# New drug combinations are not the solution

## Sweden's screening guru argues early detection is what works in breast cancer

➜ Emma Mason

If caught early, only the most aggressive breast cancers require any treatment beyond surgery, says **László Tabár**. He wants governments to provide effective population screening from the age of 40, and he would like medical oncologists to stop overtreating 'baby cancers' and concentrate on finding solutions to the small minority of hard-to-treat tumours.

In the black and white night of a Swedish winter, in a former dungeon that has long since shed its criminal associations and metamorphosed into a pleasant restaurant, László Tabár sets out his arguments in favour of population screening for breast cancer. His terms are as monochrome as the landscape and are based on the number three.

His professional life as professor of radiology at the University of Uppsala School of Medicine and medical director at the Department of Mammography, Falun Central Hospital, both in Sweden, involves three aspects: research, clinical practice and teaching. His philosophy on reducing the number of women dying from breast cancer centres on prevention, early diagnosis ('secondary prevention') and treatment. He believes that proper analysis of mammographic images of invasive breast cancers that are between 1 and 14 mm in size represents the third generation of prognostic factors for the disease – the first being based on size, grade, lymph node status etc, and the second on biological factors such as oestrogen/progesterone receptor status, HER2 status, S-phase fraction, etc.

Again and again, as I question him on the central issues of the breast cancer screening debate – Is population screening still justified? Should women as young as 40 be screened? Are intervals as short as 12–18 months really justified? Does regular screening result in overdiagnosis and overtreatment? – he urges me to return to the bigger picture and the three options a physician has to control a disease: primary prevention, early diagnosis and treatment.

Whereas for some cancers such as lung and cervical cancer, primary prevention plays the most important role (don't smoke, guard against HPV infection by condom use or the newly developed HPV vaccination), the picture is different for breast cancer, as primary prevention has a more limited effect. Women who keep fit, eat a balanced diet, don't become overweight and don't consume excessive amounts of alcohol can still develop breast cancer. So there is no effective primary prevention for this complex disease, which has many different subtypes. Treatment, particularly for advanced cancer, has a limited effect on mortality since it is given too late in the natural history

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of the disease. But early detection through mass population screening has proved to have a significant effect in reducing the number of women dying from breast cancer.

"Screening and proper treatment in the earliest phase of the disease is the most important thing to have happened in breast cancer research in the past 30 years," says Tabár. "In this time we have done so much more than in the past 3,000 years and it's very little to do with treatment of breast cancer and nothing to do with prevention. Detecting and surgically removing breast cancer in its non-palpable, *in situ* and 1–14 mm invasive phase has put an end to 3,000 years of disaster."

In 1977 the Kopparberg County Council in Sweden invited Tabár to move from his native Hungary to be director of the Kopparberg County mammographic screening programme. He moved with his family and has remained in Sweden ever since.

Tabár started work that same year on the randomised controlled trial of population-based screening, which was published in 1985 as the Swedish Two-County trial. This was the first randomised controlled trial to demonstrate successfully that invitation to mammography screening achieved a significant reduction in deaths from breast cancer.

The Swedish national mammography programme was set up as a consequence, and a number of other European countries then followed suit.

After publication of this study, mammography was offered to all women from the ages of 40 to 74 (so-called 'service screening'), and Tabár's research group analysed the results of service screening in the same two counties. This analysis included 210,000 women and was published in *The Lancet* in 2003. It compared breast cancer deaths in the 20 years before and after screening was introduced, and found that deaths from breast cancer dropped by 44% in women aged 40–69 who attended screening. Deaths among women aged 40–49 fell by 48%.

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## Outdated guidelines

Tabár is adamant that national mammographic screening programmes do not result in overdiagnosis, as alleged by critics of his studies and of population breast screening in general. He does acknowledge, however, that many women receive additional, unnecessary treatment when a mammogram detects a small, 'baby' tumour, because current treatment guidelines are based on treating palpable, advanced cancers.

"We need to prevent the big cancers by finding and removing them before they grow up," he says. "But by doing this, we also need to change the way we treat cancer. Just as we don't treat a newborn baby as we would treat a criminal grown-up, so we should not be treating these baby cancers in the same way as the advanced cancers that can go on to kill women."

