

## Educate the Educators Literature Update

In this quarter's *Educate the Educators Literature Update* we are sending you four articles that you should find interesting. The first article is by Castle *et al* and describes the prevalence of high-risk HPV DNA (hrHPV) among almost 600,000 women, 30 years and older, who were screened in the Kaiser Northern California health care maintenance organization.<sup>1</sup> Because of the enormous size of this database it should serve as the "gold standard" for determining what will be the impact of combining HPV DNA testing with cervical cytology when screening women 30 years and older in the U.S. The article is accompanied by a CDC sponsored survey of HPV DNA prevalence in the U.S. that was published in 2008 by Datta *et al*.<sup>2</sup> The CDC survey arrives at a much higher estimate than that of the Kaiser investigators.

The third article, by Bandyopadhyay *et al*, presents the experience of the Magee-

Womens Hospital in Pittsburgh in using hrHPV testing to manage women with ASC-H.<sup>3</sup> As with the Castle *et al* article, this article is important because it includes a relatively large number of cases. 1,187 women with ASC-H cytology results underwent hrHPV testing at Magee-Womens Hospital. The results of this article challenge the findings of previous studies of ASC-H since they suggest that "reflex" hrHPV testing is useful in women with ASC-H, especially those 40 years and older.

At press time the FDA has just approved use of the bivalent (HPV 16 and 18) vaccine in the U.S. for girls and women and the quadrivalent vaccine (HPV 6, 11, 16, and 18) for use in boys. This will be discussed further in the Winter Update. The bivalent vaccine has been approved for quite a while in the European Union and in many other countries such as Australia. One of the reasons for the delay in

approval in the U.S. was that the FDA had requested the end of study results from the large Phase III pivotal trial of the bivalent vaccine. The end of study results have now been published by Paavonen *et al* and are provided as the final article in the Fall *Literature Update*.<sup>4</sup>

In the "What's New" section we provide a brief Meeting Highlights from the May 2009 International Papillomavirus Conference held in Malmo, Sweden. As a final reminder – don't forget to download the PowerPoint slides documenting some of the key messages from these articles for use with your *Educate the Educators* slide set.

### ETE Editorial Committee

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## Five-year experience of human papillomavirus DNA and Papanicolaou test cotesting

Castle *et al.* *Obst. Gynecol.* 2009;113:595-600

## Papillomavirus infection and cervical cytology in women screened for cervical cancer in U.S., 2003-2005

Datta *et al.* *Ann Intern Med.* 2008;148:493-500

From a practice management perspective one of the most important variables with respect to using high-risk HPV DNA (hrHPV) testing together with cervical cytology when screening women 30 years and older is the number of women who will be hrHPV positive and require additional evaluation or follow-up. A number of studies from both Europe and developing countries have documented the prevalence of hrHPV positivity in cytologically negative women of different ages.<sup>5,6</sup> However, data from the U.S. has been relatively limited. The recent publication from Kaiser Northern California corrects this deficit since it provides hrHPV prevalence data from a large number of women undergoing routine cervical cancer screening.<sup>1</sup>

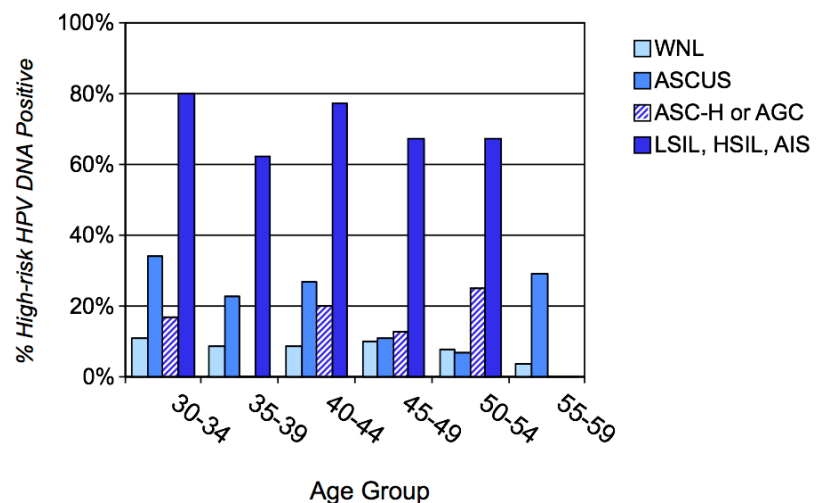
Before this publication there were just two large surveys of HPV prevalence in women of different ages in the U.S. Both were conducted by the CDC. The first included women enrolled in the National Health and Nutrition Examination Survey (NHANES). NHANES is a representative sample of the non-institutionalized civilian population.<sup>7</sup> Certain groups of women are oversampled in NHANES. These include adolescents, non-Hispanic Blacks, and Mexican Americans. A total of 2,026 women

