

Nobel-Winning Discovery of HPV–Cervical Cancer Link Already Having an Impact on Medicine

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October 16, 2008 — The breakthrough discovery of a link between the human papillomavirus (HPV) and cervical cancer — honored last week with the Nobel prize — has already been translated into applications that are having an effect on medicine.

That research led to the development of HPV testing, which has improved the diagnosis and management of early cervical abnormalities and precancerous lesions. It also led to the development of prophylactic HPV vaccines — *Gardasil* (Merck & Co) and *Ceravix* (GlaxoSmithKline) — which are expected to have a dramatic effect on the incidence of cervical cancer in the decades ahead.

But these innovations would not have been possible without the perseverance of 1 man, the scientist who proposed and then went on to prove the link between cervical cancer and HPV. The discovery caused quite a stir at the time — in the early 1980s — because the majority of experts did not believe that viruses could cause cancer, and the few who did were focusing on a different virus altogether.

Against the Dogma of the Time



Dr. Harald zur Hausen (Source: German Cancer Research Center)

That scientist was Harald zur Hausen, MD, professor emeritus currently working at the German Cancer Research Center, in Heidelberg, and former scientific director of that Center. That discovery has just earned him half of the 2008 Nobel Prize for Physiology and Medicine, which he shared with 2 French scientists who discovered the human immunodeficiency virus (HIV). It is the latest and most prestigious of several prizes he has already won for this research, including the American Association of Cancer Research's Award for Lifetime Achievement.

The Nobel citation said that Dr. zur Hausen went "against the current dogma of the time," and his proposal for a role for HPV in cervical cancer flew in the face of prevailing views in the 1970s.

"My proposal was not very welcome at that time," Dr. zur Hausen recalled in an interview recorded on nobelprize.org after the announcement. At that time, many researchers were focusing their attention on the herpes simplex virus; in fact, he delivered 1 of his first papers proposing HPV as the cause of cervical cancer at a meeting in Florida specifically scheduled to discuss herpes simplex research. "I was a lonely voice at that meeting," he said.

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It took some time to amass evidence to support the proposal. As the Nobel citation explains, Dr. zur Hausen assumed that the tumor cells, if they contained an oncogenic virus, should harbor viral DNA integrated in their genomes. But it took more than 10 years to show this, because the

process was complicated by the fact that only parts of the viral DNA were integrated in the host genome.

The breakthrough came in the early 1980s, when Dr. zur Hausen and his team found novel HPV-DNA in cervical cancer biopsies, thus discovering the tumorigenic virus type HPV 16 in 1983. A year later, the team cloned HPV 16 and HPV 18 from patients with cervical cancer. The Nobel citation notes that the team made these clones available to the scientific community, and Dr. zur Hausen commented that they were "dispersed very freely throughout the world." Ironically, others later patented and profited from this research.

Since then, HPV 16 and 18 have been consistently found in about 70% of cervical cancer biopsies throughout the world, the Nobel committee said. This research eventually led to the development of a vaccine against HPV 16 and HPV 18, which provides more than 95% protection from these infections. However, the committee was cautious in its predictions of the impact this will have, commenting that it "may reduce the need for surgery and the global burden of cervical cancer."

Revolutionary Idea Took Time to Be Accepted

The finding that HPV caused cervical cancer was "absolutely revolutionary," commented Maurie Markman MD, professor of gynecologic medical oncology at the University of Texas MD Anderson Cancer Center, in Houston, who acts as an editorial advisor to *Medscape Oncology*.



Dr. Maurie Markman

"This was the first time it was possible to unequivocally define an infectious agent as the cause of a cancer, demonstrate the process whereby the viral DNA affects the development of the cancer, and finally how a vaccine could potentially prevent the development of the cancer," Dr. Markman commented.

So revolutionary was the idea that it took quite some time for the finding to be accepted among the scientific community, commented Attila Lorincz, PhD, professor of molecular epidemiology at the Wolfson Institute of Preventive Medicine, in the United Kingdom. Many experts could not believe that a virus could cause cancer, and were focusing instead on other environmental factors and genetic predispositions, he said. "It was another 10 years before the majority of skeptics were silenced, and even a few years ago, there were still a few recalcitrant older medics and scientists."

