Detecting cancer using limited resources

Screening programmes to catch cancers earlier in low- and middle-income countries are on the increase. **By Emily Sohn**

LYNSEY ADDARIO/GETTY IMAGES REPORTAGE

Women wait to be screened for breast cancer in Uganda, where efforts are being made to catch the disease earlier.

In October 2018, while working on a public-health project in rural Uganda, physician James O'Donovan gave digital cameras to eight community health workers. His instructions were simple: "take photos of the challenges you're facing."

Along with images of malfunctioning water sources and inadequate mosquito screens, one surprising finding was the large caseload of people with late-stage cancer. Dozens of photographs, O'Donovan says, showed women with breast cancer so advanced that their nipples were bleeding. Malignant masses were large enough to be visible to the naked eye.

"It was really quite shocking," says O'Donovan, a PhD candidate at the University of Oxford, UK. "I've never encountered such advanced disease like that because it just doesn't happen in the United Kingdom."

In low- and middle-income countries (LMICs), it is common for cancers not to be diagnosed until they are at advanced stages, when treatment is more difficult. Efforts, such as the implementation of screening programmes, are being made to catch cancers earlier. In some places, new strategies and technologies are making a difference. Obstacles remain, however, including cultural barriers, logistical challenges and the ethical dilemma of whether to screen people who might not be able to access treatment. But as the burden of cancer grows, researchers are giving these challenges more attention. Communicable and childhood diseases such as pneumonia and malaria have long been prioritized in LMICs. "But the lens is starting to go to the forgotten diseases," O'Donovan says – "including cancer."

Scoping out the problem

The World Health Organization (WHO) estimates that, by 2030, as many as 11 million cases of cancer will be diagnosed in LMICs each year – an 80% increase from 2008. By the end of the twenty-first century, cancer is expected to be the leading cause of death and the greatest barrier to increasing life expectancy everywhere.

Detecting cancer early is one way to prevent deaths. But screening, which looks for signs of disease in people who are asymptomatic, is much less likely to happen in LMICs than in high-income countries, where tests such as cervical smears and mammograms are routine. Lack of infrastructure is one reason for the disparity, says Madelon Finkel, an epidemiologist at Weill Cornell Medical College, New York. Poor roads, a lack of hospitals near rural locations, the prohibitive cost of medical care, insufficient equipment and a shortage of medical workers also make cancer screening difficult, as can a reluctance to get tested, she says. And, sometimes, people don't know that the tests exist.

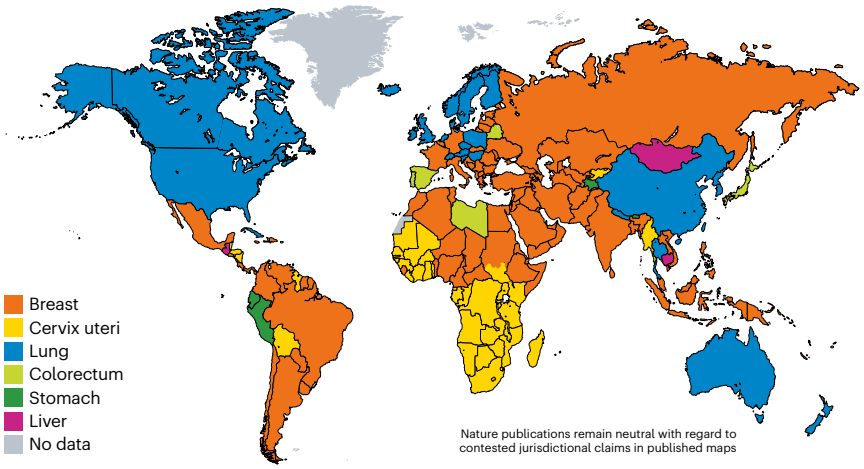
"You have an infrastructure problem, and you have a personnel problem," says Finkel, who has worked on projects in India and Tanzania. "And you have a limited ability to actually help people who test positive because,

particularly in the rural areas where I work, you have to travel quite some distance to get to a tertiary-care hospital in order to get the more definitive tests that we take for granted in the developed world."

A lack of equipment for treating late-stage cancers adds to the urgency of implementing improved screening programmes, says Omolola Salako, a radiation oncologist at Lagos University Teaching Hospital, Nigeria. In 2003, Salako started the non-profit care and advocacy facility Sebeccly Cancer Care after her sister died of kidney cancer. Nigeria, which has a population of about 200 million, is increasing its radiotherapy services. But Salako says there is still an urgent need for affordable treatment. "We don't have enough equipment to treat patients," she says.

MAPPING THE IMPACT OF SCREENING

This map of the leading causes of cancer death in women shows that cervical and breast cancer are the biggest killers in many low- and middle-income countries. Many high-income nations routinely screen for these cancers.



SOURCE: F. BRAY *ET AL. CA CANCER J. CLIN.* **68**, 394–424 (2018).

