Breast screening

What advice should we give about routine breast screening?

Informed choice is the litany. But how should we – the supposedly informed – advise our patients? JASS has followed the debate with interest and has distilled the following from the *BMJ* 2006; **332** – Dixon pp. 499-500, Jorgensen and Gotzche pp. 538-541, Zackrisson *et al.* pp. 689-692, Moller and Davies pp 691-692, and letters pp. 727-728.

General risk

A woman's overall lifetime risk of *developing breast cancer* is 8%. This is the figure for Western populations with no additional risk factors such as a family history, BRCA 1 or 2 mutations or obesity. Various factors reduce the risk, such as pregnancies, exercise and keeping an average body mass index. The risk below the age of 40 is low and rises to a maximum between 50 and 65 years. Thereafter the risk decreases.

A woman's chance of *dying from breast cancer* is low. After the age of 50 she has a 2.5% chance of dying from the disease, with the obvious corollary that she has a 97.5% chance of dying from another cause.

What does screening do?

Routine screening does not reduce the risk of cancer. The risk is not changed by the process of mammography. This may seem self-evident, but two-thirds of women in a recent survey believed it did.

What does change is the chance of picking up early cancers. The earlier a cancer is detected the better the prognosis.

The process of mammography screening diagnoses early cancers before they would otherwise be detected. Any woman who avails herself of screening has this potential benefit, and it is an important benefit.

Statistically, if 250 women decided to be screened regularly, then one less of them would die from breast cancer compared with a group of 250 women who decided not to have themselves screened.

Early detecting means effective treatment, giving excellent results. Where population screening programmes have been introduced, death rates from breast cancer are falling.

The reductions in death rates because of screening are significant – about one- to two-thirds (28 - 65%, median 46% for UK figures), so there is *no doubt screening saves lives.*

Is there a downside to screening?

There are several negative aspects of screening, which are seldom discussed.

It is an unpleasant procedure.

It is an expensive procedure, which is a significant factor where the state or medical aid programmes do not cover the costs.

There are two real problems, which are now clearly quantified

Over-diagnosis

If a woman has a slow-growing neoplasm, that is not going to cause her morbidity, and certainly is not going to kill her, then there is little point in diagnosing it.

What benefit does this diagnosis carry for her?

If such a neoplasm is discovered, she becomes a cancer patient and is treated accordingly. She goes through a process that is mentally and physically traumatic for no benefit to her or her loved ones.

This over-diagnosis rate has now been calculated and is a significant figure. Taking the same 250 women who decide to have screening, 2 of them would be over-diagnosed and treated without benefit. The problem is we cannot predict which of the 3 women who are diagnosed with breast cancer are actually going to benefit and which are going to be treated 'unnecessarily'. This is the chance a woman takes when she opts to be screened. This is part of the informed decision making data.

Over-investigation

These are the investigations that are done, and the woman turns out not to have cancer. The so-called false positives, where the woman is asked to return for further tests. It is also known as the recall rate.

These rescans, ultrasounds, magnetic resonance imagings and biopsies are real possibilities for those who choose to be screened, and carry mental and physical distress. They are not uncommon, and estimates of recalls vary tremendously, depending on the quality of the equipment used and the skill of the staff. They also depend on how often the woman is scanned, what country's figure you quote, and her age.

Over a 10-year period a woman has about a 30 - 50% chance of being recalled. This is the chance a woman takes when she opts to be screened. This is part of the informed decision making data.

At what ages should women be screened?

This depends on who you believe.

The Americans believe and promote screening from 40 or 45 onwards, but cyclical variations increase over-investigation and the returns are more marginal. Over the age of 70 the positive returns decrease to a point of being non-beneficial.

Most countries advocate screening from 50 to 69 years. The frequency of screening is between 2 and 5 years, depending on resources.

Yes, screening saves lives – but it has what zealots call limitations, and sceptics call drawbacks.

Stretch and sweep

It appears that stretching the cervix and sweeping the membranes encourage labour. Clinicians have often 'stirred things up' by cervical massage or introducing a finger through the cervix and sweeping the membranes from their application to the lower segment. This action releases prostaglandins by breaking the chorio-decidual integrity and initiates or enhances labour.

Now a trial by de Miranda *et al.* (*BJOG* 2006; 113: 402-408) shows that sweeping the membranes in women at 41 weeks precipitates labour more often than leaving such women alone. They tried to avoid formal induction at 42 weeks by sweeping every 2 days until labour commenced, and had a control group in similar circumstances which they simply monitored. The group who were swept had a 23% post-term rate and the controls 41%, so the researchers recommend the serial procedure in uncomplicated post-dates circumstances.

There were no serious side-effects, and less than 20% of women said the procedure was painful, so it seems sweeping is safe and effective.

Chlorhexidine and pregnancy outcomes

Neonatal infection is a major source of morbidity and mortality, especially in the developing world. Of the 4 million neonatal deaths annually worldwide, the overwhelming majority occur in developing countries where resources to treat maternal infection are limited – and HIV more prevalent. To prevent mother-to-child bacterial infection during delivery, various antibacterial agents can be used vaginally either as creams, gels or washes.

