0·87 (0·73–1·02) for substitution of monounsaturated fat for polyunsaturated fat. No associations were recorded for animal or vegetable fat intakes. With the same data resource, no substantial associations were identified between the intake of meat or dairy products and the risk of breast cancer.[23] However, the Nurses' Health Study II showed that intake of animal fat mainly from red meat and high-fat dairy foods before menopause was associated with a heightened risk of breast cancer.[24]

Results from another pooled analysis of eight prospective studies[25] suggest that fruit and vegetable consumption during adulthood is not significantly associated with reduced breast-cancer risk.[25] Data from five prospective studies were combined to compare the death rates of vegetarians from common diseases with those of non-vegetarians with similar lifestyles.[26] Compared with regular meat eaters, mortality from ischaemic heart disease was 20% lower in occasional meat eaters, 34% lower in people who ate fish but not meat, 34% lower in lacto-ovovegetarians, and 26% lower in vegans. No significant differences were recorded between vegetarians and non-vegetarians in the mortality rates of breast cancer, cerebrovascular disease, stomach cancer, colorectal cancer, lung cancer, prostate cancer, or all other causes combined.

To assess the risk of invasive breast cancer associated with total and beverage-specific alcohol consumption and establish whether dietary and non-dietary factors change such an association, data from six prospective studies were examined.[27] Alcohol consumption correlated with breast-cancer incidence in women; of those who drink alcohol regularly, reduction of consumption could lower the risk of breast cancer. Cigarette smoking, frequently analysed with alcohol consumption in causal studies, does not seem to be related to risk of the disease.[28]

Environmental exposures

An increased chance of breast cancer in women exposed to ionising radiation, particularly during puberty, has been widely accepted[29] even with low-dose exposure.[30] Environmental exposure to organ chlorines has been examined as a potential risk factor for breast cancer. Based on current evidence, the association between risk of the disorder and exposure to organ chlorine pesticides and their residues seems to be small, if it exists at all. In 1993, five large US studies were funded to assess the link between breast-cancer risk in women and concentrations of 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene and polychlorinated biphenyls in the blood plasma or serum;[31] combined evidence has not lent support to such an association.[31]

Possibilities of chemoprevention

In the past few years, hormonal intervention using tamoxifen has been shown to reduce the risk of oestrogen-receptor-positive breast cancer.[32] Although such findings are good with respect to proof of principle, the degree of side-effects from tamoxifen, some clinically serious and others affecting quality of life, seem to rule out the drug for general use at present.

Our knowledge of breast carcinogenesis remains incomplete. We still have no comprehensive understanding of the mechanisms of hormone action when given before or after chemical carcinogen exposure; of the relation between pregnancy and risk of preneoplastic lesions; and of the amounts, causal factors, and interactions of pregnancy-related mammotrophic factors, ligands, and receptors. Mechanisms of hormonal carcinogenesis clearly need to be elucidated. Endogenous hormonal factors certainly

have a critical role in affecting the risk of breast cancer, yet the type, critical amounts, and timing of hormones remain unknown.

Pathogenesis

Progression from healthy tissue to invasive carcinoma

Because of the longlasting debate on the preneoplastic potential of benign, proliferative lesions of the breast (ie, florid ductal hyperplasia in fibrocystic disease), a definitive progression model (similar to that for colon adenocarcinoma) has not been determined. Current knowledge on mammary dysplasia is far from reliable. Indeed, cytological or architectural dysplastic changes can be located in various non-malignant breast diseases, such as florid and columnar duct hyperplasia, adenosis, and papillomas, but their actual precancerous potential is not defined.

Atypical duct hyperplasia, first described by Page and Rogers,[33] has been regarded as the true missing link between healthy duct hyperplasia and low-grade, ductal carcinoma in situ (DCIS). Morphological features of atypical duct hyperplasia, which are intermediates of those in healthy and malignant tissues, and the substantially raised risk for subsequent carcinoma in affected women have been claimed as sufficient proof for a precancerous nature. However, genetic changes in atypical duct hyperplasia were recorded as identical to changes in fully developed DCIS, which questioned the recognition of atypical duct hyperplasia as a distinct entity from low-grade intraductal carcinoma.[34] Atypical duct hyperplasia can be regarded as a very small (<1–2 mm in aggregate diameter) neoplastic lesion that is cytologically indistinguishable from low-grade DCIS and therefore should not be defined as a precursor lesion.

Novel approaches such as gene-expression profiling will increasingly be used to ascertain the occurrence of true preneoplastic lesions in the breast. Precise identification of these precursor lesions will be vital to plan interventions for women at high risk of breast cancer and to assess the effectiveness of prevention trials. Ductal lavage has been introduced and is currently undergoing investigation. In this procedure, luminal cells from the ductal tree are obtained by cannulation of the lactiferous ducts and gentle massage of the breast.[35] Harvested cells can then be examined not only for morphological changes but also for the expression of early markers of cell transformation that eventually will be identified.[36] Currently, this procedure is being tested for validation as an additional research instrument to identify patients at high risk of developing breast carcinoma.

