AUTHOR COMMENTARIES - From Special Topics

Human Papillomavirus - July 2008
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Dr. Cosette M. Wheeler
From the Special Topic of Human Papillomavirus

In our Special Topics analysis of HPV research over the past decade, the work of Dr. Cosette Wheeler ranks at #7 by total cites, with 51 qualifying papers cited a total of 3,064 times. She also has five papers on both the 10-year and 2-year top 20 papers lists, in addition to having 10 papers featured in the Research Front Map on HPV.

In Essential Science Indicators℠ from Thomson Reuters, Dr. Wheeler's work ranks in the top 1% in the field of Clinical Medicine. Her overall citation record in the database includes 62 papers, mostly classified in the field of Clinical Medicine, cited a total of 3,799 times between January 1, 1998 and April 30, 2008.

Dr. Wheeler is a Professor in the Departments of Molecular Genetics and Microbiology and Obstetrics and Gynecology, Chief of Translational Research for the Department of Molecular Genetics and Microbiology at the University of New Mexico Health Sciences Center.

In the interview below, she talks with* ScienceWatch.com *correspondent Gary Taubes about her HPV research.

SW: What do you consider your most significant contributions to HPV research?

My group has had a couple of significant contributions related to both primary and secondary HPV prevention: one was in contributing to describing the broad spectrum of papilloma virus types infecting the human genital tract. There is a whole group of different viruses that infect the genital tract—actually over 40 of them. We worked with several groups all over the world trying to dig these out. Then we asked the question, "How stable are these viruses, and how much variation do they have?" If I see HPV type 16 in Asia, is that the same as the one in South America?

We described what might be called extended genomic intratypic sequence variance. So we first found that there were over 40 of these viruses. Then we went and looked at some of them closely, and realized there are very fixed variants of each individual HPV type studied. We demonstrated that co-variation across all regions of HPV genomes was common. This means that you can often predict the expected sequence changes that will be found in multiple regions of an HPV genome if you know the changes in just one region. Overall this information was important to the development of appropriate broad-spectrum HPV diagnostic tests and to considering possible differences of variants in risk of disease.

We worked with colleagues at the US National Cancer Institute to characterize an HPV assay that is now routinely used in cervical screening programs for the clinical management of women with atypical Pap tests. Our HPV genotype data generated through the NCI ALTS trial has also contributed to understanding the natural history of HPV infections and their disease outcomes.

I think you know that we have also been a significant contributor to the development of HPV vaccines for more than a decade.

"The vaccine is not a trivial expenditure of money when you consider that it does not eradicate risk or make Pap smears irrelevant."

SW: Could you explain what you mean by "variants" and the "stability" of the viruses?

Well, this is not like HIV, which mutates in our time period and becomes something else. Even though HPV types vary, they varied a long time ago. In our era, they're essentially fixed. Working with my colleague Uli Bernard, who was then in Singapore and is now at UC Irvine, we contributed information important to a molecular clock that tells you the rate at which these viruses have been evolving—how frequently they change.

Because human papillomaviruses, to our knowledge, are not changing rapidly and thus are apparently somewhat "fixed," we don't think some new monster virus is going to arise from the evolutionary pressures of HPV vaccination. What we showed is that HPVs vary—as compared to saying they mutate—and they did so over millennia. Nearly all animals studied have their own species-specific papilloma viruses. So you can actually correlate speciation events using phylogenetic information for these animal viruses. A collaboration of our group with Long Fu Xi at the University of Washington supported the idea that HPVs co-evolved with individual human racial groups as well.

SW: Does that mean these viruses evolve along with the species?

Yes. The idea is bigger than just what is seen in HPV infections. Common persistent viruses, parasites, and bacteria have often been infecting their host species for so long that they have co-evolved. Because of the co-evolution, these viruses don't necessarily trigger much of an immune response. These are things we all get infected with, that can go underground or cause virtually no symptoms or noticeable problems and, in some people, these are the viruses that are later associated with cancer. Epstein-Barr virus (EBV) is another example. These are super-common infectious agents—bacteria like *Helicobacter* are yet another example—and they do well in populations. They are common infections that persist without much of an immune response, but in some people, over time as they persist they can make the cells they are associated with go awry.

SW: So most people carry human papilloma virus, but it only causes disease in some of them?

Most people who get these infections get rid of them. They might have a low-grade abnormal Pap smear, but that's it—the virus almost always goes away on its own. If you look at the incidence of invasive cervical cancer in a country that has no Pap screening program, it might be between 200 and 300 persons per 100,000. But maybe 50,000 out of every 100,000 have been infected. So only 200 to 300 get a bad outcome. It's not as if the outcome is bad in everyone, or even most people. And it's not as if any of these viruses or bacteria have the intention of doing something useful for themselves by causing disease. Actually, they're very well adapted to *not* cause disease. It's when there's failure, probably due to complex host genetic factors, as well as other co-factors that are not well understood that disease happens.

