More about... Breast cancer

Fertility after breast cancer

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The desire to have a child after a diagnosis of breast cancer in women raises two central questions:

- can breast cancer survivors conceive, and
- should breast cancer survivors conceive?

Breast cancer *per se* does not influence female fertility. Similarly, surgery and radiotherapy for breast cancer do not affect fertility, although both these interventions may affect a woman's ability to successfully breastfeed. In contrast, adjuvant chemotherapy can be highly gonadotoxic, resulting in a loss of oocytes and primordial follicles. The extent of this reduction in ovarian reserve (which reflects the ability of the ovary to respond to gonadotrophin stimulation and which is in turn a marker of the remaining number of follicles) will determine whether women experience irregular menstruation, temporary amenorrhoea or permanent ovarian failure. Amenorrhoea extending beyond 12 months after adjuvant chemotherapy is often a sign of irreversible ovarian failure; however, the return of menstruation does not necessarily reflect normal fertility potential. Chemotherapeutic agents and combination regimens vary in their impact on ovarian reserve, but generally speaking cyclophosphamide and doxorubicin have the greatest gonadotoxic effect. Moreover, the risk of premature ovarian failure is influenced by the total cumulative dose of the cytotoxic drugs as well as the woman's age at the time of treatment, with women over the age of 40 years being particularly at risk. Subject to these variables the risk of premature ovarian failure can range from below 10% to over 90%. Furthermore, adjuvant endocrine therapy, such as tamoxifen, can also affect ovarian reserve, not through a direct drug effect but through the long duration of treatment during which time the pool of remaining follicles undergoes further decline.

The second question, whether pregnancy is safe and advisable in breast cancer survivors, has been the subject of considerable debate. Due to the concern that oestrogen, which is a carcinogen in the pathogenesis of breast cancer, may have a negative impact on survival (by stimulating local recurrence or the growth of micrometastases), many women have been advised against pregnancy in the past. To date we still lack prospective data on which to base the counselling and management of this group of women. There are, however, a number of retrospective studies which have documented the outcome of pregnancy in breast cancer survivors. Collectively, these studies showed either no difference in breast cancer-related outcome between women who did and who did not have a subsequent pregnancy, or they documented improved survival following pregnancy. Moreover, there is no evidence to suggest that the exposure of oocytes to chemotherapeutic drugs causes an increased risk of congenital abnormalities in subsequent pregnancies. Similarly, maternal pregnancy complications do not appear to be increased in breast cancer survivors. It would therefore appear that pregnancy after breast cancer is not detrimental and may indeed be beneficial.

Caution needs to be exercised, however, when interpreting these retrospective and heterogeneous data. The apparent survival benefit derived from pregnancy may be due to a selection bias in that women who conceive after breast cancer are healthier and have a better prognosis than those women who do not have a subsequent pregnancy. Alternatively, it has been hypothesised that breast cancer cells share common antigens with fetal cells, which trigger an immune response during pregnancy. This immune response may be protective against the growth of micrometastases.

At a practical level most experts advise that pregnancy should not be considered within the first 2 - 3 years of initial diagnosis, as this is the period with the highest incidence of recurrence. Waiting times of up to 5 years may be recommended for women with more advanced disease and/or who are advised to complete adjuvant endocrine therapy. However, these recommendations are not free of controversy, as some authors regard them as outdated. At all times delay in childbirth must be considered against the backdrop of reduced ovarian reserve as outlined above.

It is important that the issue of subsequent conception should not be approached when cancer therapy has been completed but discussed upfront in order to explore options for fertility preservation. Strategies include modification of the adjuvant chemotherapy regimen (such as choosing less gonadotoxic agents) or the addition of a GnRH analogue given at the same time as chemotherapy. Alternatively, patients may undergo assisted reproductive techniques just prior to chemotherapy with the option of freezing embryos or unfertilised oocytes, although the latter is currently not part of routine clinical practice due to, as yet, limited success. These modalities are rarely used as they result in the patient delaying the commencement of her treatment and receiving oestrogen.

When fertility-preserving strategies fail or are not feasible and premature ovarian failure ensues, egg donation or adoption are remaining options.

Further reading

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Life after cancer treatment – psychosocial adjustment issues of cancer survivors

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The development and advances in the field of oncology over the last 15 years have contributed to the fact that cancer is no longer seen as a death sentence and is currently viewed as a chronic illness. More people are surviving cancer and there is a need to find creative strategies to assist them in coming to terms with the cancer reality. Learning to live with

the uncertainty is part of the challenge the cancer survivors have to face. The following facts are worth noting:

- Over 60% of adults diagnosed with cancer will be alive in 5 years.
- In 2010, 1 out of 250 adults aged 20 - 29 will be a childhood cancer survivor.
- 3 out of 4 families will have a member affected by cancer.

According to the ASCO website:[1]

- The number of cancer survivors in the USA has increased from 3 million in 1971 to 10.5 million in 2003.
- About 66% of people diagnosed with cancer today are expected to live at least 5 years beyond their diagnosis.
- Most cancer survivors in the USA are currently 65 years or older.

In South Africa, we do not have any reliable survivor statistics. However, we can assume that there will be a similar trend.