In view of the uncertainty of the occurrence of true preneoplastic lesions of the breast, initial changes of neoplastic transformation that are morphologically identifiable are still in-situ carcinomas (either ductal or lobular). However, DCIS encompasses various lesions, ranging from low-grade to high-grade neoplasms, with remarkably different modes of presentation, histopathological features, genetic alterations, risk for relapse, and progression to invasive carcinoma.

With the ever-increasing detection rate of these in-situ neoplasms by widespread screening mammography and the fact that these cells carry an eight to 11 times relative risk for developing invasive carcinoma, are these lesions worth being defined as carcinomas despite all the accompanying clinical and psychological implications? Indeed, DCIS is not regarded as life-threatening, having an overall 10-year survival higher than 98% of affected patients.[37] But despite this non-serious status, surgery and radiotherapy for this condition are often more radical than for invasive cancer.

To emphasise the non-life-threatening nature of DCIS and reduce any psychological effect caused by the use of carcinoma as a description, the term ductal intraepithelial neoplasia has been suggested to define these cell masses, and has been subsequently revised to also encompass the candidate preneoplastic lesions (flat epithelial atypia and atypical duct hyperplasia).[38] The same procedure has been done for non-invasive lobular neoplasms (atypical lobular hyperplasia and lobular carcinoma in situ), which have been classified into a three-tiered system of lobular intraepithelial neoplasia.

Invasive breast cancer

Stromal invasion and metastasis to regional lymph nodes or distant organs are the hallmarks of fully developed breast carcinomas. Extensive histopathological examination of axillary sentinel lymph nodes by complete and serial sectioning at very close cutting intervals (eg, >60 serial sections at 50 μm intervals as used at the European Institute of Oncology, Milan, Italy)[39] has greatly improved the detection rate of axillary lymph-node association. In turn, detection is substantially associated with the definitive features of the primary breast cancer, such as tumour size and type, occurrence of peritumoral vascular invasion, multifocality, and progesterone-receptor status.[40] However, the mere presence of tumour cells in the mammary stroma or regional lymph nodes might not reliably predict clinical progression of the disease.

Results of randomised trials[39,41] have shown that the recorded number of patients with clinically overt axillary progression of breast cancer is much lower than expected, based on either the false-negative rate of the sentinel lymph-node biopsy[39] or the known prevalence of metastasis to axillary lymph nodes.[41] This difference suggests that metastatic cells might not progress to clinical disease in all patients and that only some cells are able to sustain tumour progression, which is consistent with the hypothesis that growth, progression, and clinical outcome of cancer depend on the activation of tumorigenic stem/progenitor cells.[42,43]

This redefinition is indicated by new pTNM (pathological tumour node metastasis) classifications,[44]

whereby minimum invasion (≤1 mm) is classed as pT1mic (indicating microinvasive cancer) and isolated tumour cells or tumour-cell clusters (≥0·2 mm) in the regional lymph node are no longer regarded to be metastatic and qualify to be pN0 (i+). These new classifications are intended to prevent over-staging of the disease and hence, over-treatment for the patient. Systemic adjuvant therapy is currently offered to patients according to selected clinicopathological features of the primary tumour, which include the status of oestrogen and progesterone receptors and expression of human epidermal-growth-factor receptor 2 (HER2/*neu*); such treatment is undertaken independently of the axillary node status with an equivalent survival benefit. Additionally, quantification of tumour cells circulating in the blood of patients with breast cancer could relate to duration of survival.[45]

With respect to carcinogenesis and tumour progression, the progenitor/stem cell theory conflicts with the traditional stochastic approach. According to the traditional approach, prognosis is dictated by the actual number of invasive or metastatic tumour cells, and therefore the aim of therapeutic interventions is to keep these numbers to a minimum. The progenitor/stem cell theory predicts that only some (and possibly a minority) of tumour cells are actually responsible for tumour progression and clinical outcome, and that treatment should target these cells only. Thus, specific markers of these tumorigenic cells should be identified and quantified in clinical specimens, for reassessment of prognosis by alternative methods.

The use of gene-expression profiling to breast carcinoma has already shown that differential expression of specific genes is a more powerful prognostic indicator than traditional determinants such as tumour size and lymph-node status.[46,47] These molecular assays now await clinical validation by prospective randomised trials before being introduced into clinical practice.

The MINDACT (Microarray in Node-negative Disease may Avoid ChemoTherapy) trial, sponsored by the Breast International Group and coordinated by the European Organisation for Research and Treatment of Cancer (EORTC), will use microarray technology to classify early-stage breast-cancer patients into high and low risk of distant relapse and compare this assessment with standard procedures currently used that consider traditional clinicopathological factors. The trial will test whether use of this genetic signature will prevent 10–20% of women who would typically receive traditional adjuvant chemotherapy from the inconvenience and morbidity of such standard treatment without having any negative effect in overall survival.

Diagnosis and staging

The revolution in diagnostic imaging during the past 20 years has greatly changed detection and diagnostic strategies in breast cancer. Moreover, organised screening, education programmes, and improved consciousness of the female population have substantially changed the type of patients seen nowadays compared with those a few decades ago.