Goldenberg *et al.* (*Obstet Gynecol* 2006; **107:** 1139-1146) reviewed the literature on chlorhexidine as a suitable vaginal disinfectant and/or neonatal skin wash over the last 50 years and came up with some promising information. It is effective against a broad spectrum of bacteria implicated in perinatal infections, such as group B streptococci, *K. pneumoniae* and *E. coli,* and it is non-toxic and non-irritating to mother, fetus or neonate. It is commercially available in the developing world as well as being cheap, costing less than 1 cent per application.

Chlorhexidine was originally developed as an antimalarial agent but was never used for that purpose. It is a highly cationic molecule that binds readily to negatively charged organic substrates and is slowly released over 24 hours or longer. It has a high safety profile with virtually no side-effects, and resistance reports are rare. There are wide concentrations used for vaginal examining lubricants in labour or as douches, ranging from 0.05% to 4%. There appears to be little systemic absorption and no generalised side-effects are known.

This review of all the trials published suggests that the greatest advantages of chlorhexidine use would be in situations with the highest sepsis rates, and unsurprisingly these are the places where randomised trials are least likely to be carried out. Studies from Egypt and Malawi yielded positive results, so maybe it is pragmatic to use it in such circumstances until new data confirm, or refute, its promising potential.

Previous caesarean section and future placental problems

In the broadest terms placenta praevia occurs in 0.5% and placental abruption in 1% of all pregnancies. Both carry high maternal and fetal risks, with abruption having a quoted perinatal mortality rate of over 100 per 1 000 in developed countries. Factors increasing the incidence of these conditions are important – such as smoking and especially a previous caesarean section.

Getahun *et al.* (*Obstet Gynecol* 2006; **107:** 771-776) report data quantifying the risk of a CS affecting placenta praevia and abruption chances in the next pregnancy. For placenta praevia the risk rises by 50%, compared with a vaginal birth the last time. Where the woman has had 2 previous CSs the risk doubles, giving rise to the notion of a 'dose-related' response. A short inter-pregnancy interval also increased the risk.

The risk of abruption occurring after a previous CS rises by 30% in the subsequent pregnancy over and above the background incidence (which itself is quoted at 15%). A short inter-pregnancy interval again raises the risk even higher.

Another concerning feature of increasing CS rates is the 'sharp and proportionate increase' in the incidence of placenta acreta that has followed CS trends. Estimates of a change from 1 in 20 000 deliveries to 1 in 500 in one survey are worrying (quoted by Resnick, pp. 752-754; see also Oyelese and Smulian, pp. 927-941).

Hot flushes

Temperature control is mediated via the thermo-regulatory centre in the brain. The mechanism is a basic redistribution of blood depending in core temperatures. If you feel hot, peripheral vasodilatation redirects blood flow to the skin where it cools, lowering core temperatures when it returns centrally. If you are cold, peripheral vasoconstriction plus shivering reduces surface blood cooling, conserving heat while the muscular activity of shivering generates warmth.

Oestrogen has a homeostatic effect on the thermo-regulatory centre, so when oestrogen levels drop in a menopausal woman the centre becomes labile and abnormal responses may be triggered by previously inconsequential temperature changes. The mechanism of action may be through adrenergic neurotransmission – which may explain why alpha-adrenergic agonists, like clonidine, can reduce flushing.

Another mechanism may be via serotonin neurotransmission, a theory supported by serotonin reuptake inhibitor efficacy in combating flushing. Whatever the final common pathway, most women experience hot flushes as their major symptom of oestrogen lack and are best treated by its replacement – a statement not in dispute. What is in dispute is the optimal duration of use for this indication and viable alternatives.

The Women's Health Initiative trial did nothing to answer this question, but the meta-analysis of Nelson *et al.* (*JAMA* 2006; **295:** 2057-2071) examines non-hormonal therapies with some stringency. They identify selective serotonin reuptake inhibitors, or their no-adrenaline counterparts, clonidine and gabapentin, as possibilities – but all are less effective than oestrogens. Complementary therapies are simply not considered useful at all.

The real problem is that the alternatives have not been monitored for any length of time for menopausal flushes. As Tica and Grady (pp. 2076-2078) remind us, the WHI study shows that the absolute risk of combined HRT is small, with less than one serious side effect per 1 000 women per year, so other preparations have to prove better safety records to counter their lesser efficacy – a situation that does not exist at present.

Oestrogen remains the best treatment for immediate menopausal symptoms with a clear risk/benefit profile and the non-hormonal alternatives are 'not optimal choices for most women'.

Over-assisted reproduction?

Of babies born in Europe, 2% are the result of assisted reproduction. This has helped countries of the European Union raise their birth rates, but these are still nowhere near population replacement levels (*Int J Androl* 2006; **29:** 12-16).

Surely one of the most bizarre stories about assisted reproduction must be that of Mrs Z from Russia, reported by the appropriately named Mr Leidig in the *BMJ* (2006; **332:** 627). She is a 55-year-old headmistress whose son was dying of cancer, so she persuaded doctors to freeze some of his semen before treatment was started. This was done, and 2 years after his eventual death she requested that his sperm be used to fertilise a donor egg and be implanted into a surrogate mother.

The child, Mrs Z's grandson, was born alive and well but the Russian authorities say she is too old to adopt him. The situation is further complicated by the fact that the sperm donor died 2 years ago and cannot be legally registered as the father. Since the oocyte was donated, the baby doesn't have a mother either, and since he has no parents he does not officially exist. The Registry Office wants to take him away from Mrs Z and place him in an orphanage. The case is going to court.

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