Challenges faced by cancer survivors after treatment

Despite the advances made in treatment the adjustment to the reality of learning to cope with the life after cancer treatment remains a challenge to most cancer patients and their families. The process of learning to incorporate the illness as part of the 'new normal reality' is not an easy task. This is often underestimated by the medical team dealing with cancer patients. Patients are expected to be relieved that their treatment has been completed. Proper preparation and planning for the post-treatment phases are not dealt with effectively and patients are often left feeling abandoned, fearful and hopeless at this point in the treatment process.

Proactive management and intervention of the distress level common to a patient navigating the cancer journey is needed to prevent the development of more serious psychiatric problems over time. The diagnosis of cancer exacerbates psychological and social problems.

In modern cancer care, a holistic approach to care involving the family and the patient is vital. The Institute of Medicine recommends that follow-up for cancer patients should be:

- protocol based – the guidelines should include the time frames recommended for investigations
- carried out in specialised centres or by GPs under specialist supervision.

Coaching cancer survivors in developing 'patient-active strategies'

A patient-active approach is a goal-directed and gradual approach that is determined by the patient's illness profile and treatment regimen as well as their performance status, social circumstances and personal resources prior to treatment. The approach builds open communication and mutual respect in the doctor-patient relationship with a clear patient-centred focus no matter what the treatment outcome will be. This empowerment model should include working towards creating the following opportunities for the survivor:

- Becoming involved in making active choices as part of their treatment process.
- Encouraging patients to make changes in their lives that they think are important to their treatment and recovery.
- Encouraging partnering of patients and their doctors in treatment decisions.
- Accessing resources that will provide for patients' needs.
- Coaching and encouraging the development of new attitudes towards the illness and the recovery process.

This approach adopts the COPE model widely used in psychosocial oncology.[2]

C: Creative problem-solving.

O: Optimism in staying focused on finding solutions or working towards goals.

P: Planning manageable ways to deal with emotions, problems and goals.

E: Expert information to be actively pursued to assist in proactive decision-making.

Patients and families following a 'patient-active' approach move from victim to survivor much sooner. According to Harold Benjamin, 'Combining the will of the patient with the skill of the physician – a powerful combination in the fight against the common enemy – cancer!' should be the preferred position at all times. He also stated that 'People with cancer who participate in their fight for recovery from cancer will improve the quality of their life and may enhance the possibility of their recovery.' [3]

Within this 'patient-active model':

- Patients are encouraged to take control of the illness process by building a better understanding of their cancer and its treatment and by learning to live beyond the cancer experience.
- Patients who are given relevent information are able to ask more questions and to build a better understanding of their treatment.
- This approach places greater pressure on the medical team initially as they have to field questions and provide information that will assist the patient's treatment decisions.
- Patients with access to the Internet will be inclined to question technical issues relating to the treatment such as targeted therapies, monoclonal antibodies, angiogenesis and the impact of the human genome on the development of new drugs and treatment options. Creating the space for the more analytical patients to ask questions will ensure greater compliance and a better tolerance of treatment, as well as more effective post-treatment adjustment.
- This approach requires multi-disciplinary team members to truly use all their resources and ensures that patients are referred to other professionals such as nutritionists, biokineticists, oncology social workers, psychologists or other complementary therapists depending on their own needs, thus ensuring the development of an individualised rehabilitation plan.
- The patient-active approach to cancer care will encourage patient autonomy throughout the cancer journey by taking control and working towards hope more actively in terms of the patient's own frame of reference and belief system.
- This approach disarms the conventional hierarchical medical model, with power vested in the medical team, and places patients at the centre of the care model in a way that will facilitate their own healing in a patient-focused holistic care model.
- The emotional burden carried by the medical team in terms of the patient's response to treatment and the treatment intent becomes a shared responsibility. Although communication might be challenging, and may require more preparation and input during the initial phases and at the end of treatment, the shared responsibility of this patient-active model will create a new dynamic between the patient and the medical team, leaving team members and patients feeling less overwhelmed by the burden and responsibility they are carrying.

Conclusions

Taking conscious steps towards a more equal relationship with our patients allows for greater creativity in the therapeutic relationship. Setting new standards of patient care opens up the possibility of a more democratic approach that will pave the way to greater patient involvement and innovation all through the different rehabilitation processes. This progressive treatment model will ensure patient-centred holistic care at all times and will allow the multidisciplinary team to learn from our experiences within the field of oncology. It is then that we realise, in the words of Rachel Naomi Remen, from *Kitchen Table Wisdom:* 'It is the wisdom gained from our wounds and from our experiences of suffering that makes us able to heal.' The challenge for the cancer survivors remains to live their life despite the cancer and finding an alternative story that provides meaning as they learn to be patient-active.

Useful resources for planning a patient-active rehabilitation plan

Resources to guide follow-up care of cancer patients are available internationally as standardised guidelines that can help to guide effective and scientifically based follow-up care:

1. The American Society of Clinical Oncology (ASCO), representing more than 23 000 cancer professionals worldwide, has published clinical practice guidelines on a variety of topics. Patient guides are available on the ASCO's website.
2. http://www.nccn.org/patients/patient.gls.asp
3. The Children's Oncology Group (COG) developed a resource for health care providers called Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. These guidelines are available on the COG website at http://www.survivorshipguidelines.org/