Diagnostic procedures

Procedures commonly used in breast-cancer diagnosis are mammography, ultrasonography, MRI, and PET. However physical examination remains important because a certain proportion (11%) of breast cancers are not seen on mammography.[48]

Mammography remains the most important diagnostic tool in women with breast tissue that is not dense. After menopause, mammography is generally the best method to discover tiny, non-palpable lesions.[48] By contrast, ultrasonography is the most effective procedure to diagnose small tumours in women with dense breast and to differentiate solid lesions from cystic lesions.[49] Although mammography can identify suspicious microcalcifications, it is not good at distinguishing between breast densities and has difficulty in identifying certain lobular invasive carcinomas, Paget's disease of the nipple, inflammatory carcinoma, and particularly peripheral, small carcinomas.[50]

MRI is mainly used as a problem-solving method after conventional diagnostic procedures. The technique is highly sensitive and mainly used for the screening of high-risk, *BRCA*-positive patients. It is also useful for identification of primary foci in non-palpable lesions and axillary metastases with no evidence of a primary focus, and for assessment of response to neoadjuvant chemotherapy.[51] In dynamic, contrast-enhanced MRI, images are acquired before and after patients are given a contrast substance. Malignant lesions are generally highly permeable, with rapid uptake and elimination of contrast substance, whereas benign lesions have slow-rising, persistent enhancement kinetics.[52] Although MRI has good diagnosis accuracy, the rate of false-positive cases is still high and MRI findings cannot be a sole indication for breast surgery.[53,54]

PET is presently used to discover undetected metastatic foci in any distant organ and can assess the status of axillary nodes in the preoperative staging process.[55] However, PET could fail to identify low-grade lesions and tumours less than 5 mm in size.

The use of imaging techniques to detect unknown breast cancers in women (ie, screening) was inaugurated by the Health Insurance Plan of New York in the 1960s.[56] In many randomised studies and population studies, mammography has been shown as the only screening test that can reduce mortality rates of breast cancer if a large proportion of the population used the procedure.[57] However, ultrasonography seems promising for women with dense breasts[58] such as those before menopause, and MRI has been valuable in the screening of women at high risk of breast cancer who are younger than 50 years.[59]

Staging

The TNM[44] system defines the extent of disease and is the language used to compare different cases from various centres. With respect to the primary carcinoma (T), T1 can be divided into three subgroups (T1a, T1b, T1c), depending on the size of the primary lesion. However, with new subdivisions, most instances arise in one subcategory (eg, T1c). In the era of computerised data analysis, classification is thought to be less necessary, whereas precise description of specific cases is regarded as essential and functional to the different needs of statisticians. Therefore, the T classification will probably be determined by a continuous metric description of the size (cm) of the carcinoma (eg, T0.9, T2.4). The same system could apply to nodes (N) in which the numbers of involved and examined nodes will define the condition of a patient (eg, N2/18, N7/22). Finally, we believe that the TNM should rely more on biological characteristics (eg, hormonal receptors, proliferative rates) and biomolecular aspects (eg, gene expression profile) of tumours. The present biometric, anatomical description will probably be replaced by molecular staging.

Surgery

Once imaging techniques indicate a tumour in the breast, cytological or histological confirmation is vital before further treatment is given. Cytology is effective in solid lesions, especially if sonographically guided.[60] But knowledge of the histology of the lesion is the most useful for surgeons, which can be obtained by a core biopsy. A tru-cut biopsy is the simplest method for palpable lesions that are easily reached, whereas a vacuum-assisted needle biopsy can obtain enough material for a good histological diagnosis in non-palpable or deep lesions.[61] Excisional biopsy done a few days before definitive surgery is rarely undertaken because it creates a local anatomical distortion, which makes conservative treatment difficult.

Lymphatic mapping with the sophisticated technique of sentinel lymph-node biopsy provides knowledge about the condition of the axillary nodes[62] without the need for dissection, which can be avoided when lymph nodes are not affected. Internal mammary nodes can also be easily reached and investigated during surgery, to complete the staging procedure. With respect to distant, occult metastases, systemic use of PET will help identify occult foci of cancer cells anywhere in the body.

Breast conservation is currently the most popular treatment because most carcinomas have a restricted size and large primary tumours could be reduced in size by primary chemotherapy.[63] In most breast-cancer centres, conservative surgery represents 75–85% of all operations. Total removal of the mammary gland is needed with multicentric invasive carcinomas, extensive intraductal carcinomas, inflammatory carcinomas, and large primary carcinomas not reduced enough in size by neoadjuvant chemotherapy. Scleroderma, which would preclude radiation, could be an additional indication. Early breast recurrences or second ipsilateral carcinoma of restricted size can be treated with a second conservative surgery.

Surgeons are advised to undertake mastectomies in the same operative session as reconstruction of the breast. Several options can be chosen, which range from the simple positioning of an expander to the use of musculocutaneous flaps (such as the thoracodorsal or abdominal flap [TRAM]). One method becoming widely used is the skin-sparing mastectomy that conserves an extensive section of skin, as well as the more recent skin and nipple-sparing mastectomy that preserves the nipple-areolar complex.[64]

Surgery of the axillary nodes now depends on the results of the sentinel lymph-node biopsy—if negative, unneeded axillary dissection can be avoided.[65] Identical 5-year survival rates were recorded in patients with axillary dissection and in those with axillary dissection only if the sentinel lymph-node biopsy had positive results,[39] although other clinical trials investigating long-term effect on survival are ongoing.

