



HPV infection initiates cellular transformations within the cervix that can progress to cancer. Work toward the goal of eliminating cervical malignancy has focused on 1) better cytology and HPV screening protocols, 2) more highly defined management of positive screens, and 3) broad coverage of target populations of girls and women with the HPV vaccine.

ILLUSTRATION BY KIMBERLY MARTENS FOR OBG MANAGEMENT



UPDATE ON CERVICAL DISEASE

↪ The author revisits his declaration in the 2006 Update that “we’re on the way to ending cervical cancer.” What’s happened in 3 years with screening, HPV testing, and cancer prevention?



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In the March 2006 “Update on Cervical Disease,” I began with Prof. Margaret Stanley’s exclamation “It could be the end of the affair with HPV!” That Update covered three major areas that have been nudging us closer to the possibility of someday ending cervical cancer.

I thought it time to revisit those three practical advances to see how we’re doing. As you’ll read, much has happened; one exciting prospect in 2006—human papillomavirus (HPV) vaccination—has become established in everyday practice. On the other hand, primary screening with an HPV plus a Pap test (so-called co-testing) has not yet fulfilled its promise, and type-specific HPV testing for HPV 16 and 18, expected in 2006 to be “just around the corner,” is still ... just around that corner.

And it isn’t just medicine that has changed. The World of 2009 is a markedly different place than the World of 2006. The economy of the United States is rockier than at any time since the Great Depression, and the skyrocketing cost of medical care has made health-care cost containment more important a goal than it ever has been.

So, allow me to reexamine what was “new in 2006” for cervical cancer prevention and compare where we are in 2009—thanks to interesting, important research and the effects on health care of an economic squeeze that we could not have foretold 3 years ago. I’ll also make an educated prediction about where cervical cancer prevention may be headed in, say, the next 3 years or so.

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1 “More sensitive and more objective screening” inches closer

Naucner P, Ryd W, Törnberg S, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J Natl Cancer Inst. 2009;101:88-99.

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Comforting combo: Negative Pap and HPV tests

In 2006, I discussed the Level-A evidence, cited in the 2005 ACOG Practice Bulletin, that women who have a negative HPV test and a negative Pap (i.e., a co-testing protocol) have a risk of approximately 1 in 1,000 of an unidentified CIN 2,3 or cervical cancer and, therefore, do not need another Pap or HPV test for at least another 3 years. This would seem compelling evidence of the efficacy and safety of co-testing, so the expectation might be that this cervical screening strategy would quickly become the primary protocol for women 30 years or older.

But not so fast! Even though a recent Centers for Disease Control and Prevention (CDC) survey indicates that 66% of clinicians who provide cervical screening already used co-testing by 2004,¹ recent estimates are that only one third or fewer of women 30 years or older are being screened with a Pap test + HPV test. What does this mean? Possibly, that co-testing is used by a majority of clinicians, but not routinely. There are, likely, a number of reasons that co-testing has not become standard, but hesitancy to move beyond the annual Pap test is at the top of the list.

Will we move beyond tradition?

Providing an annual Pap test to our patients has reduced the incidence of cervical cancer from second among cancers in women to 11th, and mortality from second to 113th. But a program of annual cervical cytology is not cost-efficient² even if it is protective for most

women, and the degree of protection declines among women who are screened irregularly.

Screening can be made more cost-effective by extending the screening interval. One option is to repeat the Pap every 2 or 3 years, instead of annually, for women who have had three consecutive normal Pap tests. The additional risk of cervical cancer that results from extending the screening interval to 3 years is estimated to be 3 to 5 cases for every 100,000 women³—numbers that are small but that are unacceptable to many, considering the great potential for preventing cervical cancer.

The other option is to add HPV testing to screening. Because an HPV test is more sensitive for CIN 2,3, a negative result provides long-lasting reassurance against cancer risk. **Enter, economics.** Adding an HPV test to the screen without increasing the interval is not cost-effective: It increases overdiagnosis and overmanagement and, thereby, harm.

Moving to less frequent screening is the only option for improving the cost effectiveness of cervical cancer prevention; less frequent screening reduces not only **1)** the number of tests but also **2)** detection of transient HPV infections not destined to progress and **3)** overmanagement and treatment of such benign infections. And the high sensitivity and long-term predictive value of an HPV test ensures that moving to a longer interval isn't likely to put women at more risk even if the next screen exceeds 3 years. Major studies confirm this margin of safety and validate a move to less frequent screening. Here's what we learned in the past year.