This is where Tabár believes the 'dinosaurs' need to be jettisoned. "We need an entirely new generation of people who think differently, because this is an entirely new phase of a frightening disease where we have scientific evidence to show that when we succeed in finding a cancer in a phase when it's still localised at the place of origin – we catch the genie while it is still in the bottle – it's a surgical disease and not an oncologic disease, because breast cancer is a progressive disease, not a systemic disease from inception. The outcome of the disease can be altered by early diagnosis and treatment at an early stage."

He continues, "An overwhelming proportion of the overtreatment of women with screen-detected breast cancer takes place because oncologists are still using the treatment guidelines that were in place before screening was introduced, when most tumours were large enough to be palpable and were often found by the women, not the doctors. But tumours smaller than 14 mm, which we find through regular screening, do not need to be treated the same way. For these, surgery alone is usually sufficient and they do not need radiotherapy or any other adjunctive treatment regimen such as tamoxifen or chemotherapy. These women then need regular surveillance once a cancer has been diagnosed – annual screening and follow-up for the rest of their lives – so that if they develop another tumour it too can be caught early.

"Regular surveillance is good for the patient because she knows that we will spot anything before it develops too far, and because the woman who has already developed a breast cancer runs the highest risk of developing another one. When we succeed in finding a non-palpable local recurrence or another tumour in an early phase, then these cases should be treated more extensively at that stage. But don't treat the other 85% of women who will never need it since they do not develop a local recurrence. That would be overtreatment, and to people who say that screening programmes lead to overtreatment, I say it is the oncologists who are overtreating because they are still treating according to old-fashioned guidelines."

By 'regular surveillance', Tabár means that, as part of the regular screening of the asymptomatic female population, no woman over the age of 40 should go for longer than a maximum of two years without breast screening. Since 1986 the Swedish recommendation is that women aged between 40 and 54 should be screened every 12–18 months, and women older than 55 every 18–24 months. Tabár's research group has published

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numerous articles on tumour growth rate by histologic type and patient age in order to calculate the appropriate intervals. According to their results, three-year intervals (as happens, for instance, in the UK) are too long.

Although breast cancer is less common in women aged 40–54, Tabár says they should be screened more frequently because, if they do develop cancer, it is usually faster growing and more of these cancers become more aggressive during tumour growth than in older women. If left for three years, it could be too late to find it at the small, localised phase when it is easy to treat by surgery alone.

Returning to his analogy of babies and adult criminals, he says, "During a three-year screening interval, you cannot be sure that some of the babies won't grow up into criminal adolescents. So a country that has chosen a three-year screening interval for its national programme is strongly recommended to take into account recent research results."

Tabár is clearly frustrated by the reluctance of some countries to establish national breast screening programmes. Even developing countries, with fewer resources to spare, could set up some basic form of screening he believes, and he points out that screening many women is cheaper than treating one advanced cancer. In addition, he says the same treatments that don't work on advanced cancers, do work on the smaller cancers found during screening.

"As many resources as possible all over the world should be put into early detection. Oncology treatment should be cut back as much as possible because it is toxic, expensive and is not responsible for the major part of the benefit women get. We should be focusing oncology research on the 'bad' tumours that have the propensity of progressing fast. It is time for a new era where the emphasis is shifted away from attempting to focus on combining different therapeutic regimens for metastatic breast cancer, towards an emphasis on using screening to prevent breast cancer from developing into metastatic disease. This is the new paradigm," he says.

## New prognostic criteria

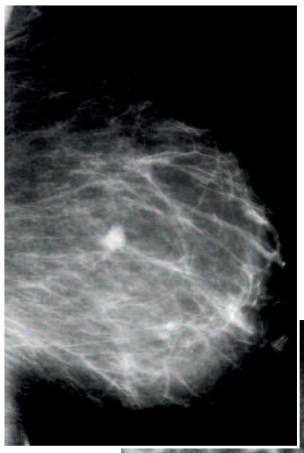
Since 1977, more than a million mammograms have been performed at Falun Central Hospital, giving Tabár a formidable archive on which to base his research. As a radiologist he has focused his attention on the form of tumours, the way they appear on the mammograms, and how they progress. Together with some of his regular collaborators – Stephen Duffy (UK), Peter Dean (Finland/USA), Tibor Tot (Sweden), Cary Kaufman (USA), Hsiu-Hsi Chen and Amy Yen (Taiwan) among others – he has carried out research that has resulted in the suggestion that the TNM classification system should be changed to take account of the mammographic appearance of invasive breast cancers between 1 and 14 mm in size.

