대한세포병리학회지
ISSN 1017-0391

자궁경부암 예방의 미래 : 세포선별검사와 HPV 예방접종의 역할

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Cervical Cancer Prevention for the Future: the Complimentary Roles of Cytology Screening and HPV Vaccination

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논문접수 : 2007 년 2월 1일
게재승인 : 2007 년 2월 5일

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Approximately 70% of cervical cancers are caused by HPV types 16/18 and thus the implementation of vaccination programmes with vaccines against HPV types 16/18 will have a major impact on the incidence of cervical cancer worldwide. However, this reduction will not be seen until several decades after full implementation of such vaccination programmes since the vaccines must be given to young adolescents before exposure to the virus and women who are already sexually active are not likely to be protected.

Both GSK and Merck insist that even vaccinated women must continue to participate in regular cervical screening by the most sensitive method available since the vaccine can only give protection against up to 70% of cervical cancers. It is unlikely that the current vaccines will be modified to include additional high risk HPV types in the foreseeable future.

While HPV testing is highly sensitive, it is not recommended for women under 30 years of age nor for vaccinated women. Additionally, HPV testing has poor specificity. The Digene Hybrid Capture 2 test is licensed for use only in conjunction with a cytology test, not as a stand-alone test, and the high risk panel has recognised cross reactivity with low risk HPV types. None of the other HPV test methods currently commercially available are FDA approved and all must be internally validated before use. This makes comparison of test results between laboratories difficult.

The most sensitive and specific screening test currently available for women of all ages is the Cytyc ThinPrep® System consisting of the ThinPrep® Pap Test (TPPT) and the ThinPrep® Imaging System (Imager). The TPPT was the first LBC system approved by the US FDA in 1996 and there are about 4,000 processors in use worldwide. The Imager was FDA approved in 2003 and over 350 systems are in routine use, mainly in the US. 40% of TPPT in the US are processed on Imager.

There is clear evidence in peer reviewed literature that the Imager increases laboratory productivity by 100% and growing evidence that Imager detects more high grade SIL than the conventional smear or manual evaluation of TPPT. This aspect is particularly important since the number of cytological abnormalities will decrease as vaccination programmes are implemented. Cytotechnologists will see fewer and fewer abnormal smears and their skills will be put at risk. By doubling throughput, Imager will allow cytotechnologists to maintain their skills.

(Korean J Cytopathol 2007;18(1):1-12)

Cervical Cancer is the seventh most common cancer worldwide but is the second most common cancer among women in developing countries. The incidence is decreasing in developed countries mainly due to the implementation of cytology screening programmes so the majority of new cases (80%) occur in developing countries. Mortality also varies across the world from 〈4/100,000 women in North America to 〉36.5 /100,000 women in parts of Asia, Africa and South America.

There is clear and overwhelming evidence that cervical cancer is caused by specific "high-risk" types of human papillomavirus (HPV). HPV consists of double-stranded, circular DNA contained within a spherical protein coat (capsid). There are over 100 different strains of the human papillomavirus but only about 30 types affect the genital tract. Some genital types are highly oncogenic and these "high-risk" HPV types are found in 99.7% of invasive cervical cancers. Types 6 and 11 have low oncogenic potential and belong to a different arm of the HPV family from HPV oncogenic types 16, 18, 35, 45 and 58.

Genital HPV infection is very common in women under 30 years of age but most infections are asymptomatic and women are unaware of being infected. More than 90% infections are acute infections and the virus is cleared just as for any other viral infection. It is important to understand that subsequent or concurrent infection with other HPV types, oncogenic and non oncogenic, is common. Thus multiple HPV genotypes are frequently found in both cytologically normal and abnormal cervical samples.

Richart et al.[1] showed that all genital HPV types induce low grade squamous lesions, which correlate with a productive infection and may appear histologically as Cervical Intraepithelial Neoplasia (CIN) Grade 1 or a Low grade Squamous Intraepithelial Lesion (LSIL). Rarely, high risk HPV types (hr HPV) may induce a proliferative epithelial phenotype (CIN3 or HSIL) that is a precursor of invasive cervical carcinoma.

The incubation period before an HPV infection becomes visible is on average 1～8 months during which HPV DNA tests may be negative. After the incubation period the first lesions appear and there follows a period of active growth for 3～6 months during which the host immune response begins to kick in and over the next 3～6 months usually effectively eliminates the virus. Thus the HPV visible infection lasts on average 9 months. For most women there is a sustained clinical remission but for some women whose immune response fails to eliminate the virus, there is persistence of the virus in the cervical epithelium and risk of progression to invasive cancer.

The risk of developing cancer increases with persistence of hr-HPV and high viral load. Since infection and resolution of infections is more common in younger women, hr-HPV is more significant if found in women over 35 years. The negative predictive value of hr-HPV is more clinically useful than the positive predictive value. Unfortunately, there is currently no effective treatment for HPV infection in the cervix.