In search of an optimal protocol

Most research on co-testing continues to come from Europe, where organized screening programs have facilitated large studies **Naucner and colleagues** used the database from the intervention arm (n = 6,257 women) of a population-based randomized trial (the Swedescreen Trial), in which a conventional



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Pap smear and HPV test were obtained from women 32 to 38 years old, to evaluate the efficacy of 10 cervical screening strategies based on HPV DNA testing alone, cytology alone, and co-testing with both tests.

Compared with screening by cytology alone, co-testing that included **1)** referral to colposcopy of all women who had an abnormal Pap and **2)** testing for type-specific HPV persistence at 12 months for women who initially had a normal Pap and a positive HPV test resulted in a 35% increase in sensitivity for detecting CIN 3+, with only a modest reduction in positive predictive value. The researchers noted, however, that the gain in sensitivity came at the expense of doubling screening tests because screening in Sweden already occurs at a 3-year interval.

Solomon and co-workers estimated that, in the very near future, 75 million Paps will be performed each year if we don't change our screening strategy from annual cervical cytology. If all screened women younger than 30 years had a liquid-based Pap every 2 years as recommended by the ACS, however, and if all screened women 30 years or older had a Pap test and an HPV test every 3 years, the number of annual Paps would decline to 34 million. Because this protocol requires a similar number of HPV tests for women older than 30 years, the total number of primary screening tests (HPV + Pap tests) would be only marginally less than the Paps performed at the present interval. But it is expected that less frequent screening would also reduce the number of transient HPV-induced cytologic events detected that require follow-up.

Are there other options?

Additional savings are possible if **1)** both the Pap test and the HPV test did not need to be performed together or **2)** the screening inter-

val could be longer than Solomon described.

Naucler and colleagues clearly demonstrated that the most effective of the 10 screening options they evaluated was **screening with an HPV test first** (the most sensitive test) followed by a Pap test (the most specific test) only on women who have a positive HPV test. This protocol increased the sensitivity for CIN 3+ by 30% over the detection rate when the Pap was the only screening test, maintained a high positive predictive value, and increased the number of screening tests over the triennial "Pap-only" protocol by just 12%. In the United States, this approach would significantly decrease the number of screening tests, and should decrease costs, compared with the number of tests and costs associated with the traditional annual Pap test.

However, whether co-testing will ever be replaced by an HPV test as the sole primary screen depends on whether we are willing to accept a small decrement in protection in exchange for a major gain in cost effectiveness. In the past, safety has trumped but, in every aspect of health care to come, this will be the trade-off debated if, as a nation, we are to make our health care more affordable.

Can a longer HPV screening interval adequately protect patients?

A basic concern that clinicians have with the 3-year screening interval is that some women may not come in for screening until 4 or 5, or even more, years. Their concern is justified; numerous studies have confirmed that extending the screening interval beyond 3 years for women screened by cytology significantly decreases protection.

How protected would women be if they were screened with an HPV test? Dillner and colleagues demonstrated in their study that women who have a negative HPV test could have their interval safely extended for at least 6 years. Their work suggests that women who are screened infrequently would be significantly protected well beyond the 3-year interval now recommended in the United States with co-testing. However, it is important to point out that no screening test is perfect, and the reduction of cancer risk to zero is unlikely.

FAST TRACK

The most effective of 10 screening options evaluated was screening with an HPV test first (the most sensitive test) followed by a Pap test (most specific) only on women who have a positive HPV test

WHAT THIS MEANS FOR PRACTICE

Although the recommended screening interval is 3 years after a negative co-test, women screened by HPV testing have a margin of safety for at least 6 years. Irregularly screened women are therefore likely to be better protected even if the next screen surpasses 3 years.



2 “Better management of screen positives”—we wait for new testing technology

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CASTLE PE, DOCKTER J, GIACCHETTI C, et al. A cross-sectional study of a prototype carcinogenic human papillomavirus E6/E7 messenger RNA assay for detection of cervical precancer and cancer. Clin Cancer Res. 2007;13:2599-2605.