One problem with this biopsy procedure is that the histological diagnosis of the sentinel node is immediately available. The traditional frozen section procedure (which takes three or four sections of the node) often does not allow recognition of micrometastases. Therefore, in about 18% of cases with negative biopsy results at traditional frozen-section examination, definitive histology could show small, undetected metastases after a few days. As a consequence, surgeons should completely and definitively examine the sentinel node during surgery, and accurately section the node (up to 60–80 sections) to avoid missing even very small micrometastases.[66] When a micrometastatic sentinel node is found, other axillary nodes are not implicated in about 85% of instances. Therefore, many surgeons now consider the option to simply monitor patients carefully with ultrasonography and PET.

DCIS is mainly treated with mammary resection. Since axillary metastases are rare, both lymph-node dissection and biopsy techniques are not indicated.[67] DCIS should not be incorporated in the TNM classification but be described according to the new ductal-intraepithelial-neoplasia system proposed by Tavassoli.[38]

Radiotherapy

Radiotherapy in breast conservation

In most developed countries, the current standard of care for patients with early-stage breast cancer consists of breast-conserving surgery, followed by 5–6 weeks' postoperative radiotherapy. Women treated with this protocol have similar prognosis to those treated with mastectomy. Although avoidance of breast irradiation

was shown to substantially raise local recurrence, the necessity of radiotherapy in breast conservation strategy is still debated.[68] Some subgroups of patients could theoretically have low risk of local recurrence, and radiotherapy can therefore be avoided.[69–71] Attempts have been made to identify these populations, which might include individuals with small, low-grade tumours that are oestrogen-receptor-positive or elderly patients resected with wide margins, but no subgroup has been identified that would be adequately treated by breast-conserving surgery alone.

Whole breast irradiation

In daily practice, radiotherapy is used on the whole breast. Probabilities of adequate local control rates and good cosmetic results are high with the use of conventional fractionation. Some data support the effectiveness of an additional dose applied to the tumour bed (ie, boost irradiation) to reduce local recurrence. The EORTC study results suggest that the patients deemed to receive the greatest absolute benefit from boost doses are those younger than 50 years and at higher risk of local recurrence (large tumour size, or positive or close margins).[72,73] However, delivery of the boosting dose raises the rate of morbidity, which reduces cosmetic outcome.

Dosage and fractionation schedules

Different radiation-treatment schedules with rapid fractionation have been used for years in centres in the UK and Canada. Results from a randomised trial support delivery of a reduced total dose in a shortened schedule (42·5 Gy in 16 fractions for 22 days) in patients with lymph-node-negative breast cancer treated by lumpectomy. These findings confirm the substantial equivalence of this rapid fractionation approach and the lengthened fractionation strategies with respect to ipsilateral local control rate, disease-free and overall survival, and cosmetic outcome.[74] A short schedule (20 fractions) with concurrent use of the boost dose is currently used at the European Institute of Oncology Milan after quadrantectomy. For patients younger than 48 years who receive an intraoperative boost dose of 12 Gy, a rapid course of external radiotherapy is used (13 fractions of 2·85 Gy each).

Partial breast irradiation

Does the entire breast need to be irradiated after breast-conserving surgery? The rationale for the use of partial breast irradiation (of the excision site and adjacent tissues only) instead of the conventional approach is based on the finding that most recurrences arise near the primary tumour location. Breast cancer seems to be a segmental disease in most patients with early-stage lesions, and reduction in local relapses has been recorded in postmenopausal patients.[70] Partial breast irradiation can be delivered by different techniques, such as low-dose or high-dose rate brachytherapy (interstitially or with an intracavitary balloon), conformal external-beam irradiation (including intensity modulated radiotherapy), and intraoperative radiotherapy. Most reports of partial breast irradiation have provided results much the same as those achieved with conventional external beam, even though some caution is needed until the safety and efficacy of such irradiation have been shown in appropriate patients and analysis of long-term treatment outcomes.[75]