participating in NHANES agreed to provide self-collected vaginal swabs that were tested for HPV DNA. HPV detection and typing were done using the Roche prototype line blot assay. The number of women 30-39 years, 40-49 years, and 50-59 years was relatively small: 328, 324, and 254 respectively. High-risk HPV (hrHPV) was identified in 18% of women 30-39 years of age, 13% of those 40-49 years old, and 7% of those 50-59 years of age. It is important to note that in NHANES, cervical cytology was not obtained, so the HPV prevalence in women with normal cytology results cannot be determined.

The second CDC survey is referred to as the HPV Sentinel Surveillance (HSS) project and is included as one

of the articles for the *Summer Literature Update*.<sup>2</sup> The HSS project enrolled 10,208 women 14-65 years of age from 6 cities across the U.S. Women were enrolled at a variety of clinical settings including 8 STD clinics, 10 family planning clinics, and 8 primary care facilities. A sample was taken for cervical cytology (either liquid or conventional) and a second sample was collected for high-risk HPV DNA testing using the Hybrid Capture 2 assay. **Figure 1** shows the prevalence of hrHPV positivity by age and cervical cytology result in women in the HSS project. The number of women in the older groups is relatively small (e.g., there were only 167 women 55-60 years old and 77 women 60-65 years of age) and

**Figure 1:** hrHPV Positivity by Cytology Result in HSS



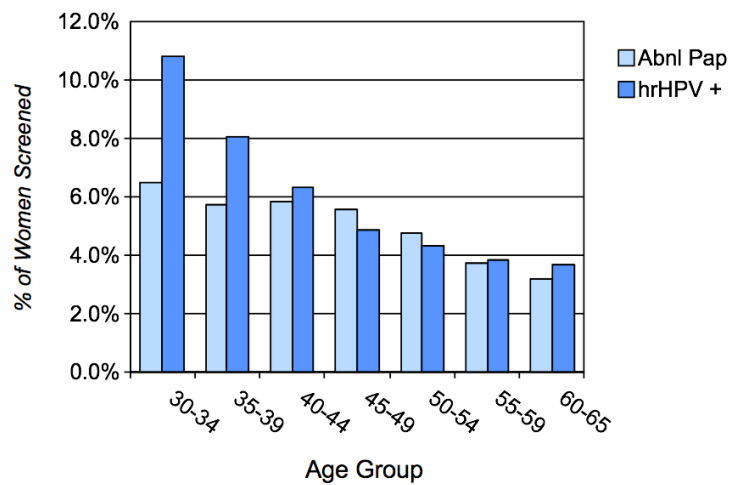
Adapted from Datta *et al.* *Ann Int Med.* 2008; 148

therefore, the estimate of HPV prevalence in these older age groups is imprecise. As expected the prevalence of hrHPV was relatively high in women with LSIL, HSIL, and AIS in all age groups. The most important finding from HSS is that the prevalence of hrHPV in women with normal cytology was 9-11% in women 30-49 years of age and 8% in women 50-54 years of age. This is higher than many of us expected and may indicate that the participants in this study are a relatively high-risk group compared to women presenting for routine cervical cancer screening in the U.S. This is evidenced by the fact that there were similar rates of hrHPV positivity among women 30 years and older enrolled from the different types of clinics (STD, family planning, primary health care).

