Strictly speaking, recurrent respiratory papillomatosis (RPP) is not cancer, but it can be just as devastating. And for researchers studying it, this “premalignant” disease offers a rare window into the usually-invisible stages that precede full-blown cancers.

RPP is caused by human papillomaviruses (HPV)—the viruses best known for causing virtually all cases of cervical cancer as well as common skin warts and genital warts. RPP involves premalignant growths that primarily affect the larynx but can also involve the trachea, bronchi and lungs. It can prove fatal if the growths occlude the airway or become malignant.

“This is a terrible disease, and the only effective treatment is surgery—as often as every 10 days in cases where papillomas rapidly recur,” says Dr. Bettie Steinberg, Professor of Otorhinolaryngology and of Microbiology & Immunology at Einstein and chief scientific officer at The Feinstein Institute for Medical Research, North Shore-LIJ Health System. She is also a member of the Albert Einstein Cancer Center’s Cancer Epidemiology Program.

Over the past 20 years, Dr. Steinberg and her colleagues have uncovered much of what is known about this devastating disease. They have also made key discoveries concerning the entire HPV class of viruses.

“Many years ago we took biopsy specimens from the respiratory tracts of people with no sign of RPP but who had come in for various kinds of respiratory-tract surgery,” recalls Dr. Steinberg. “About five percent of these random biopsies were positive for HPV—but RPP itself is quite rare, with a prevalence of only five cases per 100,000. Clearly, many people are walking around with HPV infections of their airways that are latent, meaning the virus is inactive but capable of becoming activated.” In later studies, latency was found in HPV infections of the cervix and skin and is now recognized as a basic feature of this class of viruses.

The viruses that cause RPP are “ubiquitous—virtually everyone gets exposed to them,” says Dr. Steinberg. “So we wondered why only a small subset of people develop this disease. RPP patients can ward off most other
RPP affects two distinct groups of people: the very young (in whom the disease appears between the ages of six months and two years) and adults who develop RPP anywhere from age 16 to 60 or 70. How do young children and adults become infected with HPV, the virus responsible for RPP?

“It’s quite clear now that very young patients with RPP are born to mothers who have genital warts, which are caused by the same viruses—HPV 6 and HPV 11—that cause RPP,” says Dr. Steinberg. “During birth, as these kids move through an infected birth canal, the virus gets into their mouths and then into their respiratory tracts.”

As for RPP cases that occur during adulthood, there are now two schools of thought regarding their origin. “One possibility is these people were infected with HPV at birth and their infection remained latent for years until something activated it,” says Dr. Steinberg. “The second possibility is that these cases stem from relatively recent HPV infections transmitted through oral-genital contact. We haven’t been able to determine yet which possibility is the answer or if both causes contribute to these adult-onset cases, but most investigators favor the second possibility.”

Whatever the transmission route, Dr. Steinberg is hopeful that a newly approved cervical-cancer vaccine may help eliminate RPP as a disease. The vaccine targets not only HPV 16 and HPV 18 (which cause most cervical cancers) but also HPV 6 and HPV 11, which account for 90 percent of cases of genital warts and virtually all cases of RPP.

“This vaccine has the potential for preventing the genital-tract HPV infections that are then transmitted to the airways,” says Dr. Steinberg. “Long-term population studies are now being developed to address this vaccine’s potential impact on preventing RPP.”

How Do People Get Infected?

Dr. Steinberg focused on a class of genes known as Class II major histocompatibility complex (MHC) immune response genes, which strongly influence our susceptibility to infectious diseases. A link had previously been found between certain class II MHC genes and development of cervical cancer, which is also caused by HPVs. To see if a similar link existed with RPP, she and her colleagues compared the genetic makeup of 70 RPP patients with an equal number of healthy people and also looked for genetic differences between people with mild and severe RPP.

