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BREAST UPDATE

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Angelina Jolie's decision in May 2013 to undergo genetic testing for the BRCA1 gene, and to subsequently undergo bilateral prophylactic mastectomies produced a worldwide increase in the number of women seeking advice about genetic testing and risk reduction surgery, as well as the number of women with newly diagnosed breast cancer opting for a bilateral mastectomy.

Why are women choosing to have more extensive surgery, reversing the trend of the 1980's and 90's to do breast conserving surgery, and is this a reasonable option ?

Angelina Jolie did not have breast cancer, but did have the BRCA1 gene, as did her mother who died from breast cancer. The risk of a woman without genetic risk factors developing breast cancer by the age of 80 is 8-12%. The risk in women with the BRCA1 gene rises to 65% by age 70, and the risk of developing ovarian cancer is 39%. In women with the BRCA 2 gene the risk is 45% for breast cancer and 17% for ovarian cancer.

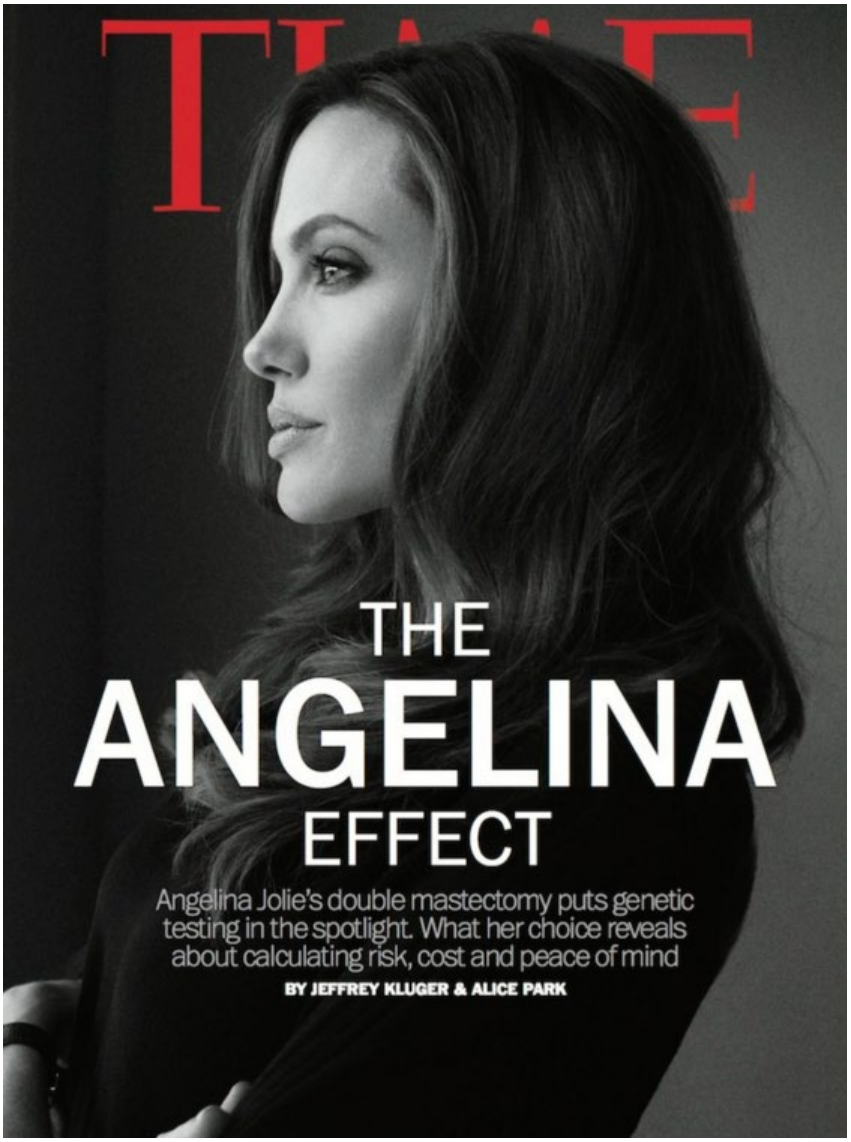
As only 5 % of women with breast cancer have a genetic mutation, most of the women choosing to have a bilateral mastectomy are having it for other reasons, the most common being the perception that it will be a better procedure to deal long term with the cancer.

For women diagnosed with breast cancer there is an increased risk of developing cancer in the other breast but the risk is low, increasing by 0,6% per year after the first diagnosis of cancer was made. A woman diagnosed with breast cancer at age 40 would thus have an 18% chance of developing cancer in the other breast by age 70.