Screening the cervix

Attempts to tackle cancer in LMICs have focused mainly on cervical cancer. According to the WHO, of the estimated 311,000 people who die from the disease each year worldwide (a toll projected to rise to 460,000 by 2040), 91% live in LMICs. Cervical cancer is an attractive target because it is simple to detect and treatable when caught early. For now, it is the only cancer that the WHO recommends for screening in LMICs.

Screening protocols in low-resource areas differ from those in wealthy countries. In high-income countries, smear tests are the main form of screening. These involve collecting cells from the cervix for lab analysis. But the tests are expensive, complicated and require well-funded health-care systems. Instead, a test called VIA (visual inspection with acetic acid) is a more realistic choice in LMICs. This inexpensive technique, which involves dabbing the cervix with a vinegar solution and watching to see if the tissue turns white, produces results in seconds instead of days. No lab analysis is needed. When possible, the WHO also recommends testing for human papillomavirus (HPV), a group of sexually transmitted viruses, some of which cause cervical cancer. HPV testing can be highly effective for the detection of cancer and can reduce mortality. But the test, which detects viral DNA, is prohibitively expensive in many LMICs.

Treatment can follow immediately with techniques that are also unique to LMICs. In high-income countries, abnormal cells are often removed with cryotherapy, which requires refrigerant gas. But that approach poses problems in LMICs: gas tanks are heavy, hard to transport and expensive to refill. Instead, some practitioners in LMICs use thermal ablation: an almost painless, anaesthesia-free procedure that uses heat to remove lesions in less than a minute. Until recently, the WHO recommended only cryotherapy. But in 2019, it released guidelines endorsing and providing guidance on how to use thermal ablation.

Thermal ablation can be carried out by non-physicians with a simple, lightweight, battery-operated device. In the pilot phase of a randomized-controlled trial in Zambia, gynaecological oncologist Partha Basu at the International Agency for Research on Cancer (IARC) in Lyon, France, and his team found that thermal ablation was safe, acceptable to women and worked as well as did cryotherapy for treating pre-cancerous cells[1] (abnormal cells that have an increased risk of becoming cancerous). Thermal-ablation therapy was as quick as cryotherapy, requiring the person to visit a clinic just once or twice.

Cervical-cancer screening programmes that use these tools have, in some cases, had clear benefits. In a randomized, controlled trial in the south Indian state of Tamil Nadu, Basu and his colleagues documented a 35% reduction in mortality from cervical cancer after a single round of screening with VIA compared with people not offered screening[2]. A different study found that, with HPV screening and follow-up, mortality fell by 50%[3]. Findings such as these have led to optimism about the potential to eradicate the cancer worldwide. "Cervical cancer can be thought of as the poster child of what can be achieved, even in lower-resource settings," says Ophira Ginsburg, director of the high-risk cancer genetics programme at New York University Langone Health.

Overcoming distrust

Despite the apparent benefits of cancer screening, participation is an issue in LMICs, Basu says. The IARC found that in India, for example, just 60–65% of eligible women take part in screening programmes, even with efforts to make services free and convenient. Surveys suggest several reasons for the reluctance. Of 469 women who did not participate in a community-based cervical-screening programme in India, about half were unwilling to be tested[4]. Of those who were reluctant, 46% said that they thought it was unnecessary to test for a disease if they didn't have any symptoms and 36% said they were scared of the test, most commonly because they thought it would be painful. Some worried that testing for cancer would make it spread, and others thought a diagnosis would mean that they would die. People also feared the cost of treatment and the anxiety that their families would experience if they were diagnosed. Of the women who were willing to be screened but didn't go, 40% said household chores prevented them from going to the clinic.

Finkel says that taking these concerns into account can greatly increase participation in screening. More than a decade ago, she began working to establish a screening programme for cervical cancer in Vellore, India. At first, she says, few turned up for the tests – many said they were scared away by the use of the word cancer in outreach materials. Then a rural hospital site began running education programmes about the benefits of screening. Now, Finkel says, women report that they are more comfortable with the idea of screening, "and they tell their friends to get tested too". Finkel says that the number of women being screened has grown from a few hundred to a few thousand each year. "In the beginning we saw many women with advanced cervical cancer," she says. "Not now."

Community health workers can help to facilitate trust. In one project in a remote region of Rajasthan, India, Basu and his colleagues trained ten local women with no

previous medical education to visit families and evaluate basic health measures such as body-mass index and smoking habits, as well as to look for signs of hypertension and diabetes[5]. The health workers also spoke to people about tobacco and alcohol use, looked for signs of oral cancer — a major problem among men in India owing to the popularity of tobacco chewing — and taught women how to check their breasts for potentially malignant lumps. They also gave women instructions on how to collect a sample for a cervical-cancer test so that they could do so privately.

The visits included extended families — crucial because earlier research found[4] that one barrier to screening was that women often didn't have the approval of their husband and family. More than 90% of the women provided cervical samples — about 50% higher than typical compliance rates. And around three-quarters of women flagged by the cervical screening attended follow-up tests, suggesting that women who took part in home-based screening were just as motivated to pursue follow-up care as were women who went to clinics.

