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RISK ANALYSIS

A dense issue

Researchers are turning to breast density to help predict cancer risk.

BY DUNCAN GRAHAM-ROWE

Mammograms have often been at the centre of controversy, particularly when it comes to deciding the age at which screening should begin. Mammography screening involves regular X-rays of the breasts to look for tumours, but this exposure to ionizing radiation also carries a risk of causing cancer. So, in many countries, including the United Kingdom and Canada, screening is recommended for all women — but only from the age of 50 (see 'Early detection'). According to a 2009 study[1] that compared 20 strategies for mammography screening in use in the United States, a 50-year-old woman undergoing screening every two years is 15–23% less likely to die from breast cancer than an unscreened woman. For a 40-year-old woman, this figure drops to 1–6%.

There are several reasons for this disparity. For a start, breast cancer is less likely to develop in premenopausal women and women under 50 (see 'The hard facts', page 50). Younger women also tend to have more fibroglandular breast tissue, consisting of connective tissue, ducts and glands. This dense tissue appears white on a mammogram (in contrast to fat, which appears black), so it can be hard to spot the white shadows of tumours. Screening younger women, who have denser breasts, therefore increases the risk of a false-positive result — when a healthy woman is mistakenly suspected of having breast cancer. This overdiagnosis can lead to months or even years of invasive testing and associated emotional stress.

Despite these obstacles, in the United States, the National Cancer Institute recommends that screening start at 40. A high-profile patient lobby group, Are You Dense Advocacy, has also been influential in passing new laws in four US states. Under these laws, radiologists must provide patients with information about their breast tissue density based on their mammograms. The rationale behind the group's campaign, called Are You Dense?, is that dense tissue might be masking tumours. The group considers that any woman identified as having dense breast tissue should have the right to this medical information so she can seek additional screening with tools such as ultrasound and magnetic resonance imaging (MRI) — a move that has not been supported by the American College of Radiology.

Daniel Kopans, a radiologist at Harvard Medical School and Massachusetts General Hospital in Boston, says: "Radiologists have no problem providing women with an estimate of breast density. The problem lies in what to do with that information." He notes that dense tissue can decrease the sensitivity of screening, but it is unclear whether adding ultrasound and MRI will be beneficial. "The problem is that we do not know if these other tests will actually save lives." The utility of mammography has been proven in randomized, controlled trials, he says, but no such trials have been carried out for screening using MRI or ultrasound.

FROM DETECTING TO PREDICTING

The problem of density is compounded by numerous studies that support an association between a high breast density and a high risk of developing breast cancer[2]. But applying this knowledge for diagnostic purposes is fraught with uncertainty. One reason is that breast tissue density can vary dramatically from woman to woman, and within an individual woman depending on her age, says Norman Boyd, who studies breast cancer prevention strategies at the University of Toronto in Canada. This makes the range of 'normal densities' too broad to be diagnostically useful for any one woman at any one point in her life.

Calculating breast density is no simple task either: it requires an accurate measurement of volume. Kopans says it is impossible to determine the volume of dense tissue in the breast by using traditional two-dimensional mammograms, without additional information (which has not been collected in studies so far). He compares the task to looking at the front of a hedge and trying to work out how deep it is. Another problem is that to work out the proportion of dense tissue in a breast, radiologists need to know the total breast volume, but there is no way to accurately establish this. The breast does not end "at the edge of the image since the entire breast can never be pulled into the machine", Kopans says.

To address these issues, Boyd's colleague Martin Yaffe, who works on digital imaging for cancer diagnosis at Sunnybrook Health Sciences Centre in Toronto, has developed an automated, objective approach to obtain an average value for breast density. This technique incorporates the thickness of the sample, the known characteristics of the X-rays emitted and X-ray absorption rates that have been calibrated for different tissues. The relative density is calculated for each pixel in the mammogram image, and these densities are combined to provide an overall value. Despite going to such an effort, Boyd and his colleagues found that this information conferred no advantage over two-dimensional measurements when predicting breast cancer risk[3].

What's more, the association between breast density and cancer risk is not clear cut. "The percentage of women with dense breasts decreases with increasing age," Kopans says. "If

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EARLY DETECTION

Testing time for screening

Early detection is widely thought to be one of the most effective ways to beat breast cancer. But the evidence supporting breast screening is in dispute — and has been for nearly a quarter of a century, since the world's first screening programme began. Mammography screening is used in many countries as the first line of defence against breast cancer in women who are otherwise not at high risk of developing the disease. And now, the United Kingdom, the first country to introduce such screening, might be the first to abandon it.