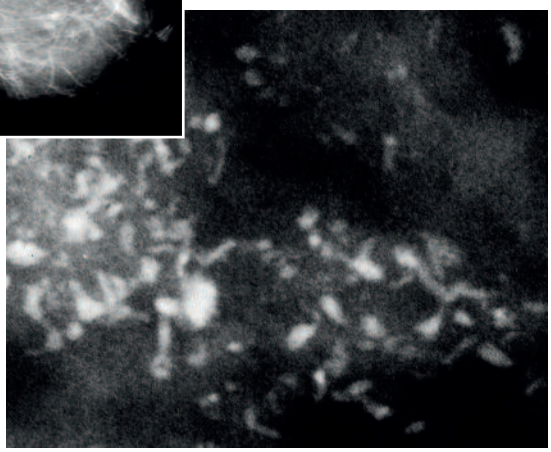
The findings showed that, when high-quality mammography was used to detect tumours, the long-term outcome for women could reliably be predicted in tumours between 1 and 14 mm in size from their mammographic appearance. This was a more accurate method than conventional TNM classification for predicting outcome and, therefore, for choosing the appropriate treatment.

Tabár and colleagues divided the tumours into five categories:

- stellate (star-shaped) without calcifications,
- circular/oval without calcifications,
- powdery calcifications with or without associated tumour mass showing on the mammogram,
- crushed stone-like calcifications with or without associated tumour mass, and
- casting-type calcifications with or without associated tumour mass.

In 715 consecutive women aged 40–69 with breast cancer 1–14 mm in size, diagnosed between 1977 and 1998 and followed through to 2001, they found that the most common tumour was the stellate without calcifications. This was found in 59% of the women and had a 95% long-term (24 years) survival rate, irrespective of node status, histological grade





Which will need more than surgical excision? Women with tumours of between 1 and 9 mm are 33 times less likely to die from their breast cancer if their mammogram looks like the left-hand image (solitary stellate tumour without calcifications) than if it looks like the one below (casting-type calcifications)

or mode of treatment. Women with tumours from the other four categories, with the exception of casting-type calcifications, also had excellent long-term survival. Tabár and his colleagues say that the majority of these women need surgery alone, especially when the tumour is in only one place, and other treatment would amount to overtreatment.

However, casting-type calcifications, which were found in just 7% of the women, had a much lower long-term survival rate: 72% for women with 1–9 mm tumours and 52% for women with 10–14 mm tumours. This was regardless of node status, grade or mode of treatment. The risk of dying from 1–9 mm breast cancer when casting-type calcifications were present on the mammogram was 33 times higher than if the tumour was stellate without associated calcifications. Tabár suggests that the focus of oncology research should be on finding better treatments for those tumours that are far more aggressive from the outset.

He would like to see far more attention paid to using screening to catch the invasive tumours before they grow bigger than 14 mm, identifying what type they are and what the real extent of the disease is, with any treatments additional to surgery being reserved only for those tumours that are multifocal in the breast or show casting-type calcifications on the mammogram; in other words, when the burden of the disease requires more aggressive treatment.

## Appropriate technology

Reducing deaths from breast cancer by catching them at an early stage through a comprehensive screening programme requires not only financial investment, but investment in training radiologists, organising systems, and in modern technology.

The Department of Mammography at Falun Central Hospital is currently investigating the value of a three-dimensional, automated, reconstructed ultrasound method for scanning the denser breast tissue often found in younger women, in which conventional mammography can struggle to detect tumours, particularly small ones. The equipment, developed by U-systems in California, with Tabár as chief medical adviser, is a fraction of the cost of a magnetic resonance imaging scanner: €150,000 compared to approximately €1million. It produces 3D ultrasound images of the dense portion of the breast so that radiologists can look at layers of the breast a few millimetres at a time, from the skin all the way down to the chest wall. With this technology they can spot a pea-sized tumour hidden in the depths of the breast, and Tabár expects that this could become a successful, additional screening tool in women with dense breasts.