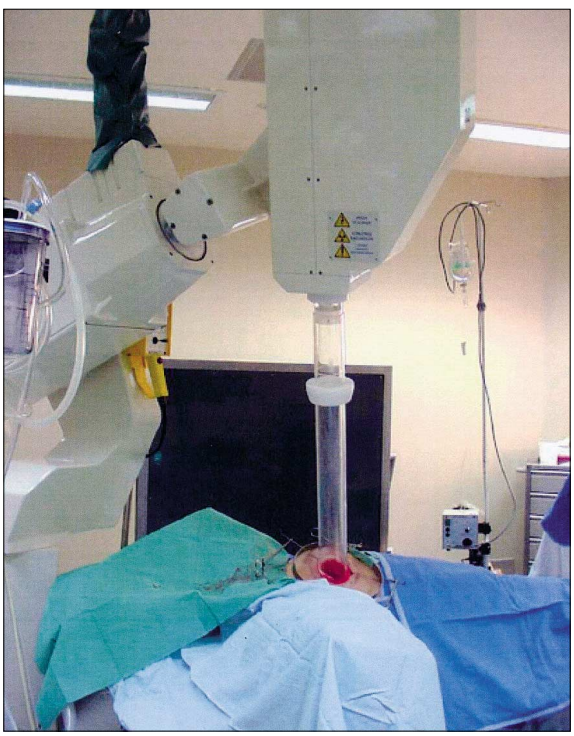


Figure 2: **Linear accelerator used for ELIOT**

Intraoperative radiotherapy

ELIOT (ELectron Intra Operative Therapy) refers to the application of a high dose of radiation during surgical intervention, after removal of the tumour (figure 2). ELIOT is currently used in early-stage breast cancer as the only treatment at the European Institute of Oncology and a prospective randomised trial is ongoing.[76,77] Two miniaturised mobile-linear-accelerators producing a variable range of electron energies are available. Apart from low costs, ELIOT is advantageous because it potentially overcomes problems related to the postsurgical accessibility of patients to radiotherapy centres and has a beneficial effect on patients' quality of life. Moreover, ELIOT use does not irradiate the skin and contralateral breast, and irradiation to the lung and the heart is greatly reduced.

Another important advantage of ELIOT is that it avoids interference with systemic therapy. ELIOT can be used also to give boost doses, and has shown improved benefits compared with conventional approaches.[78] One

boost dose of 10–15 Gy in an intraoperative session can extend surgery by just 10–20 mins, and reduces external treatment by 2 weeks, with improved wellbeing of the patient and economic advantages. Additionally, the ongoing TARGIT (TARGeted Intraoperative radio-Therapy) trial is based on the use of a low-energy radiography source to compare one fraction of radiotherapy with a conventional postoperative approach.[79]

Radiotherapy for DCIS

The role of radiotherapy in DCIS management with conservative treatment has been defined by results from three randomised trials. Addition of radiotherapy reduced the local recurrence rate by about 50% with no effect on survival,[80] and women with positive margins benefited the most. Other criteria suggested for radiotherapy after breast-conserving surgery include young age, large size of lesion, high-grade tumours, or comedonecrosis.[81,82] Despite these positive data, the best management of DCIS is still controversial. In fact, according to an analysis of a database of more than 25 000 patients treated between 1992 and 1999, almost half the women did not undergo postoperative radiotherapy after breast-conserving surgery, and a third did not have radiotherapy even in the presence of adverse histological features.[83]

Development in radiation techniques

Previously, radiation-related late complications had had frequent detrimental effects on clinical outcomes.[84] Nowadays, the target volume can be tailored to individuals, which reduces the dose to the ipsilateral lung and heart, contralateral breast, and surrounding soft tissue.[85] Use of virtual simulation allows precise irradiation with individual field shaping. Intensity-modulated beam arrangement ensures improvement of dose homogeneity. The increasing use of optic or electronic devices (or both) to monitor organ motion and daily setup variations guarantees the accuracy and safety of the delivery system.[86]

Radiotherapy in locally advanced carcinoma

Instead of mastectomy, breast-conserving surgery followed by radiotherapy can be offered to patients with locally advanced disease who respond to induction chemotherapy.[87] 340 patients treated with this combined treatment only had a total locoregional recurrence rate of 9% at the 5-year follow-up.[88] Postmastectomy radiotherapy has shown a beneficial effect on the overall survival of breast cancer.[89–91] However, breast reconstruction after mastectomy has become a standard procedure, and radiotherapy might not achieve good aesthetic results because of radiation-related fibrosis. Patients who have undergone previous irradiation on the chest wall could experience reduced vascularity of the treated tissue, with a raised risk of breast-reconstruction complications.[92] Use of radiotherapy after mastectomy is still controversial.[93–95]

Radiotherapy of metastases

With metastases in the skeleton, short courses of irradiation can palliate symptoms and prevent fractures.[96] Combination of radiotherapy and diphosphonates can raise efficacy of the treatment. Parenchymal brain metastases or carcinomatous meningitis can be treated successfully. Use of radiotherapy after complete surgical resection could lead to substantially improved control. Patients with one brain metastasis who can be treated with more aggressive therapies, including surgery and high-precision radiotherapy, are especially challenging.[97] Stereotactic radiotherapy is used also in other secondary tumour sites, such as the liver, lung, or soft tissues.[98] Development of new technical approaches challenges the dogma that reirradiation of tumour sites is impossible. In some instances, a new cycle of full-dose radiation can be given with restricted risks, to avoid demolitive surgery.[99] For example, a new breast-conserving treatment could be proposed (instead of radical mastectomy) in patients with small local recurrences after previous partial breast irradiation.

Systemic treatments

Patients who remain free of disease after adjuvant therapy compared with those needing chronic care to constantly control disease progression is the main difference between adjuvant and the metastatic treatment approaches, respectively. Adjuvant systemic therapy is given to attempt eradication of micrometastatic disease, which could potentially be present in all patients with invasive breast cancer. Its aim is to reduce relapse and increase survival. Postoperative adjuvant therapies cannot be checked for efficacy except with respect to long-term outcomes in a randomised trial population. By contrast, efficacy of systemic treatments for assessable cancer, given either before surgery (ie, primary treatments for operable or locally advanced breast cancer) or for metastases, allows judgment on the treatment effect after short-term therapeutic exposure.