How can this understanding of the natural history of HPV infection and the role of HPV in cervical cancer be used in cervical cancer prevention programmes? Primary prevention is not practical since HPV infection is linked to sexual activity. Use of condoms is not completely effective in preventing HPV infection since genital skin to skin contact alone can transfer the virus. Treatment of transient or persistent infections is not yet available although antiviral agents and even therapeutic vaccines are under development. Prophylactic vaccines currently available target only two of the thirteen hr HPV types that cause cervical cancer. Thus secondary prevention by screening and treatment of pre-invasive cervical disease (CIN3, HSIL) is the only effective option at present.

Screening of a normal population requires a different ethical approach from that more routinely used for the management of individuals with disease. The principles for screening programmes were defined in the keystone paper by Wilson and Jungner[2] in 1968. These principles are listed in Table 1. Wilson and Jungner emphasised that those who are approached to participate in screening are healthy individuals and most of them never become patients and that screening is a programme not a test. The critical principle is that the chance of benefit to the individual must outweigh any chance of harm, including psy-

Table 1. Taken from principles for screening programmes Wilson & Jungner[2] 1968

- The natural history should be well understood with a recognizable early stage
- Treatment at an early stage should be advantageous
- An appropriate and acceptable screening test should be available and offered at suitable intervals
- There should be adequate facilities for the diagnosis and treatment of abnormalities identified
- The costs of the screening programme should be balanced against the benefits it provides to the community
- Ideally all these criteria should be met before screening for any condition is initiated.
- The benefit of the screening programme should outweigh any physical or psychological harm caused by the test itself, diagnostic procedures or treatment
- Even if the screening test is in itself harmless, a "positive" or "equivocal" result may cause unnecessary anxiety and the subsequent investigations and treatment may be hazardous.
- the screening methods selected should have the lowest proportion of false-positives possible (not just false negatives).
- The provider of screening must believe that, as a result of population screening, the health of the community will be better.
- Screening programmes should be organised and require population registers and high quality information systems to measure their impact and their quality

Table 2. Brief history of cervical screening and the national Health service cervical screening programme (NHSCSP) in the UK

1967	Cervical Screening policy introduced opportunistic, women 35～64yrs 5 yearly intervals,
1976	Screening age range extended to 20～64 yrs
1988	NHSCSP launched a population based call-recall programme
1991	National Coordinating Network was established
1993	First round of NHSCSP completed
1994	National Co-ordinating Team established
1998	Second round of NHSCSP completed
2001	LBC "Pilots" for LBC and Reflex HPV
2005	National HTA evaluation of computer assisted screening

chological harm.

The World Health Organisation (WHO) first published international guidance on how to use the cervical cytology test for population screening to prevent cervical cancer in 1986. This was supplemented in 1988 with the publication of technical guidance on implementing cervical screening programmes. These were recently updated in the joint WHO / IARC handbooks of cancer prevention. Cervical cancer screening booklet published in 2005.

The UK is recognised as having a particularly successful cervical screening programme. The history of cervical screening in the UK is listed in Table 2. Initially in 1967 the UK introduced a cervical screening policy for screening every women aged 35～64 years at 5 yearly intervals. The age group was extended to 20～64 years in 1976. Since this was a policy and not a programme it was opportunistic and not organised. Unfortunately despite increasing numbers of Pap smears being taken, there was little or no impact on the invasive cervical cancer rate. Population coverage was estimated at less than 30% and more than 90% of women who developed invasive cervical cancer over 40 years of age had never been screened.

Therefore in 1988 the Department of Health introduced an organised cervical screening programme whereby every women aged 20～64 would receive a personal invitation to attend for a free cervical smear at 3～5 year intervals. This is called the National Health Service Cervical Screening programme (NHSCSP). This was originally organised on a regional basis and a National Coordinating Network was set up in order to harmonise activities across the UK. This was superseded in 1992 by a National Coordinating Team (NCT) led by Julietta Patnick as National Coordinator.

The NHSCSP priority for the first five years was to improve population coverage and fail-safe follow up systems. The priorities for the second round (1993-1998) were to improve the quality of programme co-ordination, smear taking and laboratory interpretation. The NCT has published a series of guidance documents setting targets and standards for all aspects of the NHSCSP including cytology laboratory practice, colposcopy, public health, communications with women and histopathology reporting of cervical biopsies. Quinn et al.[3] described how the population coverage increased to about 80% of eligible women resulting in a spectacular decrease in the invasive cancer rate (Fig. 2). This was achieved without a significant increase in the total number of Pap tests carried out annually. Thus all women were being screened regularly