The evidence that eventually built up for HPV was "very compelling and very cohesive," Dr. Lorincz commented. Much of it came from very large clinical trials conducted in a lot of different countries, which showed reproducibly in women with cervical cancer who had the high-risk strains of the virus (HPV 16 and HPV 18). For the most part, women without cervical cancer did not have these strains. There was also convincing molecular evidence from the laboratory showing that normal cells exposed to the high-risk strains would turn cancerous, and from animal studies showing that the high-risk strains of the virus would lead to death from cancer, he added.

Dr. Lorincz played a key role in this story as the scientist who developed the first test for HPV. That work was carried at Digene, a small company that Dr. Lorincz cofounded and that has since been bought by Qiagen (Frankfurt). Dr. Lorincz moved to the Wolfson Institute last year.



Dr. Attila Lorincz
(Source: Wolfson
Institute)

Impact on Cervical Cancer

HPV testing, introduced in the mid-1990s, has already had beneficial effects on the medical management of women with abnormal cervical changes, Dr. Lorincz said. Screening for HPV, with appropriate follow-up (such as Pap smears), leads to the identification of abnormalities and/or precursor lesions in the cervix, which can be removed fairly easily. This can reduce the future risk for cervical cancer by 99%, he said.

HPV testing is more reliable than Pap smears alone, which can miss cases, Dr. Lorincz said. Ideally, however, HPV testing and Pap smears should be used together, which does increase the cost slightly, but it results in a lower disease burden. These technologies are commonly used together in the United States, and there has been a steadily declining rate of cervical cancer in that country, he noted, which has not been mirrored in Europe.

The impact of HPV vaccination will take longer to be seen, Dr. Lorincz commented. The current target is girls 12 and 13 years old, but cervical cancer is seen mainly in women in their 30s and 40s, so there will be a lag time of a couple of decades before the vaccinated girls reach the age at which they would have been affected. But its impact could eventually be huge.

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"The burden of cervical cancer will be dramatically diminished in the coming 2 or 3 decades as a result of this breakthrough," Dr. Lorincz predicted.

"In theory, if one could vaccinate all females during early adolescence with 1 of the 2 available HPV vaccines, as many as 70% of all cases of cervix cancer might be prevented," Dr. Markman commented. "Considering the fact that worldwide cervix cancer causes approximately 250,000 deaths each year, the successful implementation of this strategy would have a major favorable impact on public health."

Dr. zur Hausen commented that HPV vaccination has been "extremely successful" and he is in favor of making the vaccines more widely available. But he also noted that the development of an HPV vaccine was slow in coming. He was very keen to push on with this work, and approached a number of pharmaceutical companies, especially in Germany. However, 1 of the first companies that initially showed interest, Behring, decided to drop the project after a market analysis they commissioned concluded that there would be no market for such a product. "It was totally wrong, of course, as can be seen today," he added.

The major disadvantage of the HPV vaccine is that it is "too expensive," Dr. zur Hausen commented. Its current price puts it out of reach of developing countries, which have the greatest need for the product, and "prices will have to go down in the future," he said. From his own contacts in Africa and other developing countries, he believes that "the willingness to be vaccinated is remarkably high, so it's more a question of how do we get it to those people and how we can get a drastic reduction in the price."

Unique Event in Oncology?

"To date, the observation of the direct and substantial link between HPV infection and the development of cervix cancer remains a unique event in oncology," Dr. Markman told *Medscape Oncology*. "While other viruses may ultimately be demonstrated to be associated with malignancy, it is unlikely such situations will be as clear-cut as observed with HPV and cervix cancer."

It is relatively uncommon for an infectious agent to be associated with cancer, Dr. Lorincz agreed, although he pointed out that there are other examples, such as hepatitis B and liver cancer, *Helicobacter pylori* and stomach cancer, and Epstein-Barr virus and Burkitt's lymphoma.

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"However, HPV is the most important, and is of major medical significance," he said. "There are about 600,000 to 700,000 cases of cervical cancer a year, and about half these women die from that, so it is a significant disease."

It's been estimated that about 20% of cancers are linked to infectious agents, so the majority of cancers are not, Dr. Lorincz pointed out. "I'm not sure that many more are going to be found. People have been looking for decades, and not a whole lot has been forthcoming. There may be a surprise, but personally, I don't expect another major cancer to have an infectious cause."

"I could be wrong," Dr. Lorincz added. "No one can know what the future will bring."

However, Dr. zur Hausen disagrees. With his life-long interest in infectious agents as a cause of human cancers, he does expect there to be more discoveries in this field, and pointed out that just last year a new virus was linked to the rare Merkel cell carcinoma. He hopes the international publicity that accompanies the Nobel prize will spur new research efforts in this field.