Neoadjuvant (primary) systemic therapy is given to patients with either locally advanced or large primary tumours as well as to those for whom response of the primary tumour might improve the chance for breast conservation (ie, treatment that is less invasive than mastectomy becomes a reasonable surgical option after response). Primary systemic therapy is also now undertaken to obtain information on the response to a given treatment.

Treatment of advanced disease

Presence of oestrogen and progesterone receptors in tumour cells shown by immunohistochemical staining is a good predictor of endocrine responsiveness.[100–102] Staining for either receptor indicates a response to endocrine therapies and an increased degree of

responsiveness to chemotherapy.[103–107] Chemotherapy is effective also in endocrine-responsive disease, but chances for a more extensive cell kill is lower for these tumours than for endocrine unresponsive tumours.[103,104]

The distinction between disease lacking expression of steroid-hormone receptors and disease showing some presence of these receptors (immunohistochemical evidence) is associated with gene-expression profiling[108–110] and with clinical course.[103,109] Recognition of such distinction needs a fundamental change of current practice in many laboratories from the reporting of merely positive or negative receptor status (which often adopts arbitrary cutoffs) to the quantitative reporting of receptor determinations.[102,111–113]

Overexpression of the epithelial growth factor receptor HER2/*neu* on tumour-cell membranes is a strong predictor for response to trastuzumab, especially if given with one of several cytotoxic compounds.[114–118] Co-overexpression of steroid-hormone receptors and HER2/*neu* has been postulated as a condition for selective resistance to tamoxifen,[119,120] but less so to aromatase inhibitors in postmenopausal women,[120] and not to tamoxifen combined with suppression of ovarian endocrine function.[121]

Adjuvant treatments

Adjuvant systemic treatments are usully offered to patients to reduce their risk of relapse. A 10-year survival lower than 90% would justify the use of adjuvant chemotherapy. In fact, one major concern about adjuvant cytotoxic treatments is that these are offered to a large proportion of patients who are either cured by local treatments or might have their small risk of relapse reduced by endocrine drugs only.

Selection of adjuvant treatments is based on the distinction between endocrine-unresponsive and endocrine-responsive breast cancer. In addition to the estimation of endocrine responsiveness, availability of results from clinical trials could be extrapolated to fit patients' conditions and preferences for tailored adjuvant treatment. Patients with endocrine-unresponsive breast cancer, characterised by no expression of both oestrogen and progesterone receptors, are offered chemotherapy for six courses.[113]

Patients with endocrine-responsive disease are offered adjuvant systemic therapy based on endocrine treatments. High risk of relapse (with metastatic lymph nodes in the operated axilla or vascular invasion) can justify some chemotherapy to precede endocrine treatment in adjuvant therapy.

Premenopausal women with endocrine responsive disease are usually offered tamoxifen with or without suppression of ovarian function.[113] Use of cytotoxic drugs before endocrine therapy is recommended if a high risk of relapse exists.[122] However, the role of both ovarian function suppression and chemotherapy is still uncertain for many of these patients, although investigative trials are ongoing.[123] Availability of aromatase inhibitors, which need ovarian function suppression, further complicates treatment choice.

Women after menopause with endocrine responsive disease are usually offered endocrine therapy with tamoxifen,[113,124] and increasingly also with aromatase inhibitors.[125] Efficacy in reduction of recurrence and mortality well beyond 5 years' treatment (carry-over effect) are the reason for its standard use. When prescribed, chemotherapy should be given before the start of tamoxifen treatment, because of evidence suggesting sequential rather than concurrent use.[126]

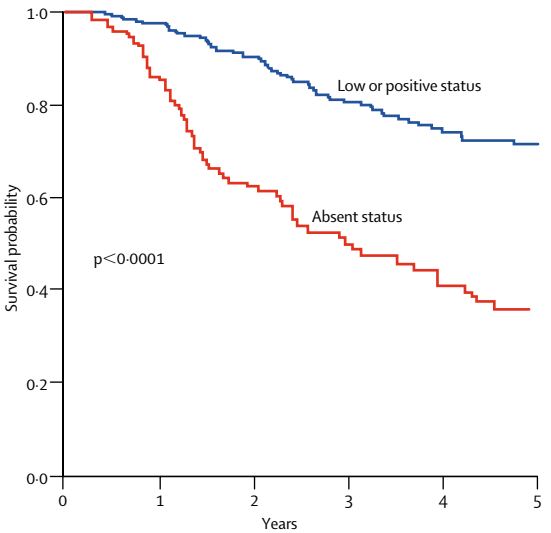
New alternatives for tamoxifen are available to treat postmenopausal women with endocrine responsive disease after surgery,[127] after 2–3 years of tamoxifen to complete standard duration,[128] or after 5 years to further reduce risk of relapse (especially for patients at high risk of relapse—ie, with node-positive disease).[129] These alternatives include non-steroidal (anastrozole and letrozole) and steroidal (exemestane) aromatase inhibitors, and are particularly valuable if contraindication for tamoxifen takes place (eg, in those with previous thrombosis or embolism, or ocular diseases such as retinal dysfunction). The IBCSG (International Breast Cancer Study Group) trial 18–98 or BIG 1–98, which compares tamoxifen and letrozole alone or in the two possible sequences, recently provided data on greatly improved disease-free survival for postmenopausal patients with endocrine-responsive disease who received letrozole compared with those who received tamoxifen. Information about the two sequences are not yet available.

