For Cancers Caused by HPV, Two Vaccines Were Just the Beginning

By Judy Peres

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When two vaccines to prevent cervical cancer reached the market several years ago, it was for once a true breakthrough and a landmark for cancer prevention research. But not, it appears, the last word.

Researchers are now working intensely on other ways to prevent infection with human papillomavirus (HPV), which causes virtually all cervical cancer and a substantial portion of several other malignancies. Clinical trials are under way, or will soon start, to test improved versions of the first-generation vaccines (Gardasil or Cervarix), second-generation vaccines that could afford broader protection at lower cost, and microbicides to be used topically to prevent infection with HPV and other sexually transmitted diseases. Stepped-up efforts are also taking place to increase use of the current vaccines.

“There’s stuff moving along,” said John Schiller, Ph.D., a senior investigator at the National Cancer Institute whose work led to development of the current vaccines. But experts are worried that these efforts—as exciting as they are—could be a double-edged sword. “We have to be sure we don’t take away the responsibility of public health officials to deliver the current vaccines because they believe something better is coming along,” Schiller said.

So researchers were pleased to see the U.S. Food and Drug Administration (FDA) approve Gardasil in December for the prevention of anal cancer. Although anal cancer is relatively rare (the American Cancer Society estimates that some 5,300 people in the U.S. are diagnosed each year), its incidence is increasing. And Karen Midthun, M.D., director of the FDA’s center for biologics evaluation and research, called its treatment “challenging.”

Merck’s Gardasil is already approved for the prevention of vulvar and vaginal cancer in females and for the prevention of genital warts in both sexes, in addition to its main indication—preventing cervical cancer. The U.S. Centers for Disease Control and the Prevention (CDC) recommends routine inoculation of preteen girls with either Gardasil or GlaxoSmithKline’s Cervarix. CDC’s advisory committee on immunization practices is now considering extending that recommendation to boys.

Although anal cancer from HPV infection can afflict both men and women, men who have sex with men are at greatest risk. Clinical data that Merck presented to the FDA showed that Gardasil prevented 78% of anal precancerous lesions in that population. On the basis of those results, the agency approved the vaccine for prevention of anal cancer in both men and women.

Schiller speculates that the approval for anal cancer may be enough to persuade the CDC to extend the recommendation to boys. (Currently, the agency says that girls should be vaccinated, whereas boys may be vaccinated.) “This could put it over the top,” he said, partly because adding the indication will improve the cost-benefit analyses of vaccinating both boys and girls.

Vaccines Underused

Public health experts are disappointed that only a minority of adolescent girls in the U.S. are getting immunized against HPV, even in neighborhoods where most are eligible for free vaccines.

Richard Schlegel, M.D., Ph.D., professor and chair of the pathology department at Georgetown University Medical Center, bemoaned that in the underserved southeast wards of the District of Columbia, only 12% of girls entering sixth grade are getting the vaccine. “Here you have a very effective vaccine not being delivered because of gross misunderstanding of HPV and cervical cancer,” he said. “It’s pretty embarrassing that, in the nation’s capital, there are places where people could be vaccinated and they aren’t because they don’t know anything about the disease.”

Most people confuse HPV with HIV (human immunodeficiency virus), Schlegel said, and hardly anyone knows that HPV causes cervical cancer. To fight that, Sherrie Wallington, Ph.D., assistant professor of oncology and the program director of the Health Disparities Initiative at Georgetown’s Lombardi Comprehensive Cancer Center, has been going into libraries and community centers to hold educational sessions for parents and daughters.

Wallington said the District of Columbia in 2009 mandated that girls going into sixth grade be vaccinated against HPV unless they opt out. Although the mandate’s intent was to ensure that the CDC and insurers pay for the vaccine, the requirement caused controversy and public backlash. “There was a huge knowledge gap,” said Wallington. “People were scared. They couldn’t make an informed decision, and they didn’t know what ‘opt out’ meant. They feared their kids would be turned away from school.” So she developed a program of four face-to-face meetings followed by a blitz of text messaging to the girls’ cell phones—a medium familiar to teenagers of all income levels.

“If the pilot program is successful in getting people to get vaccinated,” said Schlegel, “a lot more money will be going into the educational aspect of this. We got off to a bad start because the education was being done primarily by Merck, and a lot of people had questions about a conflict of interest when a company is pushing it. The FDA and the CDC weren’t enough in the forefront.”

According to Allan Hildesheim, Ph.D., chief of NCI’s infections and immunopathology branch, just over 40% of eligible American girls now get at least one dose of the vaccine, but many of those don’t complete the series of three shots which costs $360. In England and Australia, which have free, school-based immunization programs, coverage rates exceed 80%.
While not dismissing the research into new and improved vaccines, Hildesheim said, “We can make better use of what we already have.”

**The Second Generation**

Schlegel has been working with a multinational group of researchers funded by the Gates Foundation to find a way to make a more economical and stable vaccine that might be more readily available in developing countries. In many places that lack Pap early-detection programs, cervical cancer is the second-biggest cancer killer.