Type-specific HPV testing identifies highest risk

By 2006, it had become clear that testing for HPV types 16 and 18 would identify those HPV-positive women who are at highest risk of CIN 2,3+. Investigators introduced a potential management algorithm that would likely alter the care of Pap-/HPV+ women once such testing became available.

Three years later, however, type-specific HPV testing still isn't available. Why not?

One reason may be that type-specific HPV testing is much more complicated than the molecular tests that we use to identify a single virus or bacterium (e.g., *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) because the test has to identify several or more HPV types in a single assay. Proof of clinical utility requires more complex clinical studies than required for other sexually transmitted infections that have a quick therapeutic solution.

As we end the first quarter of 2009, no new HPV test or marker has yet been approved by the Food and Drug Administration (FDA) for clinical use. However, one of the three most promising candidates, HPV DNA testing for HPV 16, 18 (Invader HPV DNA [Hologic]) may be close to approval, and another, based on detection of messenger RNA (mRNA) has begun clinical trials (Aptiva mRNA [GenProbe]).

The Invader HPV (Inv2) test detects 14 high-risk HPV subtypes that are grouped in three probe sets on the basis of their interrelatedness. Results are reported as positive or negative for the entire probe set, not for individual viral types. The probe sets are:

- A5/A6 (HPV types 51, 56, and 66)
- A7 (types 18, 39, 45, 59, and 68)
- A9 (types 16, 31, 33, 35, 52, and 58).

The types in the A7 probe set are found more often in glandular lesions, such as adenocarcinoma in situ. Types in the A9 group are more often responsible for the squamous lesions of CIN 3 and squamous cell cervical cancer (although types in both groups can cause either type of lesion).

HPV E6/E7 mRNA testing for high-risk types may correlate better with the severity of lesions than HPV DNA testing—because up-regulation of mRNA from the oncogene region of the HPV genome (E6 and E7) is likely to be more predictive of which HPV-infected women are most likely to persist and progress to a high-grade lesion and cancer.

Castle and co-workers reported in their study that subjects in their study tested positive for HPV E6/E7 mRNA in 94% of cases of CIN 3 (46 of 49 women) and in all five cases of cancer. Overall, fewer specimens that were not characterized by a high-grade lesion tested positive for HPV E6/E7 mRNA than for HPV DNA.

WHAT THIS MEANS FOR PRACTICE

A move to a more efficient and, potentially, more cost-effective cervical disease screening paradigm awaits FDA approval of **1)** a type-specific HPV test or **2)** a marker test that is more predictive of which HPV-infected women are likely to persist and progress to a high-grade lesion and cancer.



Type-specific HPV testing is more complicated than the molecular tests that we use to identify a single virus or bacterium because the test has to identify several HPV types in a single assay

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3 “HPV vaccine ... in our offices” — is confirmed safe and efficacious

Joura EA, Kjaer SK, Wheeler CM, et al. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. *Vaccine*. 2008;26:6844-6851.

Centers for Disease Control and Prevention (CDC). Syncope after vaccination—United States, January 2005–July 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:457-460.

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Kuehn BM. CDC panel recommends vaccine for smokers; reviews HPV safety data. *JAMA*. 2008;300:2713-2714.

The vaccine that protects against certain types of HPV, and probably against cervical cancer caused by those types, wasn't approved by the FDA when the March 2006 “Update on Cervical Disease” was published. Preapproval expectations were high at the time; what we have witnessed since approval of Gardasil (Merck) has, in fact, exceeded earlier expectations.

As of August 31, 2008, more than 20 million doses of Gardasil have been administered. A CDC survey of 3,000 US adolescents 13 to 17 years old showed that one of every four received at least one shot of the vaccine in 2007, the first full year after approval. This uptake of the HPV vaccine during its first year is significantly better than 12% for the meningococcal vaccine and 11% for Tdap in the year after their introduction.

Is the vaccine efficacious?

Recent data from Joura and colleagues, based on more than 6 years of follow-up of women immunized with the quadrivalent vaccine, have not shown any decrease in protection from CIN 3+. There has been concern, however, that falling antibody levels that have been noted, particularly against HPV type 18, may indicate reduced protection from high-grade squamous or glandular disease.