Local South African networks dealing with breast cancer survivors

- People living with cancer website: http://www.cancer.net/patient/Survivorship
- The National Comprehensive Cancer Network (NCCN) Patient Guidelines are available on the NCCN's website.
- Reach for Recovery volunteers for breast cancer patients: http://www.reach4recovery.org.za. Their website has the list of the local chairladies.
- Cancer Buddy's from People Living with Cancer. This group provides peer-to-peer support to newly diagnosed patients by trained cancer survivors with a similar diagnosis www.plwc.org.za
- CANSA tel 08600 226622. CANSA support group information: https://www.givengain.com/cgi-bin/giga.cgi?cmd=cause_dir_news&cat=839&cause_id=1056
- Breast Health Foundation tel 083 403 1011, http://www.breasthealth.co.za

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HIV and breast cancer

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Breast carcinoma in HIV-infected patients is reported to occur at a relatively early age, with increased incidence of bilateral disease, unusual histology, and early metastatic spread with a poor outcome. However, the link between breast cancer and HIV remains controversial, and the data to support such claims are weak. Published studies are mostly from Western world centres, reporting HIV acquired by homosexual contact or intravenous drug use, have an unusually high incidence of men, and do not reflect the impact that HIV has in sub-Saharan Africa. Overall, most authors feel that HIV has little influence on the incidence and outcome of breast cancer.[1]

Patients with HIV and breast cancer present two distinct challenges to the clinician: to confirm the diagnosis and accurately stage breast cancer, and to evaluate the safety and timing of surgery and adjuvant treatment in the setting of immunocompromise.

Differential diagnosis

The differential diagnosis of a breast lump in an HIV patient is wider than usual and encompasses diagnoses not routinely encountered in practice: these include benign changes of breast parenchyma, unusual breast infections, and other neoplasms.

Gynaecomastia is more common in men with HIV infection and may be aggravated by antiretroviral therapy. Antiretroviral therapy is also associated with an increase in breast size in women. Breast enlargement forms part of a syndrome of peripheral fat wasting (lipodystrophy) and central adiposity secondary to antiretroviral therapy. Pseudoangiomatous stromal hyperplasia (PASH) of the mammary stroma, a benign keloid-like stromal overgrowth that histologically may simulate a vascular proliferating lesion, also occurs in the clinical setting of HIV infection.

Enlargement of intramammary lymph nodes, predominantly in the upper outer quadrant in HIV-positive patients, can present as a mass mimicking neoplasia. The nodes may become enlarged as part of a progressive generalised lymphadenopathy or secondary to an opportunistic infection or neoplasm.

The spectrum of opportunistic infections that occurs in the breast depends largely on the extent of immune depression. Mammary skin is subject to similar cutaneous manifestations reported elsewhere on the body that are commonly observed with HIV infection, including human papillomavirus (HPV)-induced lesions.

In southern Africa it is now not uncommon to find breast TB in the setting of HIV infection, even though the breast is thought to be resistant to infection by mycobacteria.[2] In the Breast Clinic at Groote Schuur Hospital we diagnose a new case of TB of the breast approximately every second week, an exponential increase from a decade ago. TB mastitis can present as a painless mass, bilateral or unilateral breast oedema with axillary adenopathy, or a tender localised abscess that may ulcerate to form draining sinuses. A nipple discharge can occur in all forms of mammary TB. As in other anatomical sites, confirming the diagnosis can be difficult. Histologically, destructive

caseating granulomas are strongly supportive of TB, but acid-fast bacteria are noted in less than half of tissue sections or needle aspirates.

Breast carcinoma

The first case of breast cancer in an HIV-positive patient was reported in 1988.[3] Since then, very few cases have been reported in the literature, many only with limited clinical and/or pathological details, and almost none from southern Africa, the global epicentre of the disease. An analysis of these cases suggests that breast cancer in the setting of HIV infection tends to occur at a relatively early age, with increased bilateral disease, unusual histology such as poorly differentiated or mixed tumours, and early metastatic spread with a poor outcome. It is not clear, but probable, that this merely reflects the age of patients with HIV. Patients younger than 35 years with breast cancer more commonly have a higher overall recurrence rate, a greater risk of developing metastases, and show factors associated with a poorer prognosis compared with older patients.[4]

Because the differential diagnosis of a breast lump in an HIV patient includes some less common conditions, we are wary of making therapeutic decisions based on cytology only. It is our practice to insist on histological confirmation of breast cancer, easily achieved with core needle biopsy, in view of the atypical presentation and young age of most of these patients. Information regarding oestrogen receptor status is also helpful.

Accurate preoperative staging is frequently confused by the presence of palpable lymphadenopathy, lung lesions suggestive of metastases or miliary TB, and bone marrow changes again affected by opportunistic infections.

It is difficult to make decisions about the timing and safety of surgery and chemotherapy. We have not found a major increase in immediate surgical complications in HIV patients on whom we have operated. We try, however, to delay surgery in patients who are profoundly immnunosuppressed and who meet AIDS diagnostic criteria until antiretroviral therapy is initiated and a rise in the CD4 count is documented. If the patient does not have clinical features of AIDS we perform surgery even if the CD4 count is low or the patient is not on antiretrovirals. HIV infection is considered a contraindication to the use of breast implants, largely because of the increased susceptibility to infection.