“We found that RPP patients tended to have particular variants of these class II MHC genes that weren’t present as often in healthy people,” said Dr. Steinberg. “And we found additional genetic differences when we compared patients with mild and severe RPP. So a certain pattern of class II MHC genes not only can make you more likely to develop RPP infections, but their immune systems don’t seem to ‘see’ HPV very well. Our work suggests that glitches in genes regulating their immune systems prevent them from mounting an effective response against HPV infection.”

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but to have a more severe case. One of our long-term goals is to develop a vaccine for susceptible people that would help them fight off these HPV infections."

Deaths from RPP are usually confined to Third World countries where patients lack access to surgery. But Dr. Steinberg recalls the case three years ago of a young Mississippi boy in a Medicaid HMO who needed surgery every three weeks to keep his airway open. His primary care doctor left the HMO shortly after arranging for a surgical treatment—and the hospital refused to operate without authorization from his new primary care doctor. That took too long, and the boy died. “Yes,” she notes, “that happened in the United States, with the best health care in the world.”

The two viruses implicated in RPP—HPV 6 and HPV 11—cause 90 percent of all cases of genital warts, a sexually transmissable disease. HPV 6 and HPV 11 are considered “low-risk” HPVs because they cause warts rather than cervical cancer. Yet in the respiratory tract, HPV 6 and HPV 11 clearly can cause cancer—and the chance they’ll do so depends heavily on what part of the tract they infect.

“About three to five percent of RPP patients will develop malignancies in the larynx, by far the most common site for RPP to occur,” says Dr. Steinberg. “But a subset of patients develops RPP not just in the larynx but in the trachea and lungs as well. And the consensus among specialists is that fully 80 percent of patients with RPP of the lung will develop cancer there. Something about the tissue infected by HPV influences whether cancer will occur, but we don’t yet know what that tissue component is.”

Dr. Steinberg’s special interest is finding the early steps in a cell’s progression towards cancer. “With most cancers the premalignant stage is hidden—you don’t know anything is wrong until you have a tumor that may already be fairly advanced,” says Dr. Steinberg. “So RPP seemed ideal for study, since it is predominantly a premalignant condition.” Her research into these pre-cancerous events has led to a clinical trial of a promising drug for treating RPP.

“The signals telling a cell what to do all begin with hormones, growth factors and other molecules that stimulate receptors on the cell surface,” explains Dr. Steinberg. “Once activated, these receptors transmit signals to the nucleus that program the cell to respond to that stimulus. We now know that infection by HPV alters the cell’s responses to some of these signaling pathways.”

Dr. Steinberg has focused on signals triggered by the epidermal growth factor receptor, or EGFR. Lung, prostate and several other types of cancer have faulty EGFR signaling pathways—and so do premalignant papillomas: Her team has shown that EGFR is three times more abundant on RPP cells than on normal laryngeal cells. And as is true for some of those cancers, the increased EGFR signaling in papillomas leads to overproduction of the enzyme COX-2.

“COX-2 is found at high levels in inflammatory conditions like arthritis, for which the COX-2 inhibitors Celebrex—and Vioxx before it was taken off the market—have been used for treatment,” says Dr. Steinberg. “It’s now clear that COX-2 is also elevated in many cancers and, as we have shown, in precancerous RPP as well. This is significant, since cancer is increasingly being viewed as a chronic inflammatory process.”

These findings have led to an ongoing clinical trial to see whether Celebrex can help treat patients with RPP. Plans call for enrolling 60 RPP patients—all in need of surgery at least three times a year—in a 2.5-year double-blind study comparing Celebrex with a placebo.

While the trial has not produced data yet, information is available on three patients taking Celebrex outside the study—patients with RPP so severe that they couldn’t risk being included in the study’s placebo group. One, a Texas woman, needed surgery every 10 days to keep her airways open and had lesions in her lungs that were growing—a bad sign, since lung papillomas have a high risk of becoming malignant and can also destroy the lungs.

“We’re very encouraged that all three of these patients are showing improvement on Celebrex,” says Dr. Steinberg. As for the Texas woman, “her lung lesions have stopped growing, and she only needs laryngeal surgery every four months rather than every 10 days,” says Dr. Steinberg.