Neoadjuvant (primary) systemic treatments

Systemic primary treatment is usually offered to patients with large primary tumours and aims to reduce tumour size for breast-conserving surgery.[130–132] With such treatment, physicians can also induce regression of axillary-node metastases and obtain knowledge on the responsiveness of the disease to treatment.

Endocrine therapies for patients with endocrine-responsive disease showed an improved outcome for aromatase inhibitors compared with that for tamoxifen.[133,134] Chemotherapy should be used mainly, even for individuals with endocrine-responsive disease, and the use of endocrine treatments should be reserved until after surgery.[131]

Endocrine-unresponsive disease and high proliferation rates (eg, Ki67 expressed in ⩾20% of tumour cells) are important predictors of complete pathological response to six courses of primary chemotherapy.[135] Disease-free survival is substantially longer for patients with endocrine-responsive disease than for patients who do not express steroid-hormone receptors, despite patients with endocrine-unresponsive disease being at least four times more likely of obtaining a pathological complete remission after primary chemotherapy (figure 3).[136]



Receptor status	Total patients	Total events	4-year disease-free survival (%; SE)	Hazard ratio	95% CI
Absent	129	66	41% (5)	3·22	2·28–4·54
Low or positive	265	64	74% (3)		

Figure 3: **Disease-free survival curves for women treated with preoperative chemotherapy according to endocrine responsiveness of disease**
Data displayed according to presence or complete absence of expression of oestrogen and progesterone receptors in tumours before start of treatment.[109]

Anthracyclines and taxanes are usually used for patients with both operable and locally advanced disease.[137–140] Anthracycline-based primary chemotherapy has been reported to yield a large proportion of responses in small-sized tumours with high proliferation index (Ki67) or grade, and with simultaneous overexpression of HER-2/*neu* and topoisomerase II,[141] whereas mutation of *p53* has been associated with a reduced response rate to chemotherapy.[142] Chemotherapy regimens that do not contain anthracycline (that have vinorelbine, platinum, and fluorouracil) were also recorded to be effective, especially for patients with endocrine-unresponsive disease presenting as a cT4 (ie, clinical T stage 4; a tumour of any size, which directly spreads to the chest wall or skin, and includes inflammatory carcinoma and ulceration of the breast skin) with or without inflammatory features.[143] Additionally, gene-expression profiling has been described to predict pathological complete remission in patients receiving neoadjuvant chemotherapy.[144]

Systemic treatments for women with overt metastases

Overt metastases usually indicate chronic, incurable disease. Treatments are defined according to efficacy to provide palliation and account for a heterogeneous duration of survival, which could vary from a few weeks to several decades (with an average of a few years). Treatment should increase the total duration of time with no or few disease-related symptoms and with the lowest burdens with respect to side-effects of treatment.[145] Although some trials with selected patients have shown, on average, a modest survival advantage for specific endocrine, cytotoxic, or immunological treatments (compared with standard therapy), treatment for metastatic breast cancer is still prescribed to improve quality of life through control of disease progression. Particular attention has been given to the treatment of specific complications of disease and treatment in specific organs. The established efficacy of bisphosphonates to reduce bone pain and other skeletal events in women with advanced breast cancer has also led to their routine use.

Approaches to specific populations with breast cancer

Younger women (aged less than 35 years) with breast cancer present with worse prognosis than do older premenopausal women, partly because of the more aggressive presentation of disease.[146] Treatment decision-making for very young women with newly diagnosed breast cancer is usually affected by the strong emotional involvement of care providers and by the intention to intensify treatment.[147] Endocrine therapy, which is not easy to offer to very young patients, should be investigated in hormone-responsive disease because substantial evidence shows that current approaches typically containing cytotoxic drugs are not the best.[148] These investigations should analyse the best use of endocrine approaches, such as the timing of surgery with respect to phases in the menstrual cycle role (of suppression of ovarian function), suppression of ovarian function, use of selective oestrogen-receptor modulators, and aromatase inhibitors. Issues related to chemotherapy in young patients (timing, duration, and intensity of chemotherapy) might be resolved in those with endocrine non-responsive tumours. Family plans, pregnancy, and presence of *BRCA1* and *BRCA2* mutations are of increased concern for young women.

In general, older postmenopausal women should be treated without any discrimination related to age. Any therapeutic decision-making should account for the specific condition and life expectancy of the patient. Use of adjuvant systemic therapy should be appropriate. Although patients with endocrine-responsive disease who use tamoxifen for 1 year show improved survival,[149] prescription of adjuvant chemotherapy for women older than 70 years (especially for those who are endocrine-unresponsive) relies on scarce or no information at all. Such treatment has many problems because standard chemotherapy regimens can be offered with no concern or respect to age. Specific trials should address treatment for women who are too frail to be prescribed standard therapy, yet have a long enough life expectancy to fear relapse.