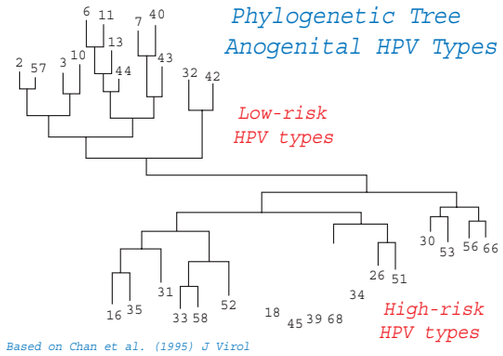

Fig. 1. Phylogenetic tree of HPV types affecting the anogenital tract (Courtesy of ASCCP)

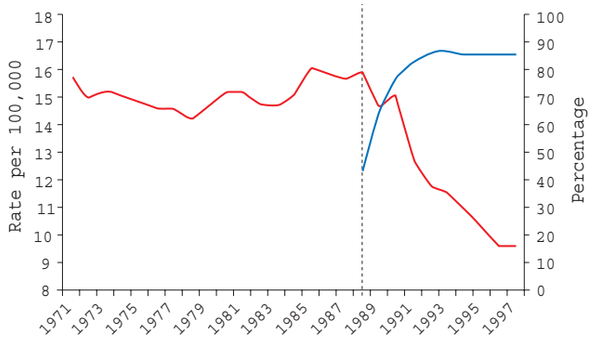

Fig. 2. Age standardised incidence of cervical cancer and coverage of screening, England, 1971–1997 Quinn et al.[3]

rather than young women being over-screened.

By end of the second round in 1998, there were 1300 fewer cancer deaths compared with 1988 and over 8,000 cancer deaths had been prevented since the organised NHSCSP was implemented. Sasieni and Adams[4] showed that screening had a minimal effect on mortality prior to 1088 but by 1997 mortality rates were dropping in every age cohort at an average rate of 7% per annum.

The NHSCSP priorities for the third five years were to maintain its current achievements and to improve the quality of the screening test by considering new technologies including liquid based cytology, reflex HPV testing and computer assisted screening.

The reason for considering these new technologies was the recognition of the limitations of conventional cervical smears. The sensitivity of a single conventional cervical smear has been assessed in published literature by several authors and meta-analyses[5-8] at about 50～60%. However

Fig. 3. A ThinPrep® Pap test slide

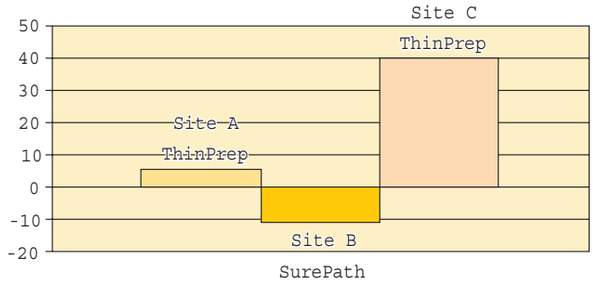

Fig. 4. Results for % change in HSIL detection vs. conventional Pap in English LBC pilots n=>100,000.

the strength of the conventional Pap test is the high specificity of over 95% i.e. the ability to give a normal result to normal women.

The inherent limitations of the conventional Pap test include: the majority of cells not put on slide but are discarded with the sampler; the cells transferred to the slide are not randomized and therefore not representative of the cells removed from the cervix; and the cellular material on the glass slide shows clumping and overlapping with many epithelial cells obscured by blood or inflammatory debris. This results in poor quality slides, false negative tests and high inadequate rates.

These limitations are overcome with Liquid Based Cytology (LBC). Instead of spreading the cellular material removed from the cervix onto a glass slide as in the conventional Pap test, the sampler is rinsed into a vial of liquid transport medium and the sample is sent to the laboratory as a cell suspension. In the laboratory a randomised aliquot is deposited in a circle on the glass slide (Fig. 3). There are several automated and semi automated devices available to carry out this step such as the ThinPrep® 2000.

With LBC, virtually all of sample is collected into the

vial; there is randomized, proportional representative transfer of cells to glass slide; the cells are evenly distributed on the slide; and obscuring material is minimized. Naturally, the additional consumables and laboratory tasks involved with LBC result in a moderate increased in cost over the conventional Pap test.

The UK is committed to evidence based medicine and all new drugs and technologies must be shown to be cost effective so why has the UK cervical screening programme changed to LBC? The Scottish Health Department was the first country to fund an independent pilot of ThinPrep® in 2001. The study involved 30,228 ThinPreps from 4 laboratories with very different profiles who part converted their workload over 6 months using the conventional Pap workload as an internal control. The results published in 2002[9] showed a marked decrease in the unsatisfactory rate and a doubling of the LSIL and HSIL rates. This was not due to overcalling the cytology results since the positive predictive value for women with HSIL cytology having an HSIL biopsy was 79.5～87.5% similar to that for conventional Pap tests. In April 2002, the Minister for Health in Scotland decided that LBC must replace the conventional smear throughout Scotland as the routine screening test and ThinPrep® is has been fully implemented in Scotland since early 2004.