Standard first-line chemotherapy (CAF) has a high risk of complications in immunocompromised patients, and is best started after antiretroviral therapy is initiated, although a response to antiretrovirals may take months. Our infectious disease clinic recommends that we simply start chemotherapy, provided the CD4 counts are reasonable, and then refer the patients for treatment. Intolerance to chemotherapy does not appear to have been a significant problem in previously reported cases or in our experience, but has been found to be a problem in other African centres, and when used appropriately has not resulted in progression of the underlying HIV infection.[5] Patients who have ER+ve cancer are started on tamoxifen in the interim, whereas ER-ve patients with AIDS may be treated with primary radiotherapy.

Kaposi's sarcoma

Kaposi's sarcoma (KS) can be localised to the breast in patients with AIDS, although it is not a common clinical dilemma in our practice. KS may present primarily in the breast or as disseminated disease with only secondary involvement of the breast. Involvement of axillary nodes by KS can result in lymphatic obstruction leading to an indurated peau d'orange-appearing breast. The mammographic and ultrasound appearance of KS lesions in the breast can be mistaken for carcinoma.[6]

Lymphoma

The breast is a recognised site for extranodal non-Hodgkin's lymphoma (NHL) in HIV infection.[7] The majority of AIDS-related NHLs have aggressive histological characteristics, are predominantly of B-cell lineage, have a high association with the Epstein-Barr virus (EBV), and demonstrate rapid clinical progression. At mammography, primary breast lymphoma can manifest either as a circumscribed mass or an indistinctly marginated, uncalcified mass. It can also present with bilateral diffuse breast involvement, without distinct focal lesions. Microscopically NHL needs to be differentiated from anaplastic carcinoma and the solid variant of lobular carcinoma. A core biopsy is usually adequate for the diagnosis, although occasionally excision of the mass is necessary.

Human immunodeficiency virus (HIV) infection may involve, directly or indirectly, virtually every organ system, including the breasts. Surprisingly, there is little research focused on breast pathology and breast cancer in patients infected with HIV.

It is important to consider the diagnosis of TB mastitis, and to know that Kaposi's sarcoma and non-Hodgkin's lymphoma may also be localised to the breast in patients with AIDS.

It remains unclear if the epidemiology, clinical scenario, pathology, and outcome of breast cancer are related, directly or indirectly, to HIV infection. Patients who are dually diagnosed with breast cancer and HIV infection face multiple treatment predicaments. Answers to these controversial issues are still needed.

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Breast screening in developing countries

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Africa bears 24% of the global burden of disease but has only 3% of the health care workforce and 1% of the world's financial resources, according to the WHO's *World Health Report 2006*.[1] The report further revealed that 57 countries are unable to meet a basic standard of health care coverage by physicians and nurses; 36 of these 'critical countries' are in sub-Saharan Africa.

Cancer statistics

Cancer is set to become the newest epidemic in the developing world. By 2020, 70% of the 15 million new annual cancer cases will be in developing countries. African countries will account for over a million new cancer cases a year, and are the least able to cope, having fewer cancer services. There are currently more than 600 000

cancer deaths annually in Africa. Lack of resources and basic infrastructure result in many Africans not having access to cancer screening, early diagnosis, treatment or palliative care. Measures such as raising awareness of cancer and initiating cancer control programmes are urgently required. The vast majority of cancers in these low- and medium-resource countries present in clinically advanced stages, substantially adding to the burden of the already limited cancer treatment services.[2]

In South Africa breast cancer is the most common cancer in women. The lifetime risk of developing breast cancer is 1 in 26 women across all population groups. Annually more than 3 000 women die from breast cancer in South Africa (www.cansa.org.za). More than 60% of women present with locally advanced breast cancer. It has been speculated that the lack of an early cancer detection programme is responsible for the majority of women presenting at a late, symptomatic stage when cure is impossible.

Early detection

Early detection followed by appropriate treatment is currently the most effective strategy to reduce breast cancer mortality. The overall success is based on the assumption that the smaller the lump detected, the better the survival outcome.

The West has successfully adopted these twin pillars as a strategy to reduce mortality from a rising incidence of breast cancer. This Western model of mass screening by mammography, together with breast self-examination and quality breast cancer treatment, has also been proposed for other countries that consider screening.

Early cancer detection consists of the following two components:

- **screening programmes** – organised efforts to detect early disease in asymptomatic populations by mass application of simple screening tests at regular intervals, and
- **early clinical diagnosis** – detection of early clinical stages of disease in symptomatic or high-risk individuals.

Both involve costs to the individual (time, travel, and payment) and health services (manpower, subsidies, treatment, and follow-up).

These components successfully implemented in developed countries for the early detection and treatment of breast cancer are costly and may also involve potential undesired harm to the individual.[3] In developing countries the implementation has been erratic owing to resource limitations.

Screening programmes

Screening tests include mammography, clinical breast examination (CBE) and breast self-examination (BSE).

Mammography

Mammography is the most commonly used screening test in developed countries. It is expensive and complex, requiring substantial financial and manpower resources. Additional cost (financial and human) is incurred when further investigations in women with abnormal mammograms do not detect any evidence of breast cancer.

The exact benefit of screening mammography and/or CBE in decreasing breast cancer mortality is unknown owing to the inconsistency of results across studies. The results range from no reduction in breast cancer mortality to a 30% reduction among women aged 50 years and older.[4]

Lack of resources and infrastructure in developing countries render this strategy untenable; where it has been attempted, the implementation has been inconsistent and unsustainable. There is also a prevailing feeling that mammography is unable to detect cancers with a poor prognosis that cannot be detected by a good CBE.