Kaiser Northern California began offering hrHPV cotesting to its members 30 years and older in 2003. After five years 580,000 women had undergone cotesting using conventional cervical cytology and the Hybrid Capture 2 assay. **Figure 2** shows the prevalence of hrHPV positivity and abnormal cytology results (defined as ASCUS or greater) by age group. In women in their 30s the prevalence of hrHPV positivity is considerably greater than is the prevalence of cytological abnormalities. However, among women in their 40s and 50s the overall prevalence of cytological abnormalities and hrHPV positivity is essentially equivalent

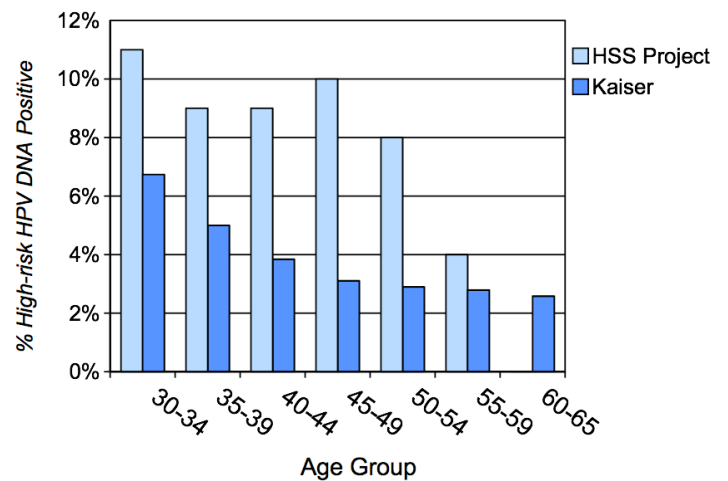
The Kaiser data differs considerably from what was observed in the HSS project in that the prevalence of hrHPV positivity in women with normal cytology results is much lower, **Figure 3**. In the routine screening population from Kaiser, the prevalence of hrHPV positivity in cytologically negative women in their early 30s is only 6.8% and drops to under 4% in women 40 years and older. This has quite important implications for clinicians considering whether or not to begin using hrHPV testing when screening women 30 years and older since it means that less than one in twenty women will need to be recalled in 12 months for retesting with both cytology and hrHPV testing.

**Figure 2:** hrHPV Positivity and Abnormal Cytology in Kaiser



Adapted from Castle et al. Obst. Gynecol. 2009; 113

**Figure 3:** hrHPV Positivity in Women with WNL Cytology



Adapted from Datta et al. Ann Int Med. 2008; 148 and Castle et al. Obst. Gynecol. 2009;113

## Adjunctive human papillomavirus DNA testing is a useful option in some clinical settings for disease risk assessment and triage of females with ASC-H Papanicolaou test results

Bandyopadhyay *et al.* Arch Pathol Lab Med. 2008;132:1874-1881

The management of women with atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H) is becoming increasingly controversial. The 2006 ASCCP Consensus Guidelines did not change the recommendation made in 2001 that all women with ASC-H be referred for colposcopy.<sup>8</sup> This guideline was based primarily on data from the large NCI-sponsored ASCUS/LSIL Triage Study (ALTS), which showed that 84% of the 110 ASC-H cases in ALTS were high-risk HPV DNA (hrHPV) positive.<sup>9</sup> Studies on the prevalence of HPV DNA positivity in women with ASC-H that were published prior to 2006 also reported relatively high rates of hrHPV positivity, ranging from 27% to 69%.<sup>8</sup> With such a high prevalence of hrHPV, "reflex" hrHPV testing was not felt to represent an efficient way to manage women with ASC-H. Moreover the high prevalence of CIN 2,3 in women with ASC-H means false negative hrHPV tests will be more of an issue in these women than in women with ASC-US.

The article by Bandyopadhyay *et al.* included in the *Literature Update* takes another look at the potential role of high-risk HPV DNA (hrHPV) testing of triaging women with ASC-H.<sup>3</sup> This is the largest study published

to date of ASC-H with concurrent hrHPV results. It is a 30-month, retrospective analysis (July 2004-December 2005) of 1187 women with ASC-H on liquid-based cytology who had concurrent hrHPV testing using the Hybrid Capture 2 assay. Many cytology laboratories in the U.S. have now switched to location-guided computer assisted screening of cervical cytology and in this report all the Papanicolaou tests were imaged using the Thin-Prep Imaging System. Over the time period of the review the overall rate of ASC-H in the laboratory was 0.6%. This is consistent with the mean rate of ASC-H in liquid-based cytology specimens (0.57%) reported by the 2003 College of American Pathologists (CAP) survey of 122 laboratories in the U.S.<sup>10</sup>