Long term survival depends on the characteristics of the first cancer and whether metastases develop, rather than if a new cancer develops in the other breast. **A contralateral prophylactic mastectomy has thus not been shown to improve long term survival rates.** Many women feel, however, that a contralateral mastectomy will give them peace of mind as they will not need to have as intense follow up breast imaging with the inevitable accompanying anxiety . It is important to note that not all of the breast tissue can be removed and even though the amount remaining is very small and the risk of developing a new cancer is also reduced, follow up imaging is still required.

The trend towards breast conserving surgery (wide local excision/lumpectomy) after 1980 was due to research showing, that combined with radiotherapy, it gave as good long term survival rates as a mastectomy, and was less deforming. Breast reconstruction techniques have improved vastly and women have much more confidence in the cosmetic outcome. As a result, more patients are opting for mastectomy and reconstruction over WLE with radiotherapy. It is possible for the plastic surgeon to achieve more symmetry if reconstruction of both sides is done at the same time and this is termed 'oncoplastic symmetrization.'

In summary, a contralateral prophylactic mastectomy does not improve long term survival in breast cancer in women without a genetic risk. If a patient still prefers this option, the pros and cons must be discussed in detail. Only women with major risk factors for breast carcinoma should be considered for prophylactic mastectomy after having had genetic counselling and testing.



The American Breast Cancer Registry *reported that the percentage of women in the 40 to 50 year agegroup opting for a contralateral prophylactic mastectomy in addition to the mastectomy for their breast cancer had increased from 2.2% in 1998 to 11% in 2011. Some institutions are reporting that the Jolie effect has doubled this, particularly in the USA.*

BREAST **RECONSTRUCTION**

Breast reconstruction is a surgical procedure that restores shape to the breast after mastectomy for breast cancer. Reconstruction is increasingly used following prophylactic mastectomy. There are a number of options for breast reconstruction. These include the use of a breast implant, or a tissue flap, or a combination of both.

IMPLANT RECONSTRUCTION

TYPES OF IMPLANTS

Implants have a silicone shell filled with either silicone gel or salt water (saline).

TYPES OF IMPLANT SURGERY

One-stage immediate breast reconstruction. The final implant is put in at the same time as the mastectomy. The breast implant is inserted under the pectoralis muscle. Occasionally a special mesh (for example acellular matrix such as Strattice™) is used to increase the space available and to hold the muscle in place.

Two-stage reconstruction: a temporary tissue expander is put in after the mastectomy. The expander is slowly expanded to the desired size to allow the skin flaps to stretch over 2 to 3 months. It is used when the surgeon believes that the mastectomy skin flaps are not healthy enough to support a full-sized implant right away. After full expansion the expander is removed and a permanent implant inserted. At this second stage, symmetry with the opposite breast, is obtained. The opposite breast can either be reduced, lifted or even augmented, to match the reconstructed breast. The two-stage reconstruction allows time for other treatment options. If radiation therapy is needed, the final placement of the implant is put off until radiation treatment is complete.

Prosthetic reconstruction is the most popular procedure performed world-wide. The procedure takes about 2 hours. There is no associated donor site and the operation is less invasive when compared with the other options. Modern silicone can replicate normal breast tissue and gives a good cosmetic result. Silicone is however, firmer and harder, and the breast does not feel the same or move in the same manner as a normal breast.

TISSUE FLAP PROCEDURES

These procedures use tissue taken from the patient's own body and consist of fatty tissue, or muscle and the overlying skin. Typical donor sites are the lower abdomen, back, thighs, or buttocks. The most common types of tissue flap procedures are from the lower abdomen (called TRAM [transverse rectus abdominis muscle] flap or DIEP [deep inferior epigastric perforator flap]), and the latissimus dorsi flap, which uses tissue from the upper back.

Recent studies show that silicone implants do not increase the risk of immune system problems. Newer types use thicker silicone gel, called cohesive gel and are known as form-stable implants, meaning that they keep their shape even if the cover is cut or broken.

DISADVANTAGES

- These operations leave 2 surgical sites and scars – one where the tissue was taken and one on the reconstructed breast.
- The scars fade over time, but never go away
- There can be donor site problems such as abdominal hernias and muscle damage or weakness.
- There can also be differences in the size and shape of the breasts.
- Because healthy blood vessels are needed for the tissue's blood supply flap procedures can be more problematic in smokers, and in women who have uncontrolled diabetes, vascular disease, or connective tissue diseases.
- Flaps require more surgery and it takes longer to recover.