Clinical breast examination

CBE refers to a breast examination performed by a trained health care worker. The Canadian breast screening trials have demonstrated similar results when comparing CBE alone with CBE and mammography.[5] These results are encouraging; consequently CBE may assume particular importance in resource-strapped countries where mammography is unavailable or expensive and disease is at an advanced stage at the time of diagnosis.

Breast self-examination

Systematic BSE has been recommended for over 70 years, despite lack of compelling evidence of its efficacy in reducing deaths from breast cancer. Numerous non-randomised trials have produced conflicting results.[6] The notion that BSE is not efficacious seems unwarranted, as many studies have demonstrated that breast cancers detected by BSE are diagnosed at an earlier stage and are smaller than in women who do not practise BSE. It is unclear whether this reduces mortality from breast cancer. A further contentious issue relates to what constitutes a competent BSE and how often it should be performed. Variations, inconsistency and complexity in suggested techniques of self-examination have been considerable and confusing.[7]

The Shanghai trial[8] has provided high-quality evidence of the lack of effect of teaching BSE. In this large randomised trial between 1989 and 1991, 266 064 female employees of the Shanghai textile industry between the ages of 30 and 64 years were randomised to the intervention group receiving instruction about BSE or to the control group. Intervention included intensive regular instruction on BSE both individually and in groups, multiple reminders to perform BSE, and reinforcement practice sessions every 6 months for 5 years. No screening was offered to women in the control group. Follow-up rates were high. The results after 10 - 11 years showed that the proportion of deaths due to breast cancer and the cumulative mortality were almost identical in both groups; the number of breast cancers was similar in both groups; and the size and stage of the cancers did not differ appreciably. Of note is that the women in the BSE group had more breast biopsies and diagnoses of benign lesions than women in the control group. The investigators concluded that intensive instruction in BSE did not reduce mortality from breast cancer. Furthermore, in the absence of mammography, BSE would be unlikely to reduce mortality from breast cancer. Women choosing to practise BSE must be informed that its efficacy is unproven and that their chances of having a benign breast biopsy may be increased.

Only a small number of women regularly examine their breasts. Surveys in many Western countries in the 1990s revealed that, despite high levels of awareness, very few women ever perform BSE (including only 21% of female doctors in the USA). The reasons range from anxiety related to the possibility of finding something suspicious, and many false-positive results, to unnecessary invasive procedures.

In lieu of BSE, women should be taught to be 'breast aware' and report unusual breast changes promptly.

It has been estimated that a mammography screening service in South Africa would cost approximately one billion rand. This is unaffordable in a country faced with more pressing challenges, and unattainable owing to a lack of skilled mammo-radiologists. A nurse-based clinical service, on the other hand, will cost 42 million rand for the entire country.[9]

One of the most basic cancer screening tools worth pursuing in developing countries is health education, e.g. that if cancer is diagnosed early it is more

likely to respond to effective treatment; and opportunities for early diagnosis via the provision of readily accessible, affordable services. Increasing awareness by the population and health care workers with regard to the early signs of cancer, empowering the public to seek early medical attention, and gearing health personnel towards early diagnosis of common forms of cancer, are tenable (and probably sustainable) means of early detection.

Initiatives in developing countries[10]

Researchers in developing countries have been seeking alternative screening programmes that are both tenable and sustainable. Focus has been on the basic screening model of health education and opportunities for early diagnosis, largely based on CBE performed by trained health care workers.

The first randomised trial of early detection of breast cancer comparing screening by CBE with no screening commenced in 1997 in Mumbai, India. A total of 75 000 women were randomly assigned to a study group and a control group. Both groups received health education about breast awareness. In the study group health workers conducted CBEs and referred those with suspicious findings for further investigation. After the first round of screening the incidence of breast cancer was found to be three times higher in the study group than in the control group. Although fewer cancers were detected after the second round of screening, these more often occurred in the screened than in the control group. The conclusions were that screening by clinical examination can be efficiently implemented and is acceptable to the population. However, many women need to be screened to detect one cancer.

Egypt was the first African country to pilot this model in Cairo in 2000. The first phase recruited 5 000 women between the ages of 35 and 64 years. All the women completed a questionnaire, and then had a CBE by young female doctors who had received special training. They also received health education on the importance of breast care and were shown how to perform a BSE. Those with an abnormal finding at clinical examination were referred for mammography and/or biopsy. In this group 8 per 1 000 women were diagnosed with cancer. This pilot study confirmed that young female doctors can detect breast cancer by clinical screening.

Other developing countries (Yemen, Kuwait and Sudan) plan to test this method of screening.

The common objective of these screening programmes is early detection of cancer and the end-point is reduction in mortality. The effectiveness of early detection has not yet been demonstrated in low-income countries, as to date none of these pilot studies has shown an impact on mortality reduction. Only a study with sufficient power will show a mortality benefit; this may require a meta-analysis embracing India, Egypt, the Yemen and Sudan. If this model is found to detect cancer early and save lives, it could prove to be a cheaper yet equally effective alternative to mammography in developing countries.[10]

Implementing early detection programmes

The decision to implement early detection programmes should be evidence based and only follow after certain prerequisites are known. These include the cancer burden (the disease should be a common form of cancer with associated high morbidity and/or mortality), whether early detection is capable of reducing morbidity and mortality, the proportion presenting with potentially curable cancer, whether early detection programmes are already in place, and the level of development of health services. If findings suggest that the majority of cancers present at an advanced stage, there is a definite need to promote early diagnosis and referral.[3] However, substantial cost is involved and in low-resource settings it may become an issue if screening programmes are introduced on a larger scale.