The new vaccine, which BioSidus is making in Argentina, will go into clinical trials in Brazil as soon as possible, said Schlegel. “It is intended to be both therapeutic and prophylactic. It can protect animals after they’ve already gotten tumors.”

Like Gardasil and Cervarix, the BioSidus vaccine is made from the L1 protein of the HPV shell. But it’s made in bacteria, rather than in yeast or insect cells, and it targets E7, an oncprotein that is always expressed in HPV-induced tumors.

“We’ve been attaching an epitope of E7 to try to induce cellular immunity against it,” Schlegel explained, “so we might be able to treat somebody who’s already infected and even has cancer.”

While Schlegel and others work on L1 vaccines, Richard Roden, Ph.D., is working on a vaccine using L2, the HPV shell’s minor protein. Roden, a professor in the department of pathology at Johns Hopkins, said the technology has been licensed to Shantha Biotechnics, now a subsidiary of Sanofi Pasteur. The polymeric L2 vaccine that Shantha is developing could be easier and cheaper to produce and should protect against more strains of HPV. It’s still in the preclinical stage, Roden said: “We’re trying to finalize our formulation.”

One weakness of the first-generation vaccines is that they target only two cancer-causing strains, HPV-16 and HPV-18. Those two strains cause about 70% of cervical cancer cases, but many other strains can cause cancer. Merck is now conducting a phase III trial of a vaccine that can protect against nine strains. A company spokeswoman said they expect to submit the results of their nonavalent vaccine trial to the FDA next year.

**Microbicides**

Another approach involves developing a microbicide to prevent transmission of HPV, among other sexually transmitted diseases.

A team at Albert Einstein College of Medicine in New York recently received a $4 million NCI grant to test a gel made from the seaweed derivative carrageenan. The group, headed by Mark Einstein, M.D., director of clinical research for women’s health, is recruiting 200 reproductive-age women for an expanded phase II trial that should begin in late spring or summer of this year.

Carrageenan was not effective against HIV in a recent phase III trial, but it was proven safe. And laboratory tests indicate that carrageenan is about 1,000 times more effective against HPV than against HIV.

“If the trial is successful, it will yield a product that empowers women to protect themselves, since they can personally control how it’s used,” Einstein said. He added that preliminary results could be available in 2012, although final results will take 3–4 years.

The Canadian Institutes of Health Research is funding a similar study, conducted by Eduardo Franco, M.D., professor of epidemiology and oncology at McGill University in Montreal. The McGill team is enrolling nearly 500 sexually active female university students for a phase IIb trial of another carrageenan-based gel that should start in mid-March. Franco said the trial aims to evaluate patient adherence to the consistent use of a microbicide, as well as the efficacy of carrageenan in preventing new HPV infections and accelerating clearance of existing infections.

One potential pitfall of a microbicide is patient compliance. “You’d probably have to use it before every sex act,” said Schiller, who is collaborating in the research. “With a vaccine, it’s one and done.” On the other hand, carrageenan-based products are “readily

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**HPV Vaccines in Development**

Here are some vaccines now in company pipelines.

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<tr>
<th>Company</th>
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<th>Vaccine type</th>
<th>Stage</th>
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<tbody>
<tr>
<td>Merck</td>
<td>Nonavalent L1 in yeast</td>
<td>Preventive</td>
<td>Phase III</td>
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<tr>
<td>ISA Pharmaceuticals</td>
<td>Synthetic long peptides of E6 and E7</td>
<td>Therapeutic</td>
<td>Phase II</td>
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<tr>
<td>Hoffman–La Roche</td>
<td>E6, E7, and interleukin 2 in recombinant vaccinia (cowpox) virus</td>
<td>Therapeutic</td>
<td>Phase II</td>
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<tr>
<td>Advaxis</td>
<td>E7 in attenuated, live <em>Listeria</em> vaccine</td>
<td>Therapeutic</td>
<td>Phase II</td>
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<tr>
<td>BioSidus</td>
<td>E7 fused to L1</td>
<td>Preventive and therapeutic</td>
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<td>Sanofi</td>
<td>Polymeric L2</td>
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<td>Indian Immunologicals</td>
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<tr>
<td>Cadila</td>
<td>L1 in recombinant measles vaccine</td>
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*JNCI News*
available, cheap, and could be used by women who can’t afford the vaccine,” he said.

Carrageenan is a common ingredient in food products and cosmetics, and it is already in use in some over-the-counter vaginal lubricants. Dr. Schiller is an inventor on US government–owned HPV VLP patents that are licensed to Merck & Co, Inc., and GlaxoSmithKline. Dr. Roden is a paid consultant of Merck & Co, Inc., and has received unrestricted educational grant funding from GlaxoSmithKline. He is also co-inventor on L2 patents licensed to Shantha Biotechnics Ltd, PaxVax, Inc., and Acambis, Inc. Dr. Schlegel is co-inventor for a patented technique to make a vaccine from HPV L1 fusion proteins.