Breast density and cancer detection

Radiologically, the breast varies according to its tissue composition. Fat is radiographically translucent and appears dark on the film. Epithelium and stroma are radiographically opaque or dense and appear light on the film. The amount of radio-opaque tissue is referred to as the breast's density, and generally the higher a woman's breast density, the greater her risk of developing breast cancer.

As well as the increased risk, high breast density makes the interpretation of mammography films more difficult, so early lesions may go undetected, leading to poorer outcomes. It is difficult to say whether it is the breast density *per se* that increases the risk, or the delay in diagnosis because of the density that is the problem.

In an attempt to resolve the issue, Boyd *et al*. from Canada (*NEJM* 2007; 356: 227-236) noted the woman's breast density at her first mammography and then carefully tracked her risk of subsequent cancer using modern techniques. In this way they hoped to eliminate the detection problem and quantify the risk of high-density breast tissue. Their results were conclusive in that women with densities over 75% were five times more likely to develop breast cancer than those with densities below 10%.

Kerlikowske in an editorial (pp. 297-299) draws these data together with other risk factors, such as age, family history and BRCA status, and makes a plea for defining each woman's risk status and advising her about mammography accordingly. The density factor is a major risk and seems especially important in women aged 50 - 55 years. Better detection methods, possibly with digital as opposed to film screening, may help but the bottom line remains – the greater the breast density, the greater the risk.

Breast cancer and genes

The management of breast cancer depends on the type of tumour and its size or spread at discovery, but there are other markers of the aggressiveness, tumourigenic capacity or invasiveness. These characteristics are now being identified by studying the tumour's genetic profile. This process, using microarray RNA probes and polymerase chain reactions for gene profiling, allows the tumour's fingerprint or its invasiveness gene signature to be established.

Particular genes are found more or less commonly in each tumour and each one's prevalence is called its expression. Seldom is a single gene over-expressed to give a tumour its aggressive characteristics, but rather a set of hundreds of genes whose combined expression gives clues to its invasiveness.

One exceptional gene in breast cancer is the HER2 growth factor gene, which is over-expressed in about 20% of all breast tumours and is associated with a poor prognosis. This has attracted publicity because the drug company Roche has produced a human monoclonal antibody against a particular domain of the gene which is proving an effective but controversial addition to treatment. The antibody is trastuzumab (Herceptin), and the latest report after a 2-year follow-up has now been published (Smith *et al*., *Lancet* 2007; 309: 29-36).

It is controversial in that it is very expensive; it is only used in patients who have early HER2-positive disease; it has side-effects; and the long-term effects of monoclonal antibody therapy are not known. It is given after surgery, radiotherapy and/or chemotherapy every 3 weeks for at least 1 year. This is a formidable regimen against an aggressive tumour but the results are significant, with those receiving Herceptin having a hazard ratio for the risk of death of 0.66 compared with observation alone after 2 years of follow-up.

Generally, though, most information about a tumour is derived from measuring the expression of a set of its genes rather than a single gene. Which genes are present and the degree of their expression gives each neoplasm its invasiveness genetic signature.

This term invasiveness genetic signature (IGS) was coined by Liu *et al*. (*NEJM* 2007; 356: 217-226), who looked at the expression of 186 genes in breast cancer tumours and matched them to outcomes. They found it was not only the over-expression of some genes but the under-expression of others that was linked to invasiveness.

It has been a formidable task to identify which genes to check and how to link each to a positive or negative influence of invasiveness. The exact genes measured may change with experience, but the authors' results showed high correlations between each tumour's IGS and the woman's clinical outcome. They stratified the tumours into two groups according to their IGS and found 10-year metastasis-free survival rates were 81% in the good prognosis group, and 57% in the poor prognosis group. It also allowed them to identify 90% of patients in whom metastases would occur.

This is a major breakthrough in 'bench to bedside' research and moves us closer to delivering 'molecular

Maternal exercise and fetal growth

In developed countries, more women are overweight or obese than ever before. When these women conceive, how will their energy intake and expenditure affect the growth of their fetus? There are already indications that overweight women who do not exercise in pregnancy are delivering heavier babies with resultant increased risks of longer labours, shoulder dystocia and caesarean sections, as well as long-term implications for the child, adolescent and adult.