Furthermore, if the aim of these programmes is to reduce mortality from cancer, they must form part of a wider cancer control strategy offering appropriate diagnostic procedures; accessible, effective treatment (free or heavily subsidised in low-income countries); and follow-up. This requires integration of and further investment in health service infrastructure to cater for additional cases resulting from early detection.

In resource-strapped countries it is initially more cost-effective to concentrate on early diagnosis rather than on screening. The Global Summit Early Detection Panel recommended that early detection efforts be focused on the education of patients and physicians, and increasing general social awareness about breast cancer.[11] The success of these programmes, as initially measured by the diagnosis of cancers at less advanced stages and later by trends in decreased mortality, relies on the infrastructure to diagnose and treat breast cancer, as well as the participation rate of the population. This is influenced by cultural factors in many developing countries. Ignorance, fear and family pressures must be addressed to ensure that women attend for examination and follow-up care.

Summary

- Any cancer control strategy must be guided by the needs of the country and be resource appropriate for that country.
- The success of any screening programme relies on test procedures that are safe, acceptable and inexpensive; the attendance of the target population; and affordable cost – both medical and economic. These, in turn, rely on research based on demographic, economic and epidemiological data.
- In developing countries the rhetoric of BSE should be modified, rather than debunked. In these countries there are high rates of late presentation due to cultural and economic factors. BSE could be regarded as one facet towards an expanding spectrum of initiatives to empower patients. Therefore BSE could provide an entry strategy towards the gradual improvement of cancer awareness and outcomes. It is hoped that this will result in the end-point of smaller tumour size at presentation and more conservative surgery.

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Herceptin

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The incorporation of the name Herceptin into everyday medical (and lay) parlance is witness to a quiet revolution that is taking place in the treatment of not only breast cancer, but other cancers and indeed a number of other, unrelated, conditions. While medical history is littered with fortuitous finds, Herceptin is not one of them. This drug was developed according to rational, scientific principles, and was designed as one of the elusive 'silver bullets' – a drug that targets specific cancer cells only, and has no effect on surrounding tissue.

What is Herceptin?

- Herceptin is trastuzumab, a humanised, monoclonal antibody that binds to the HER2 receptor.

What is the HER2 receptor?

- The HER2 receptor is a trans-membrane tyrosine kinase receptor that normally regulates cell growth and survival (as well as adhesion, migration, differentiation and other cellular responses).
- Over-expression of the HER2 receptor occurs in 20 - 30% of invasive breast cancers. Patients with breast cancers that over-express the receptor, or have a high copy number of the gene, have a decreased overall survival (Fig. 1) (see section on Herceptin in metastatic disease).
- Over-expression of the HER2 receptor is inversely correlated with expression of hormone receptors.
- It is also found in normal cardiac muscle.

How is this tested for?

- Immunohistochemistry (IHC), looking for receptor over-expression and fluorescence *in situ* hybridisation (FISH), looking for gene copy number, are the most common methods to determine HER2 status in the clinical setting. The indicators of increased HER2 production are given in Fig. 2.
- Although there is no ultimate and globally accepted gold standard, both assays are accepted as references once they are validated.
- However, non-standardised, non-validated, cheaper in-house reagents are frequently used.
- Many investigators have reported a high concordance between FISH and IHC in other countries, but in South Africa standardisation and validation of testing are still lacking.

Fig. 1. HER2-positive status shortens survival.

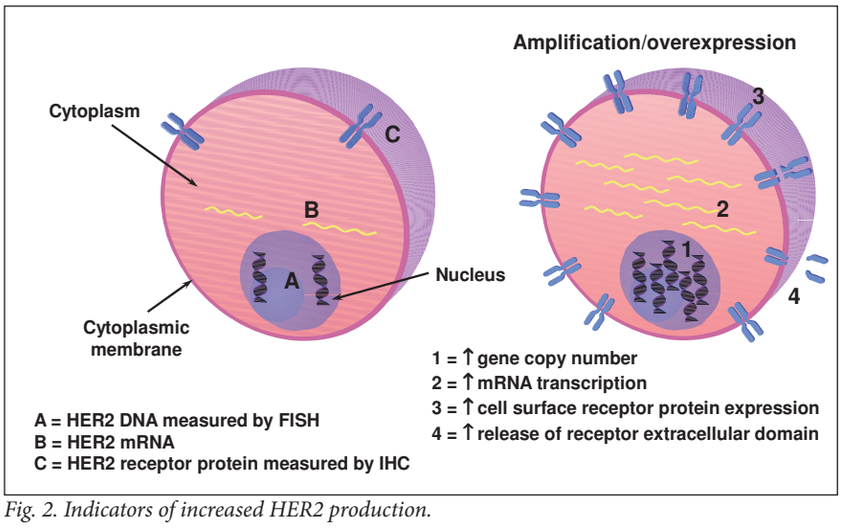

Fig. 2. Indicators of increased HER2 production.

Possible mechanisms of action of Herceptin

- Blocks the HER2 receptor.
- Accelerates the degradation of HER2 protein receptors.
- Enlists immune cells to attack and kill tumour target cells via antibody-dependent cell-mediated cytotoxicity.
- Down-regulates vascular endothelial growth factor and other angiogenic factors.