ADVANTAGES

- They do not require prostheses and can give a very satisfactory result.
- When they work well, they look more natural and behave more like the rest of your body. For instance, they may enlarge or shrink as you gain or lose weight.
- There's also no worry about implant replacement.

BREAST CANCER – SCREENING AND DIAGNOSIS

Breast cancer is very rare in young women. The incidence, however, increases with age, particularly from the age of 40. Many cancers are only detected with imaging and are not clinically apparent (screen detected breast cancer).

The value of screening for breast cancer and how often this should occur remains controversial. The American Cancer Association recommends routine annual screening mammography from the age of 40.

Women at high risk for developing breast cancer may require screening from an earlier age (strong family history of breast cancer, BRCA 1 or 2 gene positive). Screening should be commenced about 10 years before the age of onset of the breast cancer in the index case.

Annual screening mammography is recommended in women who have previously been diagnosed with breast cancer, are using HRT or have a strong family history or have other risk factors.

Diagnostic imaging is performed in women who are symptomatic. Examples include breast lump, nipple discharge, pain, change in size or appearance of the breast and nipple change.

An ultrasound of the breast is usually initially performed in women under the age of 30. They may still, however, require a mammogram. Women over the age of 30 would usually have a mammogram and an ultrasound.

BREAST CANCER CHANGES

Many women present to their doctor, complaining about a breast lump. It can be very difficult to distinguish between benign breast changes and a cancer clinically. Imaging of the breast with mammography and ultrasound is initially advised. Typically benign disease has a well circumscribed appearance on imaging whereas a cancer has an irregular/spiculated appearance.

FNAB/ core biopsies may still be indicated, depending on the clinical findings, as mammography and ultrasound do not detect all cancers, particularly in women with very dense breast tissue.

The majority of women who have mammograms, are asymptomatic. The radiological findings vary from microcalcifications (often found in ductal carcinoma in situ), mass lesions and just some distortion of the breast tissue.

Once these changes are detected, a biopsy is indicated. This is usually performed under ultrasound guidance, if the abnormality is visible. Otherwise biopsy is performed using stereotactic biopsy.

Screening MRI of the breasts is often performed in patients with a very strong family history, who are BRCA 1 or 2 gene positive and in women who may have had previous significant radiation to the chest. Some patients who are diagnosed with breast cancer require an MRI scan to try and detect any other breast synchronous cancers and to assist in treatment planning.

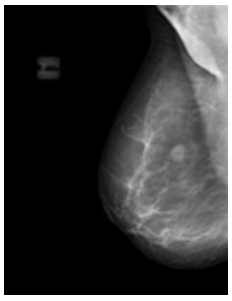
A team approach to assess and diagnose breast cancer involving the GP, Gynaecologist, Geneticist, Radiologist, Pathologist and Breast Surgeon is essential.

Breast cancer is one of the commonest forms of cancer in women. The lifetime risk of developing breast cancer is approximately 1 in 15.

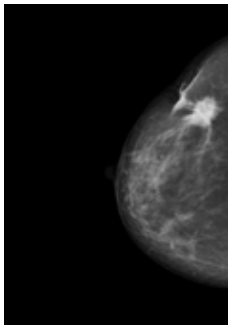
REMEMBER

- Mammography and ultrasound will detect most cancers but clinical examination of the breast is still important.
- Not all cancers can be detected with imaging.
- Perform a biopsy or refer the patient to a breast surgeon if a patient has a clinically suspicious lump, even if no abnormality is demonstarted with imaging.
- Watch out for the patient who present with a mastitis or a suspected breast abscess – an inflammatory cancer can present this way!

MAMMOGRAPHY



Fibroadenoma: well circumscribed



Breast Cancer: irregular/spiculated, "cancer the crab"

Present methods of screening for breast cancer, include:

- Breast self-examination
- Clinical breast examination (examination by a doctor)
- Mammography (which may include an ultrasound)
- MRI of the breasts.

TARGETED THERAPY FOR BREAST CANCER

Breast cancer is a heterogeneous disease encompassing multiple subgroups with differing molecular signatures, prognoses and responses to therapies.

Oestrogen Receptor Targeted Agents

Oestrogen receptors play an important role in cell proliferation, survival and invasion of ER positive breast cancer and treatments exploiting the oestrogen dependence of these tumours remains pivotal to the treatment of this disease.

The first agent that successfully targeted the oestrogen receptor was Tamoxifen, a selective oestrogen receptor modulator . It is also used in the adjuvant setting.