Overall, 49% of the 1,187 ASC-H samples were hrHPV positive. The prevalence of hrHPV positivity was 54.7% in women <40 years and 36.5% in women ≥40 years. Among the 505 women with ASC-H who had histopathologic follow-up (at least one cervical biopsy, a diagnostic excisional procedure, or a hysterectomy), CIN 2,3 was histologically-detected in only 17.2%. This is considerably less than what was found in ALTS. In ALTS, approximately 50% of women with ASC-H were subsequently diagnosed with histologically-confirmed CIN2,3.<sup>9</sup>

Because of the large number of cases of ASC-H in the current study, the authors were able to stratify their results by age group, **Table 1**. Both hrHPV positivity rate and detection of

**TABLE 1: IMPACT OF AGE IN WOMEN WITH ASC-H**

Age group	No.	% hrHPV(+)	No. FU	% CIN 2,3
10-19	68	82%	24	8%
20-29	488	58%	197	20%
30-39	302	43%	140	24%
40-49	195	35%	85	9%
50-59	89	40%	33	9%
60-69	30	13%	16	
70-79	15	20%	10	
<b>Total</b>	<b>1187</b>	<b>50%</b>	<b>505</b>	<b>17%</b>

*Adapted from Bandyopadhyay et al. Arch Pathol Lab Med. 2008; 132*

CIN 2,3 decreased significantly with increasing age. Interestingly, hrHPV status appears to be very predictive of risk of histologically-confirmed of risk CIN 2,3. Histologically-confirmed CIN 2,3 was found in 33% of the women who were hrHPV positive, but in only 1.2% of those who were hrHPV negative, **Table 2**. The hrHPV positivity rate was not influenced by the presence or absence of an endocervical/transformation zone component in the cytology specimen. Stratification of the women into two groups based on age (<40 years and ≥40 years) suggests that hrHPV testing might be particularly useful in the triage of women ≥40 years. In this older age group only 37% of the women would be hrHPV positive and need referral to colposcopy. No cases of CIN 2,3 would have been missed using hrHPV testing for triage.

**TABLE 2: IMPACT OF AGE IN WOMEN WITH ASC-H**

Age group	hrHPV (+)		hrHPV (-)	
	% of Group	% CIN 2,3	% of Group	% CIN 2,3
All women	50%	33%	45%	1.2%
< 40 yrs	55%	36%	45%	1.9%
≥ 40 yrs	37%	21%	63%	0%

*Adapted from Bandyopadhyay et al. Arch Pathol Lab Med. 2008; 132*

The article by Bandyopadhyay *et al.* concludes with a very nice literature review of the potential utility of using hrHPV testing to triage women with ASC-H. This literature review is interpreted by Bandyopadhyay *et al.* as making a compelling case for using hrHPV testing to triage women with ASC-H and their arguments will be carefully considered during the next ASCCP Consensus Conference.

It should be noted, however, that the literature review that was conducted as part of the Bandyopadhyay *et al.* article included 1,874 cases of ASC-H (exclusive of the 1,187 cases that they analyzed from Magee Women's Hospital) and in these cases the overall prevalence of hrHPV was 58% and histologically-confirmed CIN 2,3 was found in 4.9% of the hrHPV negative women.

## Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women

Paavonen *et al.* Lancet. 2009;374:301-14

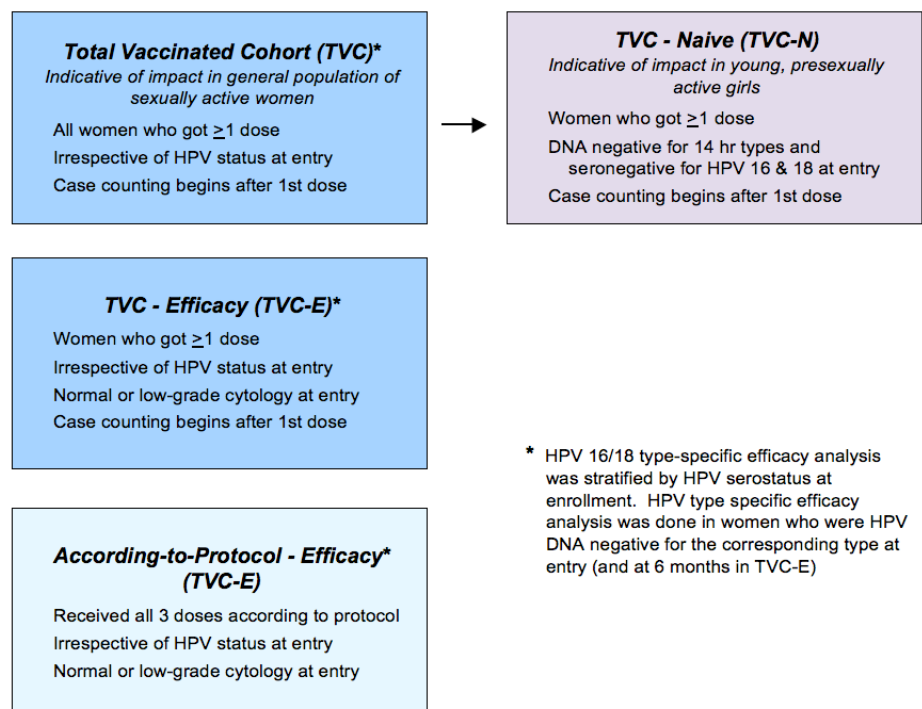
The publication by Paavonen *et al* presents the final, event-driven analysis of the bivalent (HPV 16 and 18) Phase III pivotal trial. The interim results from this trial were published in 2007.<sup>11</sup> This double-blind, placebo-controlled randomized trial enrolled 18,729 females 15-25 years of age at 135 centers in 14 countries. Enrollment was restricted to women with no more than 6 lifetime sexual partners. Women with a history of having had colposcopy or who had chronic or autoimmune disease, as well as immunosuppressed individuals were excluded. Women were enrolled irrespective of

their HPV DNA, their HPV serostatus, or their baseline Papanicolaou test. The primary objective of the trial was to determine vaccine efficacy in preventing CIN 2+ associated with HPV 16 or 18 in women who were seronegative at baseline and DNA negative at baseline and month 6 for the corresponding HPV type. In this trial cervical biopsies were tested for 14 oncogenic high-risk HPV types using a very sensitive PCR system and lesions were attributed to a given HPV type only if that specific type of HPV was identified in the lesion.

The study population can be divided

into four different cohorts for the purposes of analysis, **Figure 4**. Understanding these cohorts is important for understanding the potential impact of vaccination with the bivalent vaccine. The Total Vaccine Cohort (TVC) includes all women who received at least one dose of vaccine, irrespective of their baseline HPV DNA and serostatus and irrespective of their baseline cytology result. *TVC is representative of the general population of adolescents and young women who would undergo vaccination, many of whom will be sexually active.* The TVC-naïve

**Figure 4:** Cohorts and their Relationship in the Bivalent HPV Pivotal Trial



Modified from Paavonen *et al.* Lancet 2009;374.

**TABLE 3: VACCINE EFFICACY - HPV NEGATIVE† AT ENROLLMENT**

Group	HPV Type	No. Of Cases		Efficacy
		Vaccine	Placebo	
ATP-E ^	HPV 16	2	46	95.7% (82.9 - 99.6)
	HPV 18	2	15	86.7% (39.7 - 98.7)
TVC-E *	HPV 16	3	73	95.9% (87.0 - 99.3)
	HPV 18	2	24	91.6% (64.6 - 99.2)

† Both DNA negative and serologically negative for specific HPV type.  
 ^ According to Protocol-Efficacy Cohort  
 \* Total Vaccinated Cohort-Efficacy Cohort

Modified from Paavonen et al. Lancet 2009;374.

cohort includes all women who received at least one dose of vaccine and who also had a normal cytology result at baseline. These women had to be both DNA negative for all 14 oncogenic HPV types as well as seronegative for HPV 16 and 18 at baseline. *The TVC-naïve cohort is representative of what would be achieved when sexually naïve young girls are vaccinated.* The average length of follow-up was about 3 years. Evaluation of the baseline demographic results indicates the 15-25 year olds enrolled into the vaccine trial had had relatively few sexual partners compared to the general U.S. population. The majority (74%) had had only 1 sexual partner, and only 8% had had three or more partners. Despite this, 26% of the women had evidence of current or past infection with HPV 16 or 18 at baseline. The primary type-specific analysis of vaccine efficacy was done in women who were HPV DNA negative and seronegative for the

corresponding HPV type at enrollment. As expected, a high efficacy against CIN 2+ associated with either HPV 16 or 18 was observed in both the ATP-E and TVC-E cohorts, **Table 3**.