What we know about Herceptin in metastatic disease

- The pivotal trial was published in 2001 in the *New England Journal of Medicine*, randomising 496 patients to chemotherapy alone, or chemotherapy plus Herceptin.
- Patients who progressed on chemotherapy alone were allowed to cross over to receive Herceptin. Despite this, patients who received Herceptin upfront had increased survival at 1 year (Fig. 3).
- Herceptin has subsequently been trialed together with many different chemotherapy regimens. It is contraindicated concurrently with (but not after) anthracyclines, because of unacceptable cardiac toxicity.
- Currently, Herceptin is prescribed in the metastatic setting 3-weekly until disease progression.
- Herceptin appears ineffective at treating brain metastases, as it does not cross the blood-brain barrier.

Herceptin in early breast cancer

- Four large trials comparing chemotherapy alone to chemotherapy plus Herceptin (given either after or concurrently with chemotherapy for 1 - 2 years) have been published.

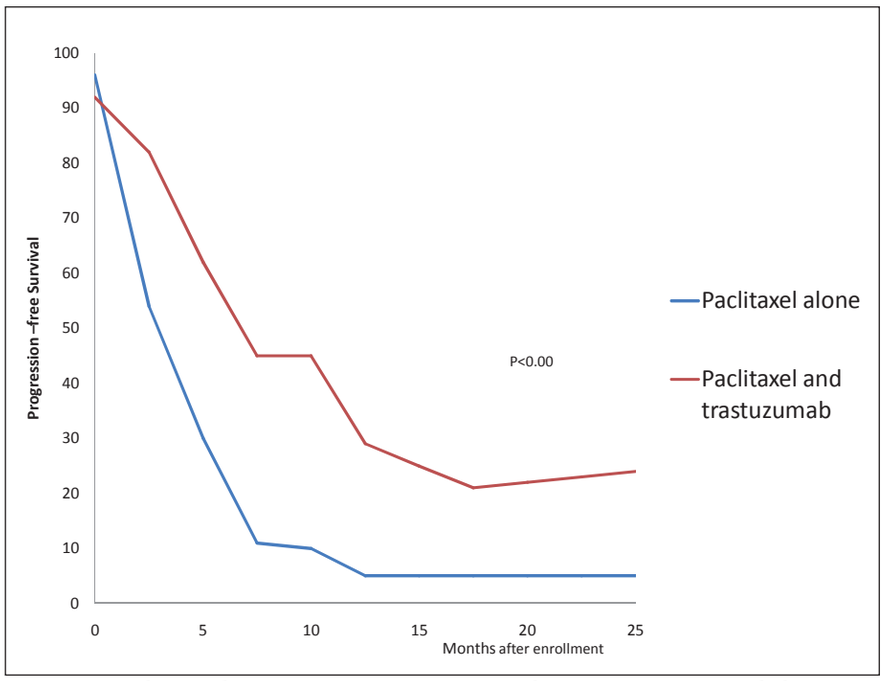

Fig. 3. Increased survival seen in HER2-positive metastatic breast cancer patients with the addition of Herceptin.

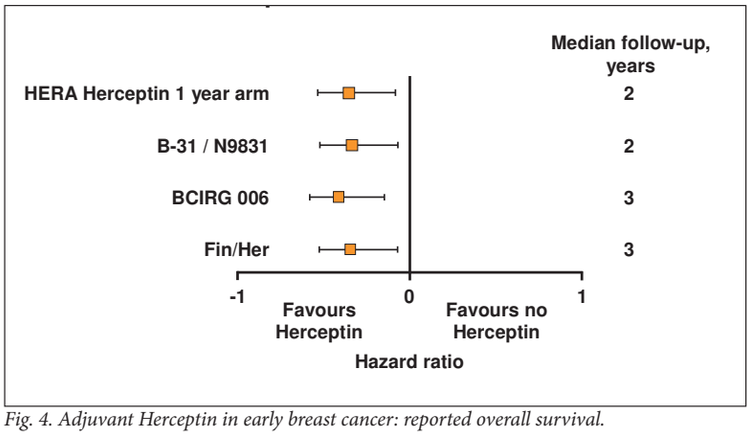

Fig. 4. Adjuvant Herceptin in early breast cancer: reported overall survival.

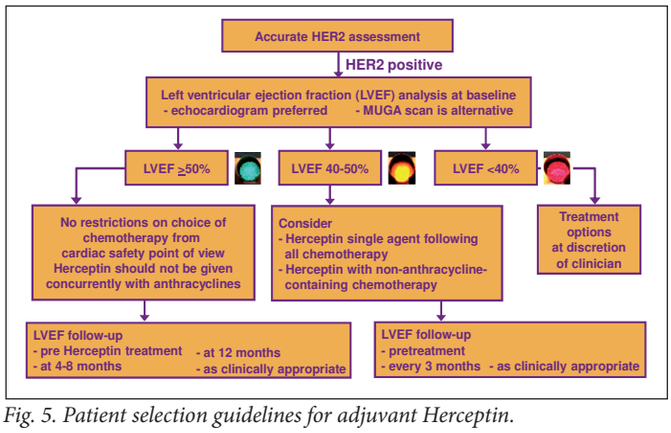

Fig. 5. Patient selection guidelines for adjuvant Herceptin.