In 2002, England implemented Pilot LBC projects similar to those that had been undertaken in Scotland. The English pilots involved 3 laboratories which fully converted to LBC. Two laboratories used ThinPrep® and one used SurePatha. They collected a total of 100,000 LBC tests over a 12 months period. In addition, reflex HPV testing was carried out on all samples showing ASC-US or LSIL (Borderline or mild dyskaryosis). The results of the LBC arm were published by Moss et al.[10] in March 2003, and showed similar results to Scottish LBC studies except there was no overall increase in HSIL detection. However the two laboratories using ThinPrep® showed an increase in HSIL detection while the laboratory using SurePath showed a marked decrease in HSIL detection (Fig. 4). This decreased detection of HSIL by SurePath has never been satisfactorily explained.

Table 3. Examples of LBC systems marketed worldwide – only the first three are FDA approved for clinical use.

ThinPrep®	*(Cytyc)*
SurePatha	*(Tripath)*
MonoPrep	*(Monogen)*
LiquiPrep	*(LGM Int)*
GluCyte	*(Synermed Int)*
CYTeasy	*(Seroa)*
EasyPrep	*(Labonord)*
Cellslide	(*Menarini)*
Cyto-Tek	*(Bayer)*
CellSpin	*(ThermoShandon)*
DNA-Cytoliq,	

(NB: This list is not exclusive)

In summary of the English LBC pilots showed: evidence of a reduction in the number of unsatisfactory specimens; increased productivity of laboratories; smear takers and laboratory staff all favoured LBC; an expectation that LBC would reduce the number of false negatives and the incidence of invasive cancer and, most importantly, robust evidence that LBC is a cost effective alternative to conventional Pap for the health service in the UK in terms of life years saved.

In October 2003 the UK National Institute for Clinical Excellence approved ThinPrep® and SurePath™ and recommended they are used as the primary means of processing samples in the cervical screening programmes in England and Wales.

There are many LBC systems on the market worldwide (Table 3). However, it is important for laboratory staff and public health departments to understand that not all LBC systems are equal or clinically sensitive. There is little or no evidence in the literature to evaluate the clinical effectiveness of many systems. It is not enough to put cells in a thin layer on the slide, the cells on the slide MUST be REPRESENTATIVE of the population of cells removed from the cervix. Only ThinPrep®, SurePath™ and MonoPrep® are approved for use in the US by the FDA. Only ThinPrep® and SurePath™ are approved for use in the UK NHSCSP. Some other LBC systems claim they are FDA "listed" or "certified" but this is not the same as clinical approval. This is simply and ONLY a certificate from FDA that the Company has a product that is manu-

Table 4. Williams et al.[11] changes in the laboratory profile before and after implementing ThinPrep®

	87408 Conventional (%) 2001 - 2002	78064 ThinPrep® (%) 2003 - 2004
Unsatisfactory	13.6	1.9
Negative	80.9	91.7
Borderline	2.5	2.6
Mild	2.0	2.3
Moderate	0.6	0.8
Severe	0.4	0.6
Others	0.1	0.1

factured in the U.S. and that the Company's manufacturing facility has satisfied the FDA's standard quality compliance based the FDA's inspection of their facility.

ThinPrep® is the only screening test that has been available in Scotland since 2004. Williams et al[11] published their data which had been gathered to monitor the effect of implementing ThinPrep® both on the local Laboratory Service and also on the local Colposcopy Service. So has ThinPrep® lived up to expectations in routine practice in Scotland?

Williams et al[11] compared the last 12 month period when the laboratory only received conventional Pap was used with the first 12 month period when only ThinPrep® was used. The study includes 87408 conventional Pap smears and 78064 ThinPreps. The decrease in total workload is explained by the significant reduction in the unsatisfactory rate 13.6% to 1.9% with fewer repeat tests. The borderline (ASC) rate was essentially unchanged, the mild dyskaryosis (LSIL) rate increased from 2.0% to 2.3% and the moderate plus severe dyskaryosis (HSIL) rates increased from 1% to 1.4% (Table 4).

These changes in reporting profile in the laboratory had a major impact on the local colposcopy service. With conventional Pap tests 24.8% of the colposcopy workload consisted of women with repeated unsatisfactory smear test results and less than 35% of women were referred with a cytology result of HSIL. Using ThinPrep® less than 1% of the workload consisted of women with repeated unsatisfactory tests and over 50% of women were referred

Table 5. Williams et al.[11] changes in the local colposcopy workload before and after implementing ThinPrep®