Community health workers can serve some of the most hard-to-reach populations in need of cancer testing, O'Donovan says. But workers can easily become overburdened, and their role in cancer screening is under-studied. Whereas thousands of studies have looked at the role of community health workers in detecting and treating childhood malaria, he says, his research turned up just 15 studies conducted anywhere in the world looking at the role of community health workers in cervical-cancer screening. For breast cancer, he found just 16 studies.

To boost screening rates, Salako says, it can help to tap into infrastructure that already exists. Since 2017, Sebeccly Cancer Care has received grants to screen people for cervical cancer in Nigeria. The grants came with mandates for how many women needed to be screened: 500 in 2017, 5,000 in 2018 and 7,000 in 2019. To reach those targets, Salako and her colleagues partnered with primary-care clinics to offer free screening tests when women came in for other reasons. They also worked with religious organizations, community leaders, women's groups and the state ministry of health, which sends employees into communities to encourage women to get screened.

Plenty of women are still scared to go to hospitals, Salako says. And those who go, find there are long waiting times for treatment and costly bills that most people can't pay because they don't have insurance. Universal health coverage is one of the Sustainable Development Goals set by the United Nations for 2030, but health systems in many LMICs still face pressures such as poor access to care and medicine, and shortages of health-care workers.

Salako's project, however, is exceeding its goals. Dozens of women have already been diagnosed with cancer and received treatment. "If everyone has access to cervical-cancer screening, then the chances of detecting cervical cancer in the pre-cancer stage is very high — and you can treat them," she says.

Beyond cervical cancer

Breast cancer has also become a focus of screening programmes in LMICs, where it is the leading cause of cancer deaths in women (with the exception of sub-Saharan Africa, where cervical cancer kills more women; see 'Mapping the impact of screening'), Finkel says. Unfortunately, she adds, the scarcity of mammogram machines and radiologists is a major obstacle to early detection of this disease.

The IARC is studying the use of a portable ultrasound device that can be operated by nurses or technicians in rural areas of China. The device causes less discomfort than a mammogram, Basu says, and radiologists aren't needed to read the results. But research is preliminary and studies have yet to show that the device is effective[6].

"The first rule of screening is you don't screen unless you can do something."

Results are more encouraging, although still inconclusive, for a simpler strategy: encouraging women to regularly examine their breasts themselves, and to seek a clinical opinion if they are concerned. Breast examination — considered a form of early detection, not screening, because it doesn't involve the medical system unless symptoms are found — has yet to be linked with lower rates of mortality, regardless of a country's income level. But research suggests that examination and education about breast cancer can increase the chances of catching cancer in its early stages[7]. Projects are also under way to look at the potential of screening in LMICs for other malignancies, including colorectal, gastric and oral cancer.

To improve both the quantity and quality of cancer-screening programmes, the IARC has launched a project called Cancer Screening on Five Continents (CanScreen5), a global database of all screening programmes, along with performance data. Accountability is an important goal, says Basu, who leads the project. As it stands, he says, some programmes cause more harm than good, with high rates of false positives that lead to unnecessary treatment and the related psychological impacts. In South Korea, for example, many young women have had their thyroids removed unnecessarily, and some have developed complications because screening programmes led to unnecessary follow-up care for small cancers that didn't necessarily require treatment[8]. CanScreen5 has qualitative data from nearly 30 countries in Europe, and is looking to accumulate data from the rest of the world. "The goal is not just instituting screening programmes," Basu says, "but making sure they're doing good."

Researchers are also exploring creative ideas and technologies to make cancer screening more accessible. One possibility is for diagnoses to be made from afar, either by remote consultations or by computer programs that use artificial intelligence to read images (see page S14). In 2019, researchers at the US National Institutes of Health and the technology-investment organization Greater Good in Bellevue, Washington, announced that they had made an algorithm to identify pre-cancerous changes in cervical images, based on a large data set collected in Costa Rica[9]. The project is now collecting data from a variety of locations to help improve the algorithm; the data will incorporate subtle differences in how the cervix can look in women from various regions. Next steps include field tests to work out how best to take high-quality photos of the cervix with smartphones, and how to equip the phones of health workers with photo-analysis software.

Ethical and logistical questions persist. Looking for cancer inherently means the number of cases increases, and many health systems can't handle the influx of new patients. "The first rule of screening is you don't screen unless you can do something," Finkel says. "One should not screen unless one can provide follow-up care to test positive cases." But others say the dynamic is more complex than that simple formulation — countries that implement screening programmes might drive more demand for treatment, which could, given supportive policies, lead to investment in more physicians and therapeutic options. As research builds on the growing impact of cancer in LMICs, and the potential for testing to make a difference, the urgency has never been greater to implement better screening and treatment programmes.

Emily Sohn is a freelance journalist in Minneapolis, Minnesota.

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