Breast cancer screening: one life saved at a cost of three overdiagnoses

An independent expert panel estimated the risks and benefits of screening for breast cancer in the UK, where women aged 50-70 years are invited for mammography every three years. It seems that for every 235 women who are invited for screening, or every 180 women who are screened, one life is saved, but three women are diagnosed and treated for a cancer that would not otherwise have become apparent in their lifetime (overdiagnosis).

Nearly a fifth of women who receive a diagnosis at screening are overdiagnosed, but it is impossible to know which ones. However, a woman who attends all invitations to mammography has only a 1% chance of being diagnosed with a cancer that would never have caused problems if she had not been screened.

These are best estimates from inadequate data, the panel emphasised. They reviewed the evidence available from the literature and heard testimonies from leading experts. Trial evidence was considered most valid, although only three of 10 available trials had been randomised properly. Together, the trials looked at nearly 700,000 women and were done between 1963 and 1991. Have improvements in treatment over the years caused problems if she had not been screened?

Effect of treatment on primary endpoints

Cancer drug shows promise for multiple sclerosis

Two manufacturer sponsored phase III trials suggest that alemtuzumab, an anti-CD52 monoclonal antibody that is licensed to treat leukaemia, may help control multiple sclerosis. Both trials lasted two years and compared alemtuzumab with interferon beta-1a, which is considered first line treatment. One trial looked at 563 patients who had not yet undergone treatment for multiple sclerosis, whereas the other trial looked at 840 people, some of whom had not responded to previous treatment with interferon beta-1a or glatiramer. The second trial tested 12 mg and 24 mg doses of alemtuzumab against interferon.

In the first trial, 22% (82/376) of patients who received alemtuzumab relapsed within two years, compared with 40% (75/187) of those who received interferon beta-1a. In the second trial, 35% (147/426) of patients who received 12 mg alemtuzumab relapsed compared with 51% (104/202) of those who received interferon beta-1a. No difference was seen in the first trial in sustained accumulation of disability (an increase of at least one point on the expanded disability status scale over six months). In the second trial, however, this outcome also improved with alemtuzumab.
Low eGFR and high albuminuria predict end stage kidney disease and death at all ages

It has been proposed that low estimated glomerular filtration rate (eGFR) and albuminuria in older people may be signs of ageing rather than disease worth treating. The literature is equivocal on this, in part because analytical approaches differ across studies. A consortium conducted a meta-analysis of individual patient data for more than 2 million people to help achieve consensus and aid the implementation of the recently revised classification of chronic kidney disease.

Data from 33 cohort studies done in the general population or people at high risk were included, as well as 13 cohort studies of people with chronic kidney disease. The studies spanned four continents and ages 18-108 years, and were carried out over four decades. Patients were followed up for up to 31 years (mean 5.8 years).

Overall, low glomerular filtration rates and high albuminuria were associated with an increased risk of dying and of end stage kidney disease, regardless of age.

In people without chronic kidney disease, the relative risk of dying with impaired eGFR decreased with age, but the absolute risk increased. For example, if eGFR of 45 mL/min/1.73 m² was compared with that of 80 mL/min/1.73 m², adjusted hazard ratios for age categories 8-54, 55-64, 65-74, and 75 years or more were 3.50, 2.21, 1.59, and 1.35, respectively. Absolute risk differences for these comparisons, however, were higher at older age: 9.0, 12.2, 13.3, and 27.2 excess deaths per 1000 person years, respectively.

In people with chronic kidney disease, age didn’t modify the association between markers of kidney function and death.

A linked editorial says that we therefore need to diagnose and treat chronic kidney disease in elderly people (doi:10.1001/jama.2012.30761), although the best way to do this is not entirely clear. We need new treatments, as well as testing of existing treatments in this population, which is likely to be most susceptible to the adverse effects of many drugs.

In people with chronic kidney disease, age and death at all ages

Potential adverse events are serious but treatable. People taking the drug need to be carefully monitored for thyroid disorders, which were seen in 16-19% of patients, as well as immune thrombocytopenia, seen in 1%. Nearly all patients had reactions associated with infusion, most commonly headache, rash, nausea, and fever. Two thirds of patients had infections, which were deemed serious in up to 2% of those taking the tested drug. Between 1% and 4% of participants taking alemtuzumab stopped taking it because of adverse events.

The drug has been used off label for a while, but recently the manufacturer withdrew it from EU and US markets and is seeking approval for treatment of relapsing multiple sclerosis. A linked editorial voices concern that when the drug reappears on the market it may be more expensive (doi:10.1016/S0140-6736(12)61768-1).

Zoledronic acid prevents fractures in men with osteoporosis

Zoledronic acid, a bisphosphonate given intravenously at a dose of 5 mg once a year, may reduce the risk of morphometric vertebral fractures in men by 67% compared with placebo. Morphometric fractures are identified by a change in shape of a bone, rather than from pain or other symptoms. About 40% of osteoporotic fractures in people over 50 years occur in men, yet until now trials that have included men have lacked clinical outcomes and only examined surrogates such as bone mineral density.

The two year placebo controlled trial looked at 1199 men aged 50-85 years, of whom three had hypogonadism and the rest had primary osteoporosis. All were given daily calcium and vitamin D supplements.

The primary outcome—one or more new morphometric vertebral fracture over 24 months—was seen in 4.9% (28/574) of men who took placebo versus 1.6% (9/553) of men given zoledronic acid (relative risk 0.33, 95% CI 0.16 to 0.70). Similar results were seen for the secondary outcome—one or more new morphometric vertebral fractures over 12 months (2.8% v 0.9% for placebo and the tested drug, respectively; 0.32, 0.12 to 0.88).

At two years, zoledronic acid reduced the risk of moderate to severe morphometric vertebral fractures by 63% (P=0.03); prevented changes in height (−2.2 v −4.5 mm with placebo; P=0.002); and improved surrogate markers such as bone mineral density at the lumbar spine, total hip, and femoral neck (P<0.05 for all). Clinically evident fractures were also less common with zoledronic acid, but this wasn’t significant (1% v 1.8% of men taking placebo; hazard ratio 0.6, 0.2 to 1.5).

Adverse events were seen in nine tenths of men given zoledronic acid and three quarters of men given placebo, most commonly fever, pain in joints and muscles, and headache. Nine men (1.5%) allocated zoledronic acid had a heart attack, compared with two men (0.3%) given placebo (P<0.05); the researchers deemed these events unrelated to the study drug.

Denosumab may reduce hypercalcaemia after transplantation for osteopetrosis

In osteopetrosis, defective osteoclasts impair bone resorption and excessive bone is formed. Haematopoietic stem cell transplantation is the only cure for this rare inherited disorder, but it is often followed by severe hypercalcaemia. A report of two cases, in children 3 and 12 years old, suggests that denosumab can help.

Both children developed hypercalcaemia within 12 days of transplantation, had low serum concentrations of parathyroid hormone, and had calcinosis on kidney ultrasound. Alkaline diuresis and treatment with calcitonin, corticosteroids, and pamidronate failed to improve hypercalcaemia in both patients before denosumab was given a chance. Serum concentrations of calcium returned to normal in both patients within two days, and normal kidney function followed suit.

The younger patient died of pulmonary hypertension—a known risk of transplantation—a month and a half later. Two years after surgery, the other patient still receives 5 mg of denosumab every four to seven weeks, which continues to normalise serum concentrations of calcium and kidney function.

Denosumab is normally used to treat osteoporosis and bone metastases.

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