Cells swabbed from the cervix are smeared on slides to spot abnormalities.

SCREENING

Testing times

Pap tests have been a mainstay of cervical cancer screening, but new tests, vaccines and knowledge might be changing that, including when and how frequently to test.

BY COURTNEY HUMPHRIES

Cervical cancer rates in developed countries have plummeted by as much as 70% since 1950 primarily thanks to intensive screening programmes using the Papanicolaou (Pap) smear test, which looks for abnormal cells of the cervical lining.

Pap tests have become a rite of passage for many women. And although screening programmes have been effective in countries that can afford to implement them, the tests are problematic. "Pap tests are notoriously insensitive," explains Eduardo Franco, a cancer epidemiologist at McGill University in Montreal, Canada. The tests only detect cancer in 50% to 75% of cases.

As cervical cancer develops slowly, repeating the test regularly can compensate for the tests insensitivity. But the frequency of testing (which has been annual in the United States and many countries, and every two or three years in others) Franco says, "is based on an admission that we have a very imperfect tool in our hand."

The role of Pap tests is changing, change driven by new tests to detect human papillomavirus (HPV) infection directly, as well as the wider recognition that the test can be too often invasive, unnecessary and a burden on women. HPV vaccination programs may help further scale back screening in the coming decades, and technologies may also help relieve the stark disparities in cervical cancer prevention worldwide. But medical organizations and governments are still struggling to identify the best approaches to deploy screening programs given the resources at their disposal.

NEW PARADIGMS FOR PREVENTION

The Pap test is a visible check for abnormal cells collected from the opening of the cervix during a pelvic exam and smeared on a glass slide. A newer method called liquid-based cytology, in which the swab is suspended in preservative fluid rather than smeared, produces more consistently useful cells. In either case, a technician looks for any abnormalities under a microscope. Women with cells showing signs of aberrant growth are referred for further examination and, if necessary, for treatment.

The past decade has seen the emergence of tests that detect HPV DNA in cervical swabs. Several versions of HPV tests are now on the market, including ones that detect any cancer causing varieties of HPV, as well as molecular genotyping assays that can specifically identify the two most carcinogenic types of the virus, HPV-16 and HPV-18. Research has found that these genotyping tests have 90-95% sensitivity; what's more the tests make it possible to intervene earlier because they can directly detect HPV infection before visible abnormalities manifest in cells.

Although HPV testing is more sensitive than Pap tests, they are not designed to identify the signs of cervical cancer.

NATURE.COM
A cost analysis
of DNA detection
versus Pap tests:
go.nature.com/ap2qqg

HPV infection is common, particularly in young women (approximately 45% of US women in their early twenties have been infected with HPV) and as many as 90% of people who test positive for HPV subsequently test negative within 6–24 months (see ‘The global burden’, page S2). A screening programme using HPV tests would identify too many young women who will not develop cervical cancer.

For older women, however, HPV testing has made a big difference. “It allows you to safely increase the screening interval,” says Jack Cuzick, who heads the Centre for Epidemiology, Mathematics and Statistics at the Wolfson Institute in London. But how best to do that has been the subject of an evolving discussion. The United States has taken a conservative approach of adopting co-screening with Pap and HPV tests for women over 30. But studies in Canada and Europe have found that administering Pap tests only after a positive HPV test is more effective.

Many governments and medical organizations are starting to recommend delaying the onset of all screening: previous US guidelines, for instance, began screening at age 18 or within three years of starting sexual activity. Franco explains that in addition to the problems with testing young women for HPV, giving Pap tests to adolescent girls and young women can lead to misleading results — they often develop minor cervical abnormalities from HPV infections that rarely progress to cervical cancer and are not clinically important — and unnecessary treatments, some of which have been linked to miscarriage and complications with future pregnancies.

Different countries have different standards. In March 2012, consensus guidelines issued by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology and the American Society for Clinical Pathology advocated not screening women before age 21, regardless of sexual history. The UK’s national screening program tests at age 25; in Australia, the national screening program currently advises women to get Pap tests every 2 years from 18 years of age. Franco, who was involved in the US consensus guidelines, says that while research has shown that testing women between 21 and 24 years of age provides only an “infinitesimal” amount of protection, extending the age to 25 has stirred debate between those who favour an aggressive approach to cancer prevention and those who believe that testing should be minimized when possible.

ECLIPSED BY VACCINE?