Molecular targets and new drugs

The rapid growth in the number of biomolecular markers and development of targeted therapeutic drugs for breast-cancer treatment began more than three decades ago after the discovery of steroid-hormone receptors.[150] Increased knowledge of several tyrosine-kinase family receptors has led to the first targeted treatment beyond endocrine therapies, the humanised murine antibody trastuzumab. Assessment of potential molecular targets has therefore become an important part of primary diagnosis to widen the range of decision-making instruments available.

HER-2

Although trastuzumab is very well tolerated, it has cardiotoxic effects that are clinically more relevant if used with anthracyclines. The best schedule, duration of treatment, and sequence of combinations, as well as relevant tests to identify patients who might benefit most from the drug remain to be established. Trastuzumab is still the only registered, biologically engineered compound for routine use in patients with advanced breast cancer.

Pertuzumab (also known as 2C4, Omnitarg) is a new recombinant humanised monoclonal antibody that also binds the extracellular portion of HER2, which causes steric hindrance and impairs receptor dimerisation.[151] Ongoing phase-I testing has shown activity in patients with breast cancer that is either HER2-negative and trastuzumab-refractory HER2-positive.[152]

Tyrosine kinase, cyclines, and proteosoma

Most tyrosine-kinase inhibitors are in preclinical investigations and only a few have been tested in patients with advanced breast cancer. Gefitinib is an inhibitor of the tyrosine kinase of human epidermal-growth-factor receptor (HER1) and has shown some antitumour activity in preclinical studies and a phase II trial of patients heavily pretreated for metastatic breast cancer.[153] Lapatinib (GSK572016) is another HER1 and HER2-reversible inhibitor that has shown phase I results of disease control in patients with advanced and trastuzumab-unresponsive breast cancer.[154]

CI-1033 is a 4-anilinoquinazoline that is a pan ErbB tyrosine-kinase inhibitor (rather than an irreversible inhibitor specific for epidermal growth-factor receptor) and has shown efficacy against breast-cancer cell lines. Some responses have been shown in early clinical investigations.[155] Bortezomib (formerly PS-341), a dipeptide analogue of boronic acid, is a potent, highly selective, and reversible proteasome inhibitor that prevents regulatory mechanisms of cellular processes.

Insulin-like growth factor (IGF)

IGF is an interesting therapeutic target in breast cancer because its ligands and receptors are often overexpressed and are implicated in proliferation, transformation, and metastasis. The IGF system includes ligands IGF-I and IGF-II, receptors IGF-IR and IGF-IIR, and six known IGF-binding proteins. These binding proteins are promising targets for the manipulation of endocrine responsiveness and resistance to trastuzumab.[156]

Angiogenesis

Much is expected of the targeting of angiogenesis for cancer treatment, because the process leads to the development of new blood vessels needed for primary tumour growth, invasion, and metastasis.[157] Bevacizumab is a recombinant, humanised monoclonal antibody to vascular endothelial growth factor[158] that has shown some efficacy when used alone in phase II clinical trials.

Several anti-angiogenic drugs have been tested for efficacy, including thalidomide, endostatin, angiostatin, SU6668, SU11248, and cyclo-oxygenase 2 (COX-2) inhibitors. COX-2 also improves the efficacy of aromatase inhibitors by increasing overexpression of tumour aromatase. Despite these inhibitors being very promising, they block prostacyclin (by inhibition of endothelial COX-2) but not thromboxane (synthesised in platelets by COX-1). Prostacyclin is a vasodilator and inhibits platelet aggregation, whereas thromboxane is a vasoconstrictor and promotes platelet aggregation. COX-2 inhibitors have been shown to lead to raised prothrombotic activity and therefore to some increased cardiovascular events in patients at heightened risk of vascular pathological changes. Thus, some trials with these substances have been stopped. An interesting and promising specialty relates to the anti-angiogenic efficacy of low-dose, metronomic cytotoxics such as vinorelbine and cyclophosphamide.[159]

Receptors as targets for radionuclides

Efficacy of targeted therapy depends on the biologically relevant quality and quantity of the specific compound. This treatment needs to reach the target efficiently and accurately and exert a selective therapeutic effect. The development of biomarkers to assess in-vivo responses and the ability to use such biomarkers as targets for specific radionuclide treatment represent great challenges in cancer medicine.[160]

Conclusions

Although care for patients with breast cancer is genuinely mutlidisciplinary, there is an important general trend to increase targeted interventions within all specialties to obtain efficacious treatment with acute and late toxic effects in organs and tissues kept to a minimum. It is within this context that progress should be viewed; development of tailored adjuvant systemic therapies and better targeted treatments for women with advanced disease. Both approaches will need an improved understanding of the target (either all tumour cells or only some of them) and its environment (stroma, vessels, and other organs).

Conflict of interest statement
We declare that we have no conflict of interest.

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