	Conventional		ThinPrep®	
	N	%	N	%
Unsatisfactory	544	24.8	11	0.5 ↓
Negative	5	**0.2**	4	**0.2**
Borderline	338	15.4	227	11.2 ↓
Mild	510	23.3	686	33.8 ↑
Moderate	430	19.6	585	28.8 ↑
Severe	317	14.5	479	23.6 ↑
? Invasive	11	**0.5**	8	**0.4**
Glandular abn.	30	**1.4**	27	**1.3**
Adenoca	3	**0.1**	2	**0.1**
Other	3	**0.1**	1	**0.0**
Total	**2191**	100	**2015**	100

with HSIL (Table 5). More importantly these referrals for HSIL had a positive predictive value for a HSIL biopsy higher than that for conventional Pap tests (PPV increased from 79.5% to 86.1%)

Over 4000 ThinPrep® Processors have been installed in laboratories worldwide with over 220 million ThinPrep® Pap Tests have been processed by 2006. In the United States at least 70% percent of all Pap tests are ThinPrep® making it the standard of care. LBC is widely used in Europe. LBC is the standard-of-care in England where ThinPrep® has 60% market share. ThinPrep® is the only screening test used in Scotland and Ireland. LBC has over 60% market share in Switzerland and about 70% market share in Belgium. LBC has been approved for routine screening in Hong Kong and Canada. In 2005, IARC / WHO approved liquid based cytology as an "effective method of cervical cancer control". Both Merck (GARDASIL) and GSK (CERVARIX) used ThinPrep® in the follow up of their study patients in the HPV vaccine trials.

What next for the UK to improve the quality of the cervical screening programmes? Having implemented LBC throughout the UK, attention has turned to considering reflex HPV testing and computer assisted screening systems which were the other priorities for the third round of the NHSCSP.

There are many methods of HPV Testing. There are HPV DNA based tests looking for the presence or absence of HPV (i.e. a screening test). This type of test includes Digene Hybrid Capture II, Roche Amplicor HPV test and a myriad of in house Polymerase Chain Reaction (PCR) tests. Alternatively there are HPV DNA / RNA based tests that are quantitative and/or qualitative. These are becoming the preferred type of test since viral load measurements are clinically useful and the detection of HPV persistence requires genotyping tests. There are other methods that actually detect cellular markers of HPV infection and associated disease rather than the HPV DNA or RNA. Prominent among this type of test is p16 INK 4a.

Thus HPV testing is not just one test but just like the cytology screening test it included several types of test methods. Also just like the cytology test, the quality will vary with the user, the type of test and the quality of the sample collected although these types of tests are less subject to human error. Digene Hybrid Capture 2 (hc2) is the only HPV test approved by FDA for the US and it is only licensed for use in addition to a cytology Pap test. Polymerase Chain Reaction (PCR) tests using consensus primers are not FDA approved since they require in house validation and thus it is difficult to compare results between laboratories.

The Digene Hybrid Capture 2® assay (hc2) high risk panel is the most established "presence/absence" HPV test. It is licensed by FDA in US for triage of women with low grade cytology. It contains a panel of 13 hr-HPV types and the positive level is set by the user at 1 or 2 relative light units. These appear to be some cross reactivity with low risk HPV types which may be responsible for false positive results. It is important to remember that the Hybrid Capture II test does not contain a control for cellularity of samples and thus an acellular sample may give a false negative result. False negative results may also occur in the incubation stages of an HPV infection when the infected cells are restricted to the basal layers of the epithelium.

The clinical uses of HPV testing in developed countries include triage in the management of women with ASC US, detection of recurrent or residual disease after treatment of CIN2/3 (i.e. test of cure), cessation of routine screening after the menopause if woman as been regularly screened and always cytologically negative and, finally, for primary screening together with cytology (DNA Pap) for women over 30 years of age in order to extend the screening interval to 3 years for women who are cytology and HPV negative. This strategy, however, carries with it high costs. Please note: Hybrid Capture II is not licensed as a stand alone screening test.

It has been suggested that HPV testing from vaginal self-sampling could be used as a primary screening test, without cytology, in developing countries. However, for HPV testing to be effective as a cervical cancer prevention tool, there is still a requirement for a screening programme to be organised, with population registers up to date, a population compliance of 〉80%, failsafe follow up systems for women with ASC US results and an adequate colposcopy service. Unfortunately most developing countries lack the infrastructure and finance to support these requirements.

The main benefit of HPV testing is its improved sensitivity for the detection of HSIL but in a screening programme sensitivity and specificity are inexorably linked and any attempt to increase one usually results in a decrease in the other. And so it is with HPV testing. The main drawback of HPV testing is its poor specificity. Since most young women come in contact with hr HPV and have a productive infection in the first 10 years after becoming sexually active, up to 30% of young women will test positive for HPV. This positive result is not in itself significant in a cervical cancer screening situation. To overcome this it has been recommended that HPV testing should be restricted to women over 30 years (or preferably 35 years) and for positive HPV tests to be further genotyped and repeated after 1 year to confirm that the same viral type is present before referring the patient for treatment.