As virtually all cases of cervical cancer are caused by HPV, it would seem that the availability of a vaccine that effectively prevents HPV infection would eliminate the need for cervical cancer screening. Most HPV vaccination programmes target girls 12–13 years old — well below screening age. “The population you’re targeting with vaccines is different from screening,” says Jane

Kim, who performs cost-effectiveness analyses in cervical cancer care at the Harvard School of Public Health in Boston, Massachusetts. It will take decades before women who were too old to be including in vaccination programmes (usually set at age 26) pass the upper screening age of 65. Moreover, current HPV vaccines protect against only the most common cancer-causing strains of HPV.

Inadequate HPV vaccination programmes are also an issue. In the United States, for instance, only half of adolescent girls have received even one dose of the vaccine, with only 30% completing all three required doses (see ‘Trials of an anticancer jab’, page S4). Vaccine coverage needs to be a lot higher before it would be prudent to recommend reduced screening, says

“If you’re going to see women infrequently, you want to get a high rate of detection.”

Mona Saraiya, a medical officer working in cancer prevention at the US Centers for Disease Control and Prevention in Atlanta, Georgia. The absence of a comprehensive system for tracking individuals’ vaccine history is adding to the need for continued screening in the United States. Franco says that countries like the United Kingdom, Canada, and Australia, which have school-based vaccination programmes and better patient tracking, are better positioned to take advantage of vaccines and eventually develop separate screening policies for vaccinated and non-vaccinated women.

Researchers are trying to model the complexities of HPV infection and cervical cancer to better inform screening and vaccination policy. In Europe, a multinational study called PREHDICT could yield a statistical model to evaluate the cost effectiveness of prevention programs against HPV-related disease. One of the study’s aims is to determine what would be the optimal way of combining screening and vaccination programmes given the health resources of a country, says its leader Johannes Berkhof, a biostatistician at VU University Medical Centre in Amsterdam. The study will also look at whether vaccination should be administered to women older than 26 years as well as to boys (who can pass HPV to women and develop HPV-related cancers and genital warts). To answer these questions, the multinational team is pooling resources such as data from longitudinal screening studies and vaccine clinical trials, and is amassing a database on the burden of HPV-related disease. The emphasis of the study will be on creating better models of the natural history of HPV infections — how they are acquired and cleared, and how natural immunity against a particular type develops — and on estimating the effects of vaccination on transmission rates.

In poor countries, cervical cancer is still a leading cause of cancer in women (see ‘Prevention comes of age’, page S11), in large part because governments cannot afford expensive

screening programmes. HPV vaccination might be a cheaper alternative to screening programs. Kim says that it’s important not to frame the issue as a choice between vaccination and screening. “The evidence for us has suggested that it would be cost effective to do both.”

The question, then, is how to screen. The success of Pap testing in the developed world has depended on frequency of testing, which is more difficult to maintain in places that lack medical resources, says Kim. HPV testing, with its higher sensitivity, offers a way around this problem. “If you’re going to see women infrequently, you want to get a high rate of detection.” But HPV tests are more expensive than Pap smears, so Kim and other researchers have been modeling the cost-effectiveness of different screening strategies. In regions of the world with the highest cervical cancer incidence and mortality, such as East Africa, HPV testing may be worthwhile if done at longer intervals — like three to five times over a woman’s life after the age of 30, says Kim.

Researchers are also trying to develop new ways to identify women at risk for cervical cancer such as swabbing the cervix with diluted vinegar turning damaged tissue white. “It’s a fairly low-cost, low-tech intervention,” Kim says. Because the vinegar swab method doesn’t require sending a sample to a laboratory, women can often be treated on the same day as the test — an important advantage for those who find it difficult to travel to a clinic.

THE FUTURE OF SCREENING

Cervical cancer screening programs may evolve as technologies develop. Recent innovations could lead to HPV tests that distinguish between specific high-risk strains. Pap tests may be further improved by adding cancer-specific markers to increase their sensitivity.

In countries that have followed the US’s frequent screening model, Pap tests are seen as a ritual of preventive care. Lengthening the interval between tests represents a change for both women and doctors. Some doctors are concerned that screening less frequently will cause them to lose contact with patients, as well as increase the chance for legal liability, says Saraiya. But she adds that the uncoupling of Pap tests from annual preventive health exams might be easier to put in practice with younger patients free of these expectations.

New tests also require patient education. HPV tests put the emphasis on testing for a virus rather than cancer, with possible stigma and relationship stress that come with a sexually transmitted infection. “Women are used to Pap testing, but they haven’t equated it with a sexually transmitted infection,” says Saraiya. “It’s important that we’re crafting the correct counselling messages,” she says, so that women continue to understand the long-term benefits of screening. ■

Courtney Humphries is a freelance writer based in Boston, Massachusetts.