Human Papillomavirus and Oral Cancer: Looking Toward the Clinic

By Caroline McNeil

Head and neck cancer researchers are considering clinical studies, including a proposed cooperative group treatment trial, that would investigate the link between human papillomavirus (HPV) and some oral cancers. Although the studies are still in the planning stage, they mark a new turn toward the clinic for an area that up to now has centered mostly on epidemiologic and laboratory studies.

Over the past decade, population studies have established an association between HPV and some tumors in the oropharynx (tonsils, soft palate, posterior pharynx, and base of tongue). Much remains unknown about the biology and natural history of oral HPV infection, but evidence of its association with these tumors is so strong that the International Agency for Research on Cancer concluded, in a monograph published in December, that there is “sufficient evidence in humans for the carcinogenicity of HPV16 in the oral cavity and oropharynx.”

Now researchers are beginning to ponder the clinical implications of this link. Especially intriguing to many are data suggesting that HPV-positive oropharyngeal tumors respond better to treatment than HPV-negative tumors. That finding has given rise to important clinical questions, including the one to be addressed in the proposed trial: Can HPV-positive tumors be treated less aggressively than HPV-negative tumors? That finding has given rise to important clinical questions, including the one to be addressed in the proposed trial: Can HPV-positive tumors be treated less aggressively than HPV-negative tumors because of their increased sensitivity to chemotherapy and radiotherapy?

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The risk factors are completely distinct and do not overlap,” said Maura Gillison, M.D., Ph.D., a Hopkins cancer researcher and lead author on this study as well as the New England Journal of Medicine article. “These are actually completely different cancers that happen to occur in the same place,” she said.

Others demur. This is “very groundbreaking work,” said Jatin Shah, M.D., chief of the head and neck service at Memorial Sloan-Kettering Cancer Center in New York, “but it remains to be proven that these are distinct pathological entities.” Tissue samples from HPV-positive and HPV-negative tumors look alike, he argues. And although HPV-positive patients have a better chance of responding to chemoradiation, the reasons are unknown. “This is a very provocative question,” he said. “We need more research in the lab to answer it.”

The question is particularly urgent in oropharyngeal cancer because of the acute and prolonged toxicity of current treatments, Shah said. The treatment can result in lifelong problems with swallowing and speech. And for HPV-positive patients, who are more likely to be young, that can mean many decades of severely impaired quality of life.

Still Hypothetical

Nevertheless, Shah and others warn against modifying the standard treatment now. Forastiere, who chairs the head and neck committee of the National Comprehensive Cancer Network, said that “it would be premature to make practice changes … quite dangerous, really.” The cancer network’s 2008 treatment guidelines for oropharyngeal cancer will not mention HPV status, she said.

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The link between HPV and oropharyngeal cancer also raises the possibility of targeting those tumors with a therapeutic vaccine. At Hopkins, Gillison and her colleagues have completed a phase I trial with an experimental treatment vaccine and are now analyzing the data. After 2 years of follow-up, she said, all 18 patients in the trial were doing well.

And if further studies confirm that HPV-positive patients have better response rates and survival, their improved prognosis could affect the staging system for head and neck cancers. Though a long way off, that possibility is already the subject of conjecture. Gillison said that, someday, HPV-positive and HPV-negative tumors might be staged as two separate diseases, in the way that small-cell and non–small-cell lung cancer are.

Shah, who chairs the head and neck section of the American Joint Committee on Cancer, which develops, maintains, and
revises the tumor–node–metastasis staging system used in most cancers, said that one possibility would be to consider HPV status as an additional factor that influences prognosis. This factor may be considered in the future, he said, and could be similar to the way additional factors affect stage in other cancers. In thyroid cancer, for instance, anyone younger than 45 years is downstaged to a stage 1 or 2, even with distant metastases.

But HPV's effect on oropharyngeal staging is still hypothetical, Shah emphasized. The joint committee is not considering any changes to the current system. “The time may come when HPV status will be a factor,” he said, “but there needs to be a lot more science before that.”

Prevention and Screening?
The link between HPV and oropharyngeal cancer also has potential implications for prevention. Will it ever be possible, for instance, to detect precancerous changes in the oropharynx, as in the cervix, with the help of HPV-based screening?

Detecting signs of oral HPV infection is not difficult—in oral rinses, for instance. But finding evidence that the viral DNA has been integrated into oropharyngeal basal cells and identifying submucosal, premalignant changes before they become visible is “a bit trickier,” Gillison said.

An even more fundamental barrier to screening is a lack of knowledge on how, or even whether, persistent oral HPV infection progresses to premalignant changes in the oropharynx.

“We don’t know what the infection looks like in premalignant cells. We don’t know if premalignant lesions in the oropharynx relate to HPV,” said Aimee Kreimer, Ph.D., in the division of cancer prevention at the National Cancer Institute in Bethesda, Md. “It’s so new. We don’t know the natural history of oral HPV infection.”

Shah said that studies are needed to show whether oral HPV infection progresses to dysplasia, as it does in cervical cancer. Doing so would take a prospective, longitudinal study of people with HPV infection, followed by visual detection of premalignant changes, he said. Or researchers might look for surrogate markers of progression by using random biopsies. “I don’t know if anyone is doing this, but it would be an exciting project,” he said. “It’s the logical next step.”

One smaller step toward understanding the natural history of HPV oral infection is a study, now in a pilot stage, designed to look at the persistence of these infections, Kreimer said. The study will be nested in a larger study—led by Anna Giuliano, Ph.D., at the H. Lee Moffitt Cancer Center in Tampa—which is monitoring men to evaluate anal and penile HPV infections.

Primary prevention of oropharyngeal cancers is another possibility that intrigues HPV researchers. Current HPV vaccines, designed to prevent cervical cancer, could theoretically prevent HPV-positive oropharyngeal cancers as well. Both Merck’s Gardasil and GlaxoSmithKline’s Cervarix (which was approved in Australia but not yet in the U.S.) target HPV16, which is implicated in most HPV-positive oropharyngeal cancers. And animal studies suggest that vaccination will prevent oral cancers. Hopkins researchers have proposed a prevention study to Merck, but when contacted for this article, a company spokesperson said that it is not currently working on plans for such a trial.

However, other studies may provide some data on this issue. Kreimer said that
the NCI is considering adding an oral HPV component to its follow-up study of women in Costa Rica who participated in a trial of GlaxoSmithKline’s prevention vaccine. The study would compare the prevalence of oral HPV infection among women who received the vaccine with women who did not.

More studies—of all kinds—are likely. The NCI head and neck steering committee will convene a state-of-the-science meeting in November to help identify and prioritize research needs, said Claudio Dansky Ullmann, M.D., NCI’s lead for head and neck cancer trials, who serves on the steering committee. “We will bring the top experts in this area to discuss the current status of things and, we hope, to lay a platform plan for the development of future translational and clinical studies to advance the field,” he said.

And there seems little doubt that some of those studies, such as the proposed treatment trial, will explore whether HPV-positive and HPV-negative patients should be treated differently. “We find the data indicating that HPV-positive and HPV-negative cancers are distinct disease entities to be compelling,” Forastiere wrote in an e-mail. “Consequently, we are factoring this into clinical research questions and trial designs going forward.”

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