SW: Was the highly cited 2002 *New England Journal of Medicine* vaccine the proof of principle for the HPV vaccine? (Koutsky A, *et al*., "A controlled trial of a human papillomavirus type 16 vaccine," *N. Engl. J. Med*. 347[21]: 1645-51, 21 November 2002)

Yes. That work told us that this vaccine actually worked, based on this study in about 2,000 women. Then there were the phase III trials, which, of course, are always required and the most influential. My group at the University of New Mexico did the first phase I trial of the Merck vaccine with investigators at Indiana University. The phase I study was actually published after the phase II study reported in the *New England Journal*. This was because they were conducted so close in time and it was more important to present the proof of principle results. We have been one of the leaders bringing HPV vaccines forward beginning at phase I all the way through phase III.

SW: How has the vaccine itself evolved through this past decade?

It started off as a monovalent vaccine—one papilloma virus type in the vaccine. The first trial we did in New Mexico was HPV type 11. That was the first phase I of the Merck "product." The one in that 2002

New England Journal of Medicine paper was the monovalent type 16. Type 11 was a model for various complicated laboratory reasons. Type 16 is the main virus in cervical cancer—that's one you want for a vaccine. So type 16 was the proof of principle. In this study, there were41 cases of HPV16 infection in the placebo group and none in the vaccine group.

Then came the quad-vaccine that had types 6, 11, 16, and 18. That was the prototype for the Gardasil vaccine. GlaxoSmithKline was trying to bring forth their bivalent vaccine— for HPV 16 and 18 during this same time and we have also worked on these vaccines for the past seven years.

SW: Do you think that all young women should be vaccinated to prevent cervical cancer?

It depends on what is meant by "all young women." I disagree with the recommendation to vaccinate all girls and women between the ages of 11 and 26.

SW: Why?

Because Pap screening works well in sexually active women. We have reached a plateau on the impact of Pap screening. We've reduced rates of cervical cancer by 70-80% of what they used to be 40 years ago. We pay about five to six billion dollars a year to do that in the United States.

We have a residual amount of the disease that we've been unable to conquer. As much as 60% of that is attributable to people who don't go to the doctor as recommended for Pap tests. Without getting these women screened we are potentially not going to reduce cervical cancer rates any further. That's where the vaccine comes on the scene. We know these vaccines are prophylactic and do not seem to help therapeutically. If you're already infected, they therefore won't help you. As the population ages—we're talking populations, not individuals—the average number of lifetime sexual partners increases. Genital HPVs are sexually transmitted infections. By the time women are 23 or 24 years old, the average number of lifetime sex partners in a population is about four. And that number, that kind of information, is probably underestimated because women underreport in a society that considers multiple lifetime sexual partners to be undesirable. The bottom line is that the maximum benefit of current HPV vaccines is primarily realized in presexually active adolescents.

There are other aspects of my perspective. Can you think of a single example where the US government has said, "Let's go out there and spend billions of dollars to vaccinate a population that's already largely been exposed to any agent particularly one where most people will get rid of it on their own?" In effect, we're saying. "We can't tell exactly who has been exposed, but even if they have been exposed, they may get some benefit if there is one or more of the HPV types in the vaccine that they haven't already seen." We're not talking about the normal, garden-variety vaccine at $10 a shot. We're talking about $120 a shot with three shots needed to achieve protection.

SW: How effective is the vaccine? Won't it at least protect women who don't already have the virus?

"...the ultimate question we want to answer is what difference will all this work over the past two decades make?"

These vaccines are highly effective in females who are naïve to the HPV types in the vaccine. This means that they work best or are most effective in sexually naïve individuals. The primary mode of genital HPV transmission is sexual intercourse although there are other modes that are much less common. These current HPV vaccines however only target a few types of virus. They don't allow vaccinated girls or women to not get Pap smears. You still have to get Pap tests because 30-40% of cervical cancers are caused by virus types that aren't in the vaccines. So the five to six billion we spend in the US on Pap smears doesn't go away at least until we really figure out what screening modifications are safe and have achieved very high vaccine coverage.

The vaccine is not a trivial expenditure of money when you consider that it does not eradicate risk or make Pap smears irrelevant. On the other hand, if we had a multivalent vaccine that targeted, say, 8-10 virus types, constituting maybe 90-95% of the human papilloma viruses that cause cervical cancer, then that would be a good thing. In theory we could virtually eliminate screening as we know it. Then I'd say, "OK, vaccinate women up to age 40," because now there is greater benefit to more women and better cost-effectiveness in terms of healthcare expenditures.