In premenopausal women with early-stage disease, 5-years of adjuvant tamoxifen reduces the risk of breast cancer recurrence by 39% and breast cancer mortality by 30%. The recent ATLAS trial, indicated that 10 years of tamoxifen was associated with a 25% lower recurrence rate and a 29% lower breast cancer mortality rate, compared with 5 years of tamoxifen treatment.

A number of other agents have also been developed. These include aromatase inhibitors (AI) that inhibit oestrogen production in postmenopausal women and fulvestrant that down-regulates the ER.

In postmenopausal women with early stage disease, multiple large adjuvant trials have demonstrated that monotherapy with an AI for 5 years or a switching strategy (AI to tamoxifen or tamoxifen to AI, total duration of therapy of 5 years) is superior to tamoxifen alone.

In the metastatic setting, aromatase inhibitors have been shown to improve overall survival compared with tamoxifen in postmenopausal women.

Menopausal status, cost, toxicity and acquired resistance determines the choice and sequence of use of these agents.

HER2-Targeted Agents

The Her2 gene is amplified resulting in over-expression of the Her2 receptor in approximately 18-20% of breast cancers. This promotes cell growth and survival and is thus associated with a higher risk of relapse and poorer survival.

Trastuzumab/Herceptin is a monoclonal antibody that targets the Her2 receptor. The benefit of adding trastuzumab in combination with chemotherapy has been demonstrated in studies of both adjuvant and metastatic patients.

Unfortunately, not all patients with Her2+ breast cancer respond to trastuzumab therapy (primary resistance) and in the metastatic setting, tumours that initially respond to trastuzumab often develop treatment resistance (acquired resistance).

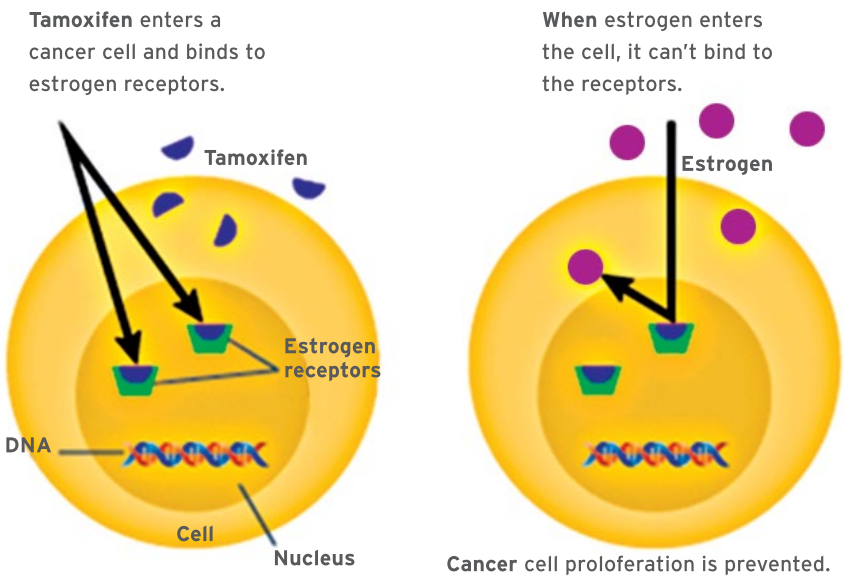
Agents such as lapatinib (a tyrosine kinase inhibitor directed against the Her2 receptor) have been developed that have activity in tumours resistant to trastuzumab.

Further agents developed such as TDM1, which is a trastuzumab-chemotherapy conjugate that allows the introduction of a cytotoxic agent directly into cells identified by their cell surface Her2 receptor, and Pertuzumab that targets the Her2 receptor at a different subdomain compared to trastuzumab are also available.

Triple Negative Breast Cancer (TNBC)

This is an aggressive disease lacking a therapeutic target. Much work is currently underway to both identify a target and to develop corresponding therapeutic agents.

Tamoxifen Blocks Estrogen Receptors



A greater understanding of the underlying biology of breast cancer has resulted in the development of therapeutic agents directed at specific targets. These therapies aim to block the growth and spread of cancer cells whilst limiting damage to healthy cells. Some of these agents have shown remarkable activity and have become standard of care in patients with breast cancer.

Breast cancer can be subdivided into 3 major subtypes:

- hormone receptor-positive tumours - expressing oestrogen and/or progesterone receptors (ER and PR)
- Her2 amplified breast cancer
- triple negative breast cancer - lacking expression of ER and PR receptors and Her2.

CONCLUSION

Current treatment options for breast cancer are moving toward nontoxic, potent targeted therapies that can be tailored to an individual patient's tumour. The development of resistance to all of these therapies is an ongoing challenge.