AOTEA PATHOLOGY
- CLINICAL UPDATE

AOTEA PATHOLOGY

NOVEMBER 2014

Changes to Human Papillomavirus Reporting for Cervical Smears

By Dr Peter Bethwaite and Collette Bromhead PhD

Aotea Pathology now reports the presence of high risk HPV genotypes 16 and 18 on all HPV positive cervical smear results

HPV are DNA tumour viruses that cause epithelial cell proliferation at the site of infection and are highly specific for their target epithelium. The 100 different types of HPV are classified according to their degree of genetic relatedness, of which fourteen of the anogenital tract types are classified as high risk (hrHPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) because they are capable of causing cancer in the lower genitourinary tract epithelium of both men and women.

The natural history of HPV infection starts with exposure which results in a productive viral infection that often causes mild cytological abnormalities such as Low-grade Squamous Intraepithelial Lesions (LSIL) or Cervical Intraepithelial Neoplasia (CIN1) shown in Figure 1.

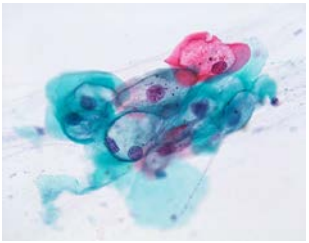

Figure 1a. HPV infection – koilocytotic change in squamous epithelial cells

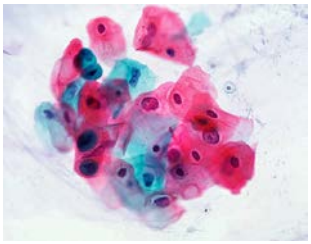

Figure 1b. LSIL –mature squamous cells showing nuclear enlargement, bi-nucleation and orangeophilia

These cellular changes are merely a marker of HPV infection of which most are transient and cleared without treatment. Persistent infection with HrHPV has a risk of developing into invasive cervical cancer, a risk which is considerably higher with an HPV16/18 infection than the other 12 HrHPV genotypes.

HPV16/HPV18 genotyping can identify women at highest risk for high-grade cervical disease, and this additional risk stratification may be used in formulating patient management decisions.

In a US cohort study, older women aged >30 years enrolled in the Kaiser Permanente health plan in Oregon who had negative cytology at study entry were followed up over a 10-year period. Approximately 20% of women with HPV16 infection were subsequently diagnosed with either CIN3 lesions or invasive cervical cancer and similarly HPV18 infection was associated with a risk of 17-18% for the same outcomes. In comparison, women infected with non-HPV16, 18 genotypes had a risk similar to that in uninfected women (Meijer et al).

Similarly a Danish follow-up study, which assessed the role of persistent HPV infection in a large cohort of younger women aged 20-29 years from the general population, identified a risk for CIN3 or cervical cancer of 47% within 12 years of follow up among women infected with HPV16. The corresponding risk among women with HPV18 infection was 19% but among women infected with other HrHPV genotypes the risk was only 6%. ***Importantly, those women with persistent HPV16 infection over a 2 year period had an almost 50% risk of developing CIN3 or cancer (Kinney et al).***

Local Hr HPVdata from ASCUS smears reflects that seen internationally

In their metanalysis of HPV positivity in women with equivocal or low-grade cytology results, Arbyn et al showed that on average, 43% of women with atypical squamous cells (ASCUS) were HrHPV positive (range 23-74%). In women with LSIL, the pooled positivity rate was 76% (range 55-89%) (Arbyn et al 2009). These results are consistent with those seen at Aotea Pathology: in the 5 years to September 2014, 47% of ASCUS smears with were positive for HrHPV while 73% of LSIL smears were positive.

Our regional data shows high rates of infection with non 16/18 HrHPV types in ASCUS smears (32.2%), consistent with lower rate of progression to CIN 2 or worse in these cases. However, in the 5 years to September 2014, 10.2% of regional ASCUS smears were infected with HPV16 and/or18 while 4.1% were infected with HPV 18 only. This is comparable to the findings of the large ATHENA longitudinal study (Addressing THE Need for Advanced HPV Diagnostics) which found HrHPV genotype prevalence in ASCUS smears of 8.2% for HPV16, 2.9% for HPV18 and 21.4% for 1 or more of 12 other HrHPV types – see table below (Stoler et al 2011).