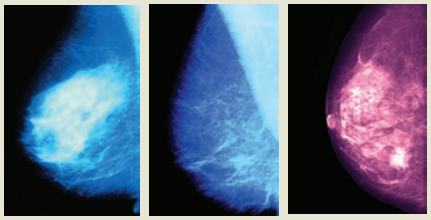
An independent review of the UK's National Health Service (NHS) breast screening programme, the first such review in the country, was announced in October 2011 by Mike Richards, the government's national cancer director. The same month, in an open letter published in *BMJ*[4], Richards explained that the purpose of the review was to put to rest criticisms of screening: namely, that the risks outweigh the benefits. The review is due to conclude by summer 2012, he says.

One problem with screening is that not all tumours are destined to kill. Peter Gøtzsche, director of the Nordic Cochrane Centre in Copenhagen, Denmark, and a long-time critic of screening, says that current screening methods indiscriminately pick up all tumours. Some of these would regress, he says, and others would grow so slowly that the patient would die from another cause.

The current UK screening review was triggered by a meta-analysis published in the well-regarded *Cochrane Database of Systematic Reviews* in January 2011 (ref. 5). This review collated and analysed the results of several clinical trials of breast screening, covering more than 600,000 women, and concluded that it is "not clear whether screening does more good than harm". According to the review, for every 2,000 women screened over a ten-year period, only 1 will have a prolonged life as a result. In addition, 10 healthy women will be diagnosed and treated unnecessarily, and a further 200 will suffer psychological distress because of false-positive findings. Gøtzsche, who led the review, adds: "Cancer screening creates cancer patients."

Many researchers critical of Gøtzsche are reluctant to speak openly. This is partly to avoid a public slanging match, but also out of fear of being perceived as partisan and losing credibility as objective collaborators with their peers. One expert, speaking on behalf of colleagues, agreed to talk to *Nature Outlook* only on the condition of anonymity.

Gøtzsche's detractors claim that the Cochrane analysis is flawed: the study deemed that several trials had been inadequately randomized and so gave them a lower weighting in the overall calculation. If the full results of these trials — as detailed in the Cochrane review — were included, then screening would be shown to save lives, they say. They also argue that there is no proof that tumours ever regress by themselves without treatment.



A young woman's breast (left) might conceal a tumour (right), unlike in older women (centre).

Gøtzsche argues that the outcome of the analysis was not affected by the weighting. He also cites evidence derived from Denmark's unique situation: regional variation in the health programme means that, for more than a decade, only 3 out of 16 regions (20% of the female population) were screened. "We are the only country in the world that has a control group," he says. His 2010 analysis of these screening data[6] showed that, over a ten-year period, breast cancer mortality was lower among women living in regions where screening was not provided than among those in screened regions.

Critics say that regional demographic variation could account for much, if not all, of this difference. Moreover, they argue that Gøtzsche fundamentally misunderstands the impact of screening: the introduction of screening should lead to a sharp increase in the incidence of breast cancer as new cases are quickly discovered and then to a decline with time. The Cochrane review assumed that these rates should eventually return to pre-screening levels; although it found that post-trial levels were lower, they did not fall back to baseline. But others argue that screening should lead to higher incidences that remain above baseline, partly because detecting cancers earlier will increase the incidence for a given age.

The argument has even brought into question the independence of the NHS review panel. Daniel Kopans, a radiologist at Harvard Medical School and Massachusetts General Hospital in Boston and a long-time champion of screening, points out that one of the five panel members, Doug Altman, sits on the advisory board of the Nordic Cochrane Centre. Altman's presence is a potential conflict of interest, he says. The panel "needs to objectively analyse the papers that have been generated by Gøtzsche and the Nordic Cochrane Centre".

Richards rebuffs these criticisms. "We chose people who are distinguished statisticians or breast cancer clinicians but who had never published on the topic of breast screening," he says. "Altman has indeed worked with the Nordic Cochrane Centre and been a co-author of papers with Gøtzsche, largely on the topic of the methodology of meta-analyses and not in relation to breast screening."

Breast cancer screening is expensive — costing nearly £100 million (about US$160 million) a year in the UK — and has a small risk of direct harm. So screening will always be under pressure to show a benefit. Gøtzsche maintains that scrapping screening will spare many women the anguish and harm caused by overdiagnosis. But Kopans and others strongly disagree. Abandoning screening in the UK would be tragic and felt worldwide, says Kopans. "I have little doubt that the death rate would increase once again." **D.G.-R.**

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density is a major risk, then why does the risk of breast cancer increase with increasing age?" From Boyd's perspective, a more useful diagnostic metric might be found in individual trends. The rate at which breast density decreases varies between individuals, and Boyd suspects this that rate might have predictive utility. Boyd and colleagues are preparing a paper investigating this relationship.

If Boyd is right and change in density can predict breast cancer risk, then dense tissue should no longer be thought of as interfering with the detection of tumours but rather as helping to improve detection. And for the first time there might be a way to calculate a woman's risk of breast cancer that is specific to the changes occurring in her body. ■

Duncan Graham-Rowe *is a freelance science writer based in Brighton, UK.*

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