In a detailed study of women's exercise patterns in pregnancy, Perkins *et al.* from the US (*Obstet Gynecol* 2007; 109: 81-87) showed that in women less than 165 cm tall, the effect of physical activity on fetal growth was minimal. In taller women, presumably free of 'short-stature' constraints, the amount of exercise they took did have a pronounced effect on the babies' weight, an effect of 600 g between sedentary women and those who participated in regular aerobic exercise such as walking or jogging.

The authors believe that even vigorous physical activity has a positive effect in keeping fetal growth within normal limits and reducing intrapartum risks

Nitroglycerin and preterm labour

Preterm delivery remains the greatest cause of neonatal mortality and morbidity. The incidence is rising and means of treating it have been unable to show significant benefit to the neonate, immediate or long-term. However, a Canadian trial just published may change that (Smith *et al.*, *AJOG* 2007; 196: 37-39).

Treating women who had regular painful contractions with nitroglycerin between 24 and 32 weeks showed a delay in delivery of 11 days, compared with placebo. This overall result was highly significant and the treatment appeared most effective between 24 and 28 weeks. The nitroglycerin was delivered by transdermal patch and all patients were given steroids. Unsurprisingly, the delay resulted in measurably better neonatal outcomes in mortality and less lung disease. The number needed to treat was 10 to enjoy the overall improvements.

The trial was meticulous and the bottom line probably grossly understated the case when the authors say that the use of nitroglycerin 'may result in a major cost saving and longer-term health benefits'.

Watch this patch!

Sex workers

High-profile events remind the medical profession that they have obligations of protection. The publicity around the murder of five sex workers in one area of the UK spurred the *BMJ* to an enlightening editorial on the topic of protecting workers in the oldest profession.

They are no doubt an at-risk group, having the highest mortality of any section of women, and suffer victimisation and marginalisation. In addition, countries like the UK have antiquated laws discriminating against sex workers, which confuse morality and legislation. Goodyear and Cusick (*BMJ* 2007; 334: 52-53) assert that the law should protect workers, irrespective of the perceived morality of their trade, and that prostitution should be removed from criminal law.

They label the status quo 'unacceptable moral cowardice' and challenge politicians to follow the example of New Zealand, whose Prime Minister, Helen Clark, legislated to de-criminalise sex work in 2003. She said the move was for the welfare of a vulnerable group and not related to morality.

A correspondent to the *BMJ* takes the argument several steps further. Owens (2007; 334: 170) suggests that sex workers raise their client's self-esteem, especially if they come from the less fortunate strata of society. They could also use their skills in participating in the recovery of stroke victims. They certainly are masters, or the female equivalent, of non-verbal communication.

Menorrhagia management

The official definition of menorrhagia is the loss of more than 80 ml blood per regular cycle. The condition is debilitating although seldom life-threatening, and attitudes to the management have changed considerably from surgical to medical approaches, with the range of both possibilities expanding to the point where 'hysterectomy must be the last option' (Mayor, *BMJ* 2007; 334: 175).

The UK National Institute for Health and Clinical Excellence (NICE) produces Guidelines, and their suggestions for the management of heavy menstrual bleeding make interesting reading (www.nice.org.uk/CG44):

- where uterine pathology is excluded, the first-line treatment they recommend is the levonorgestrel-releasing intrauterine system
- second-line medical options are tranexamic acid, non-steroidal anti-inflammatory drugs or combined oral contraceptives, followed by norethisterone (15 mg daily cyclically from days 5 to 26) or depo-injectable progesterone.

The surgical options offer an array of possibilities, with dilatation and curettage firmly relegated to history:

- endometrial destruction by thermal ablation, resection, laser treatment and other means are all effective, but must be selected where fertility is not a major issue and where large fibroids are not symptomatic
- where fibroids are present, again there are medical and surgical approaches, with GNRH agonists and mifepristone versus uterine artery occlusion by embolisation or laparoscopic interruption using clips and/or diathermy
- myomectomy and hysterectomy are the classic surgical responses to fibroids that are causing symptoms, and again there are different approaches to the routes and instrumentation involved. Open laparotomy, laparoscopically-assisted procedures and the vaginal route are options that depend on operator skill and physical findings.

Specifically, the surgical management of fibroids has been compared with embolisation. A Scottish group undertook a randomised trial of embolisation versus open surgery for symptomatic fibroids and looked at economic factors, complications both short-term and a year later, plus quality of life outcomes (REST Investigators, *NEJM* 2007; 356: 360-370). Their results were encouraging, with similar outcomes at 12 months with symptom scores better in the surgery group but a shorter hospital stay and more rapid recovery in the embolisation group.