Table I. Herceptin toxicity

Side-effect	Treatment
Acute hypersensitivity (<10%)	Antihistamines, anti-inflammatories, steroids
CCF (5 - 10% depending on diagnostic criteria)	Usually resolves on stopping Herceptin. Treatable with afterload reduction, glycosides and diuretics
Nausea (extremely rare)	Metoclopramide
Myelosuppression (extremely rare)	Granulocyte colony-stimulating factors

- One small trial (FinHer), which looked at chemotherapy versus chemotherapy concurrent with 9 weekly doses of Herceptin, has been published.
- All have shown improved survival (possibly Herceptin given concurrently with chemotherapy will prove better than Herceptin alone) (Fig. 4).

International recommendations are that Herceptin be given either together with, or after the completion of, chemotherapy, for 1 year. However, in South Africa, cost constraints have meant that the majority of medical aid plans will authorise Herceptin for 9 weeks only, according to the FinHer protocol. While these data look very exciting, it is important to be aware that the total number of patients given Herceptin, and the standard chemotherapy arm in the FinHer trial, number less than 100.

Table I lists the possible side-effects of Herceptin as well as the recommended treatment. Fig. 5 gives patient selection guidelines for adjuvant Herceptin.

Further reading

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Lapatinib (Tykerb)

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Since the advent of DNA cloning and sequencing in the mid 1970s it has become clear that a large family of protein kinases exists which mediates most signal transduction in the human cell. Almost all human protein kinases have now been identified (total 518) and constitute 1.7% of all human genes. To use a computer analogy, protein kinases are the 'DOS of the cell' and control virtually all cellular processes including metabolism, transcription, cell cycle progression, cytoskeletal rearrangement, cell movement, apoptosis, and differentiation. The paradigm is now of the 'human kinome'. A full understanding of the structure and function and interactions of all the protein kinases is a long way off.

One large subgroup is the tyrosine kinases (TKs), which enzymatically transfer phosphate to tyrosine residues (protein phosphorylation) and play a critical role in intracellular communication along what

are often called cytokine cascades. There are two main classes:

- receptor TKs, which are large transmembrane proteins with a catalytic intracellular kinase domain
- non-receptor TKs in the cytosol, nucleus, and on the inner surface of the cell membrane.

The tyrosine kinases are often dysregulated in malignancy. The epidermal growth factor receptor (EGFR) family contains the EGFR, HER, VEGFR, PDGFR. They are transmembrane TKs derived from closely related genes and are all important in cell signalling and function.

Approximately 20% of breast cancers have a constitutive over-expression of the HER2 (ErbB2) receptor with resultant aberrant signalling and an aggressive phenotype of breast cancer. The monoclonal antibody trastuzumab (Herceptin), which targets the extracellular domain on the HER2 receptor, has been a major advance with real benefits seen in the clinic.

Another approach has been to target the intracellular domain of these tyrosine kinases. Lapatinib (Tykerb) is an oral small molecule that reversibly and potently inhibits the receptor TK activity of both the EGFR (ErbB1) and HER2 receptors. Lapatinib has now been through preclinical studies and phase 1, 2 and 3 clinical studies and has shown impressive activity in HER2-positive metastatic breast cancer, both first-line and in heavily pretreated patients, both as a single agent and in combination with standard chemotherapy agents. Toxicity is generally mild (grade 1/2), with the most common adverse reaction being diarrhoea (46%) and rash (30%) – these are predictable and are managed proactively. Serious toxicity (grade 3/4) is uncommon (<1%).

The most exciting aspect is the fact that lapatinib is really the first of many targeted intracellular agents in breast cancer and already numerous other tyrosine kinase inhibitors aimed at many aspects of the cytokine cascade are in clinical development and being studied in breast cancer. There is a long way to go to a full understanding, but the era of truly targeted anti-cancer therapy has dawned.

Single Suture

Toys as distractions for burn victims

Children who need burn dressings changed suffer excruciating pain and doctors often use television, movies or computer games to distract them from the pain. Now an interactive 'toy' has been shown to be even more effective in reducing the pain reported by children, according to the toy's designer – Sam Bucolo of the Queensland University of Technology in Brisbane, Australia.

The toy is called Ditto and is a circular touch-screen unit that maximises sensory distraction by using motion sensors and vibration feedback. The child tilts the gadget to navigate through a story or a game as he or she searches for hidden objects along the way. The child can even look underneath things by tipping the Ditto upside down.

New Scientist 2008; 6 September: p. 27.

Single Suture

Fish oil doesn't improve cognitive function in the elderly

In a study that is good news for endangered fish stocks, a team in The Netherlands have found that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation does not improve cognitive performance in the elderly.

They investigated the effect in a double-blind placebo-controlled trial involving 302 cognitively healthy individuals aged 65 and older for 26 weeks. Cognitive performance was assessed using an extensive neuropsychological test battery that included the cognitive domains of attention, sensorimotor speed, memory, and executive function.

The mean age of the participants was 70 years, and 55% were male. Plasma concentrations of EPA-DHA increased by 238% in the high-dose and 51% in the low-dose fish oil group compared with placebo, reflecting excellent compliance. Baseline scores on the cognitive tests were comparable in the three groups. Overall, there were no significant differential changes in any of the cognitive domains for either low-dose or high-dose fish oil supplementation compared with placebo.

Neurology 2008; 71: 430.