There is also emerging evidence of the psychological impact of a positive HPV test. HPV positive women are significantly more anxious, distressed and concerned

about test result due to a perceived risk of developing cancer and lack of understanding of what these test results mean. There are no means of identifying when or from whom infection occurred and currently, there is no medication to cure incident or persistent HPV infection.

More recently attention has turned to using HPV RNA or other markers of persistent HPV infection such as p16 which may be more useful as a screening test.

Computer assisted screening offers a more optimistic development. Computer assisted screening has been promised for decades but recently systems that are clinically effective are becoming available. The first systems to be approved by FDA in 1995 were PAPNET (NSI) and AutoPap 300QC (Neopath) but for quality control of cervical cytology only. The PAPNET system was withdrawn from the market when NSI went into liquidation. It took a further four years (1999) before the AutoPap300 (now called FocalPoint Slide Profiler) was approved for primary screening of conventional Pap tests. In 2006 two systems have FDA approval: TriPath FocalPoint Slide Profiler (AutoPap300) and Cytyc ThinPrep® Imaging System.

The FocalPoint processes conventional smears or SurePath slides. It is only approved for evaluation of routine screening tests and laboratories must exclude tests from "high risk" patients (e.g. hospital clinics, previous abnormality, symptoms, etc). The sort rate can be user defined but FDA has approved a sort rate is 20%. Slides below this level can be archived without human review and the remaining 80% of slides must be fully screened manually. The recently marketed FocalPoint GS System does relocate suspicious cells down the microscope to the reviewer but this new system is NOT approved by FDA and there is little evidence in peer reviewed literature for its clinical efficacy.

An accurate cytology result requires both "locator" and "classification" skills. Computers are good at continuously scanning objects to identify any that meet the chosen algorithm without suffering fatigue or inattention. The human is better at diagnosing whether the cells identified are normal or abnormal. Thus the ability of a system to present suspicious fields down the microscope to the cytotechnologist is extremely important.

The ThinPrep® Imaging System "ThinPrep Imager" is the other system currently FDA approved for use in cervical screening. It consists of a fully automated Processor and a number of separate Imager Review Scopes which can be directly connected to the processor or at a distant location (ThinPrep® MultiCyte Imaging System). The ThinPrep® Imager uses proprietary glass slides and a special ThinPrep® Pap Stain. The slides have special marks on them to allow accurately relocation of areas of interest on the Imager Review Scope. The ThinPrep® Stain is a variant of the Papanicolaou stain but uses a very high quality standardized haematoxylin and a special rinse agent. It is reproducible, standardized and almost stoichiometric and thus allows accurate estimation of the DNA content of nuclei.

The ThinPrep® Imager™ uses optical cellular selection algorithms. Abnormal cells have larger darker nuclei therefore the algorithms look for the "biggest, darkest" objects on the slide but dismiss overlapping nuclei that might appear "big and dark". The algorithms also looks for nuclei in clusters that may represent either glandular or endocervical cells

The ThinPrep® Imager is an interactive system which has the ability to improve diagnostic accuracy while increasing laboratory throughput. The ThinPrep® Image Processor identifies objects of interest and records the XY coordinates of the worst 22 fields of view for review by the cytotechnologist. Thus the cytotechnologist looks at 22 fields in every ThinPrep® slide (~20% of circle). Thus there is double assessment of every slide, once by the computer and then by the cytotechnologist. Review of all 22 selected fields allows determination of specimen adequacy and of any infections that may be present. If all 22 fields are normal, the evaluation is complete and slide can be signed out. If one or more suspicious cells are found, the Review Scope automatically moves to full review of the entire slide using the motorized stage with a variety of user defined scanning modes. The Review Scope has been ergonomically designed for maximum user comfort and speed. Thus the ThinPrep® Imager combines

machine advantage tirelessly locating rare events with human advantage of the interpretation of cellular changes and making judgement calls.

In the ThinPrep® Imager clinical trial for FDA approval published by Biscotti et al,[12] there was 99% agreement of whether the ThinPrep® slide was satisfactory or unsatisfactory. For all sites combined, Imager review showed similar sensitivity vs. manual review for LSIL + and higher specificity vs. manual review for HSIL+. Cytotechnologist screening rates using Imager were typically doubled.

FDA approved the ThinPrep® Imager for routine use in cervical screening in the US in June 2003. Since that time about 350 Imagers are in use worldwide with more than 15 million ThinPrep® Pap tests have been reported using Imager. Over 40% of ThinPrep® tests in the US are imaged. Evidence is emerging of a negative predictive value for an Imaged ThinPrep® close to that of HPV DNA testing while maintaining a high positive predictive value. The ThinPrep® Imager is now beginning to be used in laboratories in Europe and in Asia.