SW: So what message would you give to women in general when they're thinking about getting this vaccine?

I would tell women 18 and under that the vaccine is a good and reasonable cervical cancer prevention approach. They must still remember to get regular Pap tests even if they receive the vaccine. For

women over 18, they should discuss their past sexual history with their providers to determine whether HPV vaccines are likely to be beneficial. All women vaccinated or not should get Pap tests and continue with cervical screening until we have, hopefully, a better vaccine and new recommendations. Better vaccines are certainly on the horizon. Here's my philosophy: I'm hopeful that the next generation vaccine will be realized and, in the meantime, with current first-generation HPV vaccines, we can invest in implementing the clinical platforms that are necessary to deliver to those who will benefit most.

The thing is that after kids are five years old and they get their last vaccine and go off to school, they basically go to the doctor only as required for sports physicals or acute illnesses. There's no routine health care for adolescents, and we're going to need some kind of adolescent vaccine platform that really works if we're going to get the vaccine to people who are young enough to really benefit.

SW: What are you focusing on in your current research?

Two things. We are evaluating a large population sample of all the circulating HPVs in the state of New Mexico by sampling residual liquid Pap smear materials. Then we have established an information system that is monitoring all Pap smears, all HPV tests, and all cervical pathology collected on New Mexico residents. After spending a career hoping to make a difference in the clinical management and prevention of HPV related disease, I want to see if the improvements that have been developed will really make a significant difference.

SW: Don't we know that it makes a difference?

The truth is that we have no idea what really happens in the US with screening. That's not the same thing as knowing that screening works. The questions are who gets screened, and how often? Never before have there been US population-based surveillance programs for Pap smears. There are cancer registries. We know a lot about cancer. We know virtually little about population-based cervical screening. Then I want to see what HPV vaccines actually reduce including abnormal Pap tests which should be reduced long before we ever see any reductions in cervical cancers. To do that we need a Pap smear registry that can tell you what was happening before the vaccine coverage was high and then what it looked like afterward; what's changed? We will want to ultimately link the Pap smear information with the New Mexico Statewide Immunization Information System (NM-SIIS).

So one component of doing molecular epidemiology is conducting population-based surveillance. I want to know what diseases are being diagnosed and what the behavior of the population is. Do women really get Pap smears every year? Every two years or every three years, etc.? What's the average screening interval and how does this differ by age, race, and ethnicity? Right now, no one really knows, and much of what we believe happens is based on telephone surveys of a few women and obviously only women with telephones. This is the first population-based data that will be able to tell us precisely what is occurring.

And because of our other project, we'll be able to say what the prevalence is of the specific HPV types circulating in the population. So if the vaccine works in the population, not just in a clinical trial, which I think it will, what will be the impact? Will it be what we expected? And will there be other problems that we didn't anticipate? Will women get Pap tests as recommended who are vaccinated? Maybe HPV types that aren't in the vaccine will increase in their prevalence? We don't expect they will, but as with many interventions, we can't really predict everything when we are in fact dealing with individual people and Mother Nature.

So that's what I'm currently doing, evaluating our state population. My lab now collects about 17,000 or 18,000 specimens per month and we now have a database of about 1.5 million records. This is one of the largest projects like this ever done. And the ultimate question we want to answer is what difference will all this work over the past two decades make? I also wanted to develop and contribute something that I could pass on when I retire, so my work wouldn't come to an end just because I was no longer actively involved. What we are doing now is for the long-term good of the public. We will be able to tell people including policymakers what this vaccine does and does not do. And as we make changes in screening, we can see if they're really good or bad. We expect that over time HPV testing will possibly replace Pap tests in primary screening and we'll have established an ability to collect data in real populations beyond clinical trials. We won't just be relying on theory or phone surveys. I'm very excited about this.

SW: When do you expect to begin having meaningful results?

We just started to see the tip of something meaningful with our data from 2006 through the end of 2007. That's our first full two-year interval. We could see how many women got a Pap smear in the population

during that time; how many got one in 2006 and then came back again one year later. By the end of 2008, we'll have three full years of data and that will begin to become really useful. In particular we hope to improve our abilities to identify disparities in the delivery of primary and secondary cervical cancer prevention strategies.

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Dr. Cosette M. Wheeler's most-cited paper with 721 cites to date:

Koutsky LA, *et al.*, "A controlled trial of a human papillomavirus type 16 vaccine," *N. Engl. J. Med.* 347 (21): 1645-51, November 21, 2002. Source: *Essential Science Indicators* from Thomson Reuters.

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