HPV Genotype in ASCUS Smears	ATHENA 2011	Aotea Pathology 2009-2014
HPV 16 *Including 16 and/or 18 and or any of 12 other HrHPV types*	8.2%	10.2%
HPV 18 *Including HPV 18 and any of 12 other HrHPV types*	2.9%	4.1%
Other *Any of 12 HrHPV types excluding 16 and 18*	21.4%	32.2%

That our local data is comparable to that from ATHENA is significant because the trial went on to show that upon biopsy of the women with HPV16/18 positive ASCUS smears and there was a steady increase in association with worsening grade of CIN. Overall, 8% of HPV16/18+ women had normal biopsies, CIN1 was found in 18%, CIN2 in 44% and 61% had CIN3 or worse (Stoler et al 2011). Clearly, the risk of disease in this group can be stratified on the basis of the infecting HPV genotypes (see Figure 2).

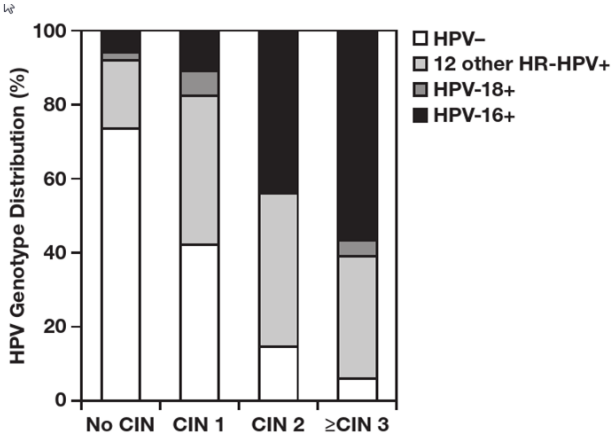

Figure 2. (after Stoler et al 2011)
Distribution of HPV results according to stage of cervical disease in 1,578 women with ASCUS cytology (ATHENA Study) shows increasing risk of for high grade lesions with HPV 16 infection.

The clinical implications of the enhanced risk for CIN2 or worse associated with being HPV16+ are worthy of our consideration, especially since this ability to genotype HrHPV results is inherent in our current cobas 4800 testing system. Whilst the risk of CIN2 or worse in women with ASCUS infected with other HRHPV types is high enough to warrant colposcopy, more aggressive disease ascertainment at initial colposcopy and more intensive follow-up is warranted for HPV16+ women with ASCUS not found to have CIN2 or worse.

Collectively the results of these and many other studies emphasise the importance of identifying those women with HPV16, 18 infections.

Aotea Pathology now reports the presence of HPV16/18 in smears

Since 2009 Aotea Pathology has used the cobas 4800 HPV Test for women meeting the 2008 NCSP guideline requirements. This molecular test simultaneously detects the DNA of 14 HrHPV types: HPV-16 individually, HPV-18 individually, and 12pooled HrHPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Until recently we have only reported the qualitative presence or absence of any of the high risk HPV types in a cervical smear and this information is used by the National Cervical Screening Programme to make management decisions in low grade SIL cases and test of cure situations.

We will continue to report this information and it will still inform management decisions within the programme.

Since the 3rd of November we have also reported the results for high risk HPV types 16 and 18 on all HPV positive cervical smear results. We anticipate this new information will be valuable in assisting decision making at colposcopy.

This is a change we have made independently of the National Cervical Screening Programme and there are no associated changes in the Guidelines for Managing Women with Abnormal Smears, 2008. However, Dr Hazel Lewis, clinical leader of the NCSP has indicated the NCSP are modelling upcoming changes in screening policy as they plan transition into an exciting new era of dual prevention through vaccination and HPV primary screening (Wright et al 2014).

For further information please contact:

Dr Peter Bethwaite, Lead Pathologist for Cytology

Phone: 04 3815944 or Email: pbethwaite@apath.co.nz

References

cMeijer CJ, Berhof J, Castle PE et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer.* 2009;124:516-520

Kinney W, Stoler MH, Castle PE. Special commentary: patient safety and the next generation of HPV DNA tests. *Am J Clin Pathol.* 2010;134:193-199

Arbyn M, Sasieni P, Meijer CJ, et al. Chapter 9: clinical applications of HPV testing: a summary of meta-analyses. *Vaccine.* 2006;24*(suppl* 3):S3/78-S3/89

Stoler MH, Wright TC, Sharma A, et al. High-Risk Human Papillomavirus Testing in Women with ASC-US Cytology. *Am J Clin Pathol.* 2011;135:468-475

Wright T, Saville M, Lewis H and Yeong ML. Expert forum: a local and global perspective on Cervical Screening with HPV. *Research Review* 2014, Auckland University of Technology