There seems little to choose between embolisation and open surgery for fibroids, but the possibility of pregnancy arises after embolisation and obviously hysterectomy ensures the end of bleeding problems.

Embolisation was first used in the early 1990s by Ravina to treat fibroids in women at high risk during surgery. Later it was employed to reduce fibroid volume prior to myomectomy to reduce blood loss, then used for primary treatment of fibroids. More than 100 000 procedures have been carried out since then, mainly in the US and Western Europe by radiologists. Via the femoral approach, catheter access is gained to each uterine artery and standardised embolic agents 500 - 700 µm in size are released to occlude the arteries – not only those thought to be supplying the fibroids (Tulandi, *NEJM* 2007; 356: 411-413). Complication rates are around 10% and reports on pregnancies thereafter indicate high miscarriage and preterm labour rates, so patients have to be fully informed about these possibilities. Where pregnancy is desired, and in infertile women, myomectomy still remains the treatment of choice.

Embolisation and laparoscopic occlusion of the uterine arteries have now been compared by Hald *et al*. (*Obstet Gynecol* 2007; 109: 20-27). They used a combination of occluding clips on the uterine arteries and the utero-ovarial ligaments were coagulated with bipolar forceps, thus reducing uterine perfusion to the collateral circulation.

Both techniques resulted in a greater than 50% reduction in menstrual flow as assessed by pictorial charts and patients' perceptions. Six months' follow-up also reflected comparable results, allowing the authors to state that laparoscopic occlusion is a promising method but at this stage should still be confined to expert experimental situations.

The last word is that hysterectomy remains a reasonable alternative and is, after all, definitive.

staging' of malignancies.

HIV

Survival

In countries where highly active antiretroviral therapy is freely available, the prognosis for a person living with HIV is similar to someone with type 1 diabetes (Lohse *et al.*, *Ann Intern Med* 2007; 146: 87-95). A Danish survey shows that HAART remains effective over time, despite fears of side-effects and multidrug resistance, so there is hope for HIV-positive people in countries that have the resources plus the political will.

Self-testing for HIV

The days of pre-test counselling prior to HIV testing are numbered. In fact, treating HIV as an exceptional disease makes it more special and probably increases stigmatisation, so most authorities no longer demand it. This emancipated attitude should be taken further to include self-testing for HIV, argues Frith (*BMJ* 2007; 334: 243-245).

The UK is pushing patient autonomy and asking people to take responsibility for their own health. This includes presenting themselves for screening, so surely the legalising of self-testing for HIV is compatible with such responsible behaviour? Suggestions that people would be incapable of carrying out the test or reading the results appear unfounded, judging from studies in the USA, and false-positives will, like all positive results, need professional confirmation.

The narrow view of HIV as a dreaded, prejudice-ridden disease needs to change and the UK government has the opportunity to come up with an enlightened response to HIV self-testing.

Mother-to-child transmission

Nevirapine is an important antiretroviral agent in the prevention of mother-to-child transmission of HIV. Not only is it central to the prevention of transmission peripartum, it is also used in combination with other drugs outside of pregnancy.

Where no interventions are used, MTC transmission rates are around 40% and a single dose of nevirapine will nearly halve transmission and is commonly the only means of reducing transmission in developing countries.

There are drawbacks to its use, not least of which are reports about resistant strains developing after a single dose at delivery. These reservations about its peripartum administration were researched by Lockman *et al*. working in Botswana (*NEJM* 2007; 356: 135-147) and indeed, compared with placebo, there was an increase in HIV mutations resistant to nevirapine in those mothers given the single dose at delivery.

This deleterious effect lasted 6 months, after which time the single-dose effect seemed to have worn off and antiretroviral regimens, including those with nevirapine, were just as efficacious in reducing viral loads. This needs to be taken into account when initiating nevirapine-containing regimens in postpartum women. The resistance is even higher in infants given peripartum nevirapine in whom the prophylaxis did not work. These children not only acquired HIV but developed nevirapine-resistant mutations at high levels.

Circumcision

It appears that circumcised men have about half the risk of uncircumcised men when it comes to acquiring HIV through vaginal intercourse. Two trials in Kenya and Uganda were halted when interim reports showed greater than 50% reduction in risk (Rohr, *BMJ* 2007; 334: 11). The Langerhans cells of the foreskin are particularly vulnerable to HIV penetration, which is thought to explain the protection offered by their removal.

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Editor