To clarify the matter, these investigators evaluated efficacy data on the 40% of vaccine subjects who were anti-HPV 18-seronegative

at the end of the study. Despite the inability to document antibodies to HPV 18 in these subjects, **efficacy against HPV 18-related CIN 3 or adenocarcinoma in situ remained high at 98.4%** compared with the placebo group. These results suggest that vaccine-induced protection is high despite lower-than-detectable anti-HPV 18 titers.

How safe is it?

The safety of the HPV vaccine was studied in seven clinical trials in more than 21,000 girls and women 9 to 26 years old before it was licensed. The conclusion was that **this is a very safe vaccine**. But much has been made in the media—and even in a few peer-reviewed articles in the medical literature—that nevertheless questions the safety of Gardasil, and there is little doubt that clinicians who administer the vaccine have been bombarded with questions about this by their patients.

As of August 31, 2008, there were 10,326 Vaccine Adverse Event Reporting System (VAERS) reports of adverse events following Gardasil vaccination in the United States: 94% were considered nonserious and 6% were serious. These numbers appear great, but a 6% rate of serious adverse events is only about one half of the 10% to 15% rate observed after other vaccines made their debut.

VAERS, one of three systems utilized to monitor the safety of all vaccines after licensing and marketing in the United States, is open to the public. This means that it collects data without verifying the relationship of the adverse event to the vaccine other than proximity of timing. In a joint July 2008 Web-site posting, the CDC and FDA said: “In some media reports and on some web sites on the Internet, VAERS reports are presented as verified cases of vaccine deaths and injuries. *Statements such as these misrepresent the nature of VAERS surveillance system.*”

FAST TRACK

There has been concern that falling HPV antibody levels, particularly against type 18, may indicate reduced protection from high-grade squamous or glandular disease

As part of ongoing surveillance, the CDC met in October 2008 to review Gardasil safety data. A synopsis of findings follows.

Minor adverse events

Reports of nonserious adverse events include syncope, pain and swelling at the site of injection (the arm), headache, nausea, and fever. The most common side effect reported to VAERS is syncope.

The FDA-CDC report emphasizes that syncope as a vasovagal reaction can occur after any vaccination, particularly in an adolescent. Syncope is not serious unless the patient is injured as she falls.

Major adverse events

Of course, greatest concern over the safety of the HPV vaccine is with reports of major adverse events following administration—including death. The October 2008 FDA-CDC review says that careful evaluation by medical experts of all serious reports has not found a common medical pattern to suggest that any were caused by the vaccine. Here is a summary of serious adverse-event reports submitted to VAERS between June 8, 2006, and August 31, 2008.

Guillain-Barré syndrome has been reported after vaccination with Gardasil. This rare disorder occurs in 1 or 2 of every 100,000 adolescents, and can be caused by any of several infectious agents. The FDA and CDC report no indication that Gardasil increases the rate of Guillain-Barré syndrome in females above the rate expected in the general population.

Blood clots have been reported in the heart, lungs, and legs of women after vaccination with Gardasil. In most cases, thorough evalu-

ation identified other risk factors for clotting, including use of an oral contraceptive.

Death. There have been 27 reports in the United States of death among females who have been given the vaccine. The FDA-CDC review of each case has not documented a common pattern to these deaths to suggest that the vaccine was the cause of death. Here is a breakdown of those 27 reports:

- 3 related to diabetes or heart failure
- 3 to a viral illness, including meningitis
- 2 to drug use
- 2 to blood clots
- 5 are still being evaluated
- 1 report of a seizure disorder (patient had a history of seizures)
- 11 reports in which the cause of death is: unknown; cannot be evaluated because the person's name or the death is unverified; or is still under review while medical records are obtained. 🚫

WHAT THIS MEANS FOR PRACTICE

- Anti-18 antibody detection is not a good marker for determination of efficacy of the HPV vaccine for prevention of lesions caused by HPV 18.
- To prevent syncope-related injury, the CDC and FDA recommend that you keep patients in a seated position, observed, for 15 minutes after vaccination with Gardasil.
- Proceed with confidence in administering the HPV vaccine. The FDA-CDC report concludes that “based on all of the information we have today, CDC and FDA have determined that Gardasil is safe to use and effective in preventing 4 types of HPV. The CDC and FDA will continue to monitor the safety of Gardasil.”



The most commonly reported minor adverse effect of Gardasil has been syncope—although vasovagal syncope is known to occur after any type of vaccination

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