A good screening programme, argues Tabar, will use a number of different tools in order to screen effectively and to reach the correct diagnosis for a woman. He thinks the ultrasound tool is remarkable but, as a believer in evidence-based medicine, he

At a fraction of the cost of an MRI scanner, it can spot a pea-sized tumour hidden deep in the breast

# "Women need to be educated about screening so they can demand a better service from their governments"

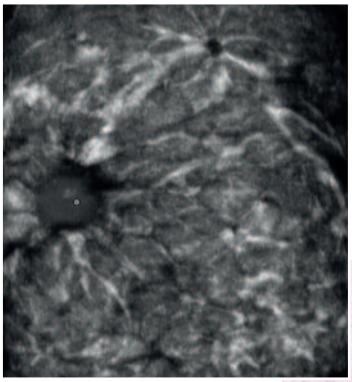
insists that it needs to be tested in proper randomised controlled trials. A trial of the ultrasound tool started in the US this February. "Every method has its limitations," he says. "For instance, ultrasound doesn't see calcium and mammograms do; however, mammograms are not good at detecting subtle density differences in dense breasts. MR is good for assessment of the extent of the disease, but not good for population-based screening, because of the expense and the time that it takes."

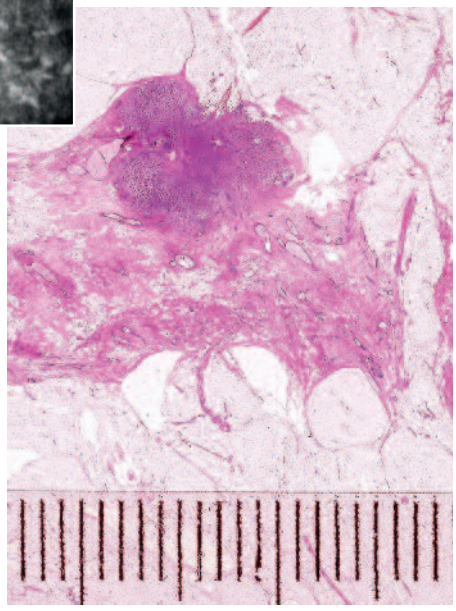
Tabár's department aims to offer a one-stop shop to women who are referred or called back for assessment after having attended one of the region's mobile breast cancer screening units. Their initial mammogram will have been viewed by two doctors who read the mammograms independently from each other, and then consult and reach a consensus before the selected women are called into the department for assessment of the finding. On arrival they are assessed via physical examination, additional mammographic examination, ultrasound and, if necessary, immediate biopsy. In the case of fine-needle-aspiration biopsy, they will receive all the results while they wait. Then the radiologist summarises all the examination results for the woman. This is important in a big country such as Sweden, where women may have travelled several hours from as far away as the Norwegian border for their assessment.

Swedish women demand the best and expect regular mammograms from the age of 40, says Tabár. He believes that women in other countries need to be educated to understand more about breast cancer and screening so that they too can demand a better service from their national governments.

Tabár invests a considerable amount of time and energy in teaching and training radiologists, writing books with his colleagues that are full of colour illustrations to show exactly what they are talking about, carrying out research, publishing numerous papers and encouraging students and colleagues to carry out their own research with their own data, because he believes the reproducibility of research is important. Aged 65, he works 16- to 18-hour days, making do with five or six hours sleep a night ("sleeping is a waste of your life," he says) and his students tell him that he doesn't lead a normal life.

"My work is 99% perspiration and 1% inspiration. I work hard but I love every moment of it. I don't have to do it, I could retire and my wife (a radiologist) has already retired. But this is a tremendous time to be working in the field of breast cancer research. We are the first generation of physicians who have stepped into a virgin territory (the era of non-palpable breast cancers), white snow that nobody else has trodden on, and we have a chance to make a real difference to women."





Caught on 3D ultrasound. This 'baby' tumour (right) was imaged (above) using a new screening method currently being trialled in the US (U-Systems, San José, Calif.), which may be of particular use in women with dense breast tissue