The bivalent vaccine has an efficacy of 95-96% against HPV 16 associated

CIN 2+ lesions in HPV 16 naïve women and an efficacy of 87-92% against HPV 18 associated CIN 2+ lesions in HPV 18 naïve women. This represents the expected results of vaccinating sexually naïve adolescents. However, since current ACIP recommendations for use of the quadrivalent HPV vaccine include “catch-up” vaccination of all females through age 26, irrespective of whether or not they are sexually active, many experts believe vaccine efficacy in women in the general population, irrespective of their HPV DNA or serostatus, is of equal importance. The cumulative incidence of CIN 2+ associated with HPV 16 or 18 in the TVC group is shown in **Figure 5a**. Within 36 months of vaccination there is a significant difference in the cumulative number of cases of CIN 2+ in the vaccine versus the placebo group; and this difference increases

**Figure 5: Cumulative Incidence of CIN 2+ in the TVC Group**

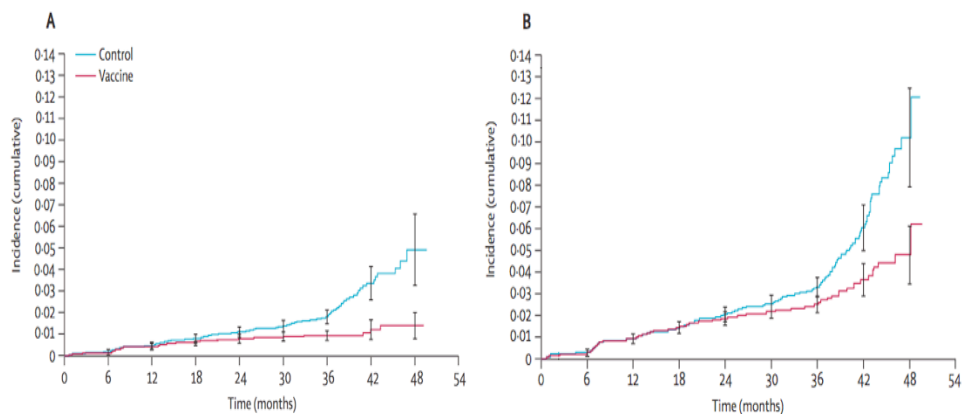


Figure 5A includes only CIN 2+ lesions associated with HPV 16 or 18 whereas Figure 5B includes all CIN 2+ lesions, irrespective of associated HPV type.

Paavonen et al. Lancet 2009;374.

at 42 and 48 months. When an endpoint of CIN 2+ associated with any oncogenic HPV type is used, the curves have a similar shape, but efficacy is somewhat diminished, **Figure 5b**. Another important finding of this trial is that vaccination reduced the number of colposcopy examinations and the number of cervical excision procedures in both TVC and TVC-naïve cohorts, **Table 4**.

The bivalent HPV vaccine appears to have a similar safety profile to the quadrivalent HPV vaccine since the proportions of women with serious adverse events, medically significant conditions and new onset of chronic diseases are similar in the vaccine and control groups in the pivotal Phase III trials. The number of pregnancies, congenital anomalies and

Group	Number of Cases		Efficacy
	Vaccine	Placebo	
<i>TVC</i> ^			
Colposcopy	1107	1235	10.4% (2.3 - 17.8)
Excisional Procedure	182	240	24.7% (7.4 - 38.9)
<i>TVC-Naive</i> *			
Colposcopy	354	476	26.3% (14.7 - 36.4)
Excision Procedure	26	83	68.8% (50.0 - 81.2)

^ Total Vaccinated Cohort  
\* Both DNA negative and serologically negative for specific HPV type

*Modified from Paavonen et al. Lancet 2009;374.*

spontaneous abortions were also similar in the two groups.

This article presents in depth cross-protection induced by the bivalent vaccine against other oncogenic HPV types such as 31, 33, 45, 52, and 58.

Cross-protection is becoming a very important topic and in the 2009 *Winter Literature Update* we will provide you with several articles describing the effects of both the bivalent and quadrivalent HPV vaccines on cross-protection.

## What's New? Meeting Highlights 2009 International Papillomavirus Conference

The 25<sup>th</sup> International Papillomavirus Conference (IPC) was held May 8-14 in Malmo, Sweden. This was the largest papillomavirus conference to date and included numerous presentations and posters on various aspects of the biology of HPV, cellular and humoral immune responses targeting HPV, the HPV vaccines, and cervical cancer screening and prevention. We canvassed several ASCCP members who attended the IPC to find out what they thought the highlights of the meeting were. Some of the presentations that they were particularly excited about are described below.