Clinical evidence from routine laboratory use of the ThinPrep® Imager in the US has been presented at the American Society of Cytology (ASC) in November 2004 (11 abstracts), November 2005 (13 abstracts) and November 2006 (21 abstracts). ASC abstracts are published in Acta Cytologica and Cancer Cytopathology Supplements. Common themes from these abstracts include: increased productivity in laboratories, equivalent identification of unsatisfactory samples and, interestingly, increased detection of HSIL.

At the American Society for Colposcopy and Cervical Pathology Biennial Conference in April 2006, two studies were presented that demonstrate the accuracy and cost-effectiveness of the ThinPrep® Imaging System. Cibas et al.[13] presented the "Age-Specific Detection of High Risk HPV DNA in Cytologically Normal, Computer-Imaged ThinPrep® Pap Samples". The authors stated that "The HR HPV rates in women with a cytologically negative, computer-imaged ThinPrep test result appear to be extremely low. If these findings are confirmed in future studies, current screening guidelines supporting the addition of HPV testing to the liquid-based Pap test in women over 30 may need to be re-considered".

Gemmen et al.[14] presented a poster entitled "A Health Economic Model to Determine the Cost-Effectiveness of Cervical Cancer Screening Methods". The authors used a state-transition Markov model to evaluate the cost effectiveness of 5 different screening strategies: the conventional Pap smear; the ThinPrep® Pap test; ThinPrep® plus Imager; the conventional Pap smear plus Hybrid Capture II for women over 30 years and ThinPrep® plus Hybrid Capture II for women over 30 years. Their analysis concluded that the ThinPrep® Imager screening method is the most cost-effective screening strategy followed by ThinPrep® alone, with the total costs for these strategies being far less than both strategies employing HPV DNA testing."

There have been several publications in peer reviewed journals considering the clinical and cost effectiveness of the ThinPrep® Imager.

Dziura et al.,[15] published a study of performance of an imaging system vs. manual screening in the detection of squamous intraepithelial lesions of the uterine cervix. The authors compared two matched historical cohorts; 27,525 manually screened ThinPreps from 2003 with 27,725 ThinPreps plus Imager from the same period in 2004. The study evaluated diagnostic rates, biopsy follow-up for ASC-H and HSIL and high-risk HPV positivity. The results showed improved sensitivity for all grades, improved specificity for ASC-H and HSIL based on biopsy confirmations and a 9.5% decrease in high-risk HPV detection in the Imager vs. manual cohort. The authors concluded "In this study the ThinPrep Imaging System proved superior to manual screening in the detection of cervical SIL. Biopsy follow-up showed that the significant increase in HSIL diagnoses in the imager group was due to the detection of true disease rather than false positive cytologic diagnoses. The merger of mind and computer in the ThinPrep Imaging System has created a better Pap test."

Lozano[16] compared 39,717 ThinPrep® Imager cases with a historical cohort of 87,267 manually screened ThinPreps The results showed that Imager increased the

Table 6. Data from Sydney ThinPrep® Imager study[17]

55,164 split samples	CC	TPI	Significance
Unsatisfactory samples	3.09%	**1.78%**	(p 〈0.001)
LSIL	1.97%	**3.07%**	(p 〈0.001)
HSIL	0.7%	**0,98%**	17% increase (p 〈 0.001)
ASC H	0.54%	**0.42%**	(p 〈0.0028)

detection of HSIL+ by 38% and LSIL+ by 46% over manual screening. The authors concluded that Imager "significantly increased the cytologic detection of cervical abnormalities compared to manual screening"

In papers presented at the British Society for Clinical Cytology and the International Academy of Pathology in September 2006, Richards et al described how the ThinPrep® Imager detected more high grade lesions than conventional cytology in the independent study funded entirely by Douglass Hanly Moir Laboratory and the University of Sydney. This paper has been accepted for publication in the BMJ.[17] One of the co-authors of this paper is Davey who published a meta-analysis of LBC in the Lancet in 2006.[18] This meta-analysis combined the results from different LBC systems and β models of devices and has been widely interpreted as being highly critical of LBC. In fact the article is critical of the quality of the publications on LBC rather than LBC itself and the current paper shows the superiority of ThinPrep® Imager over the conventional Pap test in cervical screening. In deed the paper is entitled "Is the ThinPrep Imaging System the future of Cervical Screening in Australia?" mirroring the view of many Australians? Study designed by Elizabeth Davey - addressed previous study deficiencies

The Sydney Imager study was carried out in a very large private laboratory reporting over 200,000 Pap tests per annum. 55,164 patients attending for a routine Pap tests had an additional ThinPrep® prepared from the same sample but the conventional Pap test was prepared first i.e. a split sample. The result for each was read and recorded entirely independently and the laboratory computer programme was re-written so that the most severe result was sent to the referring doctor. There was histological confirmation of high grade results and the histology was reviewed by a single pathologist. The results are summarised in Table 6.