### ***Therapeutic Vaccination Against HPV 16:***

C.J.M. Melief from the Leiden tumor immunology group presented the results of an uncontrolled clinical trial in which they used a therapeutic vaccine consisting of synthetic long peptides from the E6 and E7 regions of HPV 16 to vaccinate 20 women with VIN 3. E6 and E7 are the two primary oncogenes of high-risk HPV types. Women received three vaccinations with an HPV 16 E6/E7 vaccine and the vaccine appeared to be safe and have no significant side effects. After 12 months of follow up,

vaccination was associated with either a reduction in lesion size or clearance of the lesion in 75% of the women and complete regression of the VIN 3 lesions in 45% of vaccine recipients.

### ***Accuracy of Colposcopy in the Quadrivalent HPV Vaccine Trials:***

M. Stoler and the Gardasil investigators presented the results from 760 women who had a colposcopically-directed cervical biopsy within 6 months of undergoing a LEEP. Most, 92%, of these women also underwent a colposcopy immediately prior to undergoing their LEEP. At the second, pre-LEEP, colposcopy investigators were instructed to take a single cervical biopsy from what they consider to be the "worst appearing" area. Overall, the initial colposcopy with cervical biopsy failed to diagnose 42% of the CIN 3/AIS lesions detected in the subsequent LEEP specimens. Failure to detect CIN 3/AIS at the initial colposcopy was significantly correlated with the number of biopsies that were taken. Taking a single cervical biopsy from the "worst appearing" area immediately prior to LEEP resulted in an even poorer performance. A single-directed cervical biopsy failed to detect 66% of

the CIN 3/AIS lesions subsequently identified in the LEEP specimen.

### ***Comparative Immunogenicity of the Bivalent and Quadrivalent HPV Vaccines:***

M. Einstein presented an observer-blinded comparative immunogenicity trial of the bivalent and quadrivalent HPV vaccines. This trial enrolled 1,106 females 18-45 years of age. Immune responses were evaluated using several different assays. These included antibodies against HPV 16 and 18 in both serum and cervicovaginal lavages (CVL) that were identified using both ELISA and a pseudovirion-based neutralization assay developed at NCI. They also measured memory  $\beta$ -cells in serum using ELISPOT. In HPV 16 and 18 naïve women the levels of neutralizing antibodies against HPV 16 were 2.3-4.8 times higher at one month post vaccination in different age groups of women who received the bivalent HPV vaccine compared to the quadrivalent HPV vaccine.

### ***New Rapid HPV Diagnostic for Low-resource Settings:***

Preliminary results obtained using a new rapid HPV test were presented by J. Schwizer who works at a

company called Arbor Vita. This test is designed to detect the E6 oncoprotein of selected high-risk types of HPV using a high affinity E6 monoclonal antibody. The test takes less than 90 minutes to process and uses a simple "dipstick" type format. There are two versions of the test. One is designed to detect HPV 16, 18, and 45. The other detects HPV 16, 18, 45, 33, 58, and 52. In a pilot study of 44 cervical swab samples taken from Chinese women with known cervical disease status, 19 of 19 samples from women who were either pathology negative or had biopsy-confirmed CIN 1 tested negative using the HPV 16, 18, and 45 test. In contrast, 5 out of 7

women with CIN 3 lesions and 8 out of 9 of these with cervical cancer who were PCR positive for HPV 16, 18 or 45 tested positive using the new E6 oncoprotein test.

***WHO Recommendations on Use of HPV Vaccines in National Immunization Programs:***

K.L. Irwin of the WHO presented the main findings of the recent April 2009 WHO position paper on the use of the two HPV vaccines in national immunization programs. This position paper is based on recommendations made by the Strategic Advisory Group of Experts (SAGE) on Immunization.<sup>12</sup> WHO now recommends that routine HPV vaccination be included in

national immunization programs- provided that prevention of cervical cancer or other HPV-related diseases constitute a public health priority, vaccine introduction is programmatically feasible, sustainable financing can be secured, and the cost-effectiveness of vaccination strategies in the country or region is considered. The key target population should be females 9-10 years through 13 years. HPV vaccine should be introduced as part of a coordinated strategy to prevent cervical cancer and other HPV-related disease. The WHO cautions that introduction of HPV vaccine should not undermine or divert funding from effective screening programs.

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