ThinPrep® Imager showed a significant reduction in unsatisfactory and inconclusive samples, a significant increase in sensitivity for squamous lesions (Low and High Grade) and a significant increased specificity for high grade squamous lesions. All this was achieved at twice the screening rate

In summary the the ThinPrep® Imager is both clinically and cost effective with a NPV close to that of HPV testing but with better specificity. In the post vaccination era, when the number of abnormal samples is expected to decrease and cytotechnologists will see fewer abnormal cases, the ability to evaluate double the number of tests per day will be important in maintaining skills. The ThinPrep® System offers the most appropriate way forward for a state-of-the-art Cervical Cancer Prevention Programme.

Finally what might be the impact of HPV vaccines worldwide? Clearly a vaccine that prevents HPV infection, which in turn prevents cervical cancer, would be a powerful addition to cervical cancer prevention strategies. If proven effective, the vaccines may have an impact on the incidence of cervical cancer in decades to come.

There are at least two vaccines under development. The Merck vaccine (GARDASIL) was approved by FDA in 2006. It is a quadrivalent vaccine for HPV types 6, 11, 16 and 18 and has been shown in clinical trials to be 100% effective at preventing infection by these HPV types for at least 4.5 years post immunization. By including low risk types 6 and 11, the vaccine may also appeal to men for the prevention of genital warts. Vaccinating men with these types may help to protect unvaccinated women by reducing the population pool of HPV. Glaxo Smith Kline (GSK) has also developed a bivalent vaccine (Cervarix) against HPV types 16 and 18. It is not yet FDA approved but there are some suggestions that it may be more potent than the Merck vaccine.

The incidence of the different HPV types found in cer-

vical cancers varies geographically across the continents but types 16 and 18 consistently account for between 55% and over 70% of cancers. This does mean, however, that at least 30% of cancers contain other high risk HPV types and would not be prevented by the current vaccines. At least an additional 11 HPV high risk types are associated with the development of cervical cancer. Many women harbour more than one high risk type of HPV at any time as many as 6 different high risk HPV types are frequently found in a single cervical sample. Furthermore we cannot predict the effect of removing types 6, 11, 16 and 18 from the reservoir of HPV types.

Three doses of the vaccine must be given over a period of 6 months according to a strict time sequence. We do not know how effective vaccines will be if this strict vaccination regime is not followed nor for how long the vaccines will remain effective or whether "booster" vaccination will be required. Indeed we do not know whether such booster vaccination will be equally effective. The total cost for the three doses of vaccine (excluding the clinician's fee) is in the range of 600US$ Thus it is expensive.

The population effect on cervical cancer rates will depend on the percentage of the population vaccinated and how well they maintain their immunity levels over time. Vaccines, to date, have only been tested on young women who have not yet been sexually active and who have no evidence of HPV DNA prior to starting the vaccination programme. The published follow up period of the study group is 4.5 years.

It is important to remember that a productive HPV infection can take many months to become clinically detectable and it is on average at least 9 months before the virus begins to be eliminated. It takes on average about 7 years for a lesion to progress from CIN1 (LSIL) to CIN3 (HSIL) with only about a 20% progression to CIN3 and about another 7～10 years for CIN3 to progress to invasive cancer again with only about a 30～40% progression rate. Thus rigorous follow up will be required to determine whether CIN3 or invasive cancer have been prevented in vaccinated women.

The Merck vaccine has been approved by FDA in US for young girls and young women aged 9～26 years who have no evidence of HPV infection or CIN. It has subsequently been approved in Europe for young girls and young women aged 9～26 years and in Australia for both boys and girls aged 9～26 years.

GARDASIL information sheets state the following caveats: Vaccination does not substitute for routine cervical cancer screening. Females who receive GARDASIL should continue routine cervical cancer screening. As with all vaccines, GARDASIL may not fully protect everyone who gets the vaccine. GARDASIL will not protect against diseases caused by non vaccine HPV types. There are more than 100 HPV types; GARDASIL helps protect against 4 types (6, 11, 16, 18). These 4 types have been selected for GARDASIL since they cause approx 70% of cervical cancers and 90% of genital warts. This vaccine will not protect you against HPV types to which you may already have been exposed. GARDASIL works best when given before you and your child has any contact with certain types of HPV (i.e. HPV types 6, 11, 16 and 18).

The bottom line is that even after a formal vaccination programme has been established and implemented with full compliance, both non-vaccinated and vaccinated women will still require regular cervical screening with the most sensitive and specific test currently available.

In summary there will be a continued need for cytology based cervical screening programmes for many years (decades) to come. Liquid based cytology plus imaging is likely to be more acceptable as a primary screening test than HPV testing since no treatment for the infection is available.

DR MCGOOGAN EXTENDS A WARM WELCOME TO EVERYONE TO ATTEND THE 17th INTERNATIONAL ACADEMY OF CYTOLOGY CONGRESS IN EDINBURGH SCOTLAND IN MAY 2010.

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