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Screening Methods in Prevention of Cervical Cancer

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1. Introduction

In this chapter I present the evidence about the performance of existing cervical cancer prevention technologies and discuss how HPV testing can be integrated. All screening and diagnostic test, including HPV DNA, and biomolecular tests, cervical cytology, colposcopy are the markers of risk of cervical cancer.

A summary and update of recently published meta-analyses and systemic reviews on clinical applications of HPV DNA testing is provided in this chapter.

1. triage of women with equivocal or low grade cytological alterations.
2. follow-up of women with abnormal screening results who are negative at biopsy
3. prediction of the therapeutic treatment of CIN
4. primary screening HPV test, lonely and combination with traditional Pap smear to detect the precancer lesions.

2. Screening

Screening is a public health activity to detect disease among people thought a priori to be well. In the United States, the major cervical screening target is treatable CIN3 (or, to be especially cautious, CIN2), not invasive cervical cancer, for which treatment causes far more morbidity and is less certain to succeed. Therefore, cervical screening distinguishes between the few women who might become patients because they are at highest risk of cancer and the overwhelming majority of women who are at far lower risk. Screening that targets the common, minor, and typically benign cytological and histological evidence of acute HPV infection cannot be cost-effective because the risk of invasive cancer is so low However, finding a woman with CIN3 is considered a screening success because she has a high risk of invasive cancer and can be treated before cancer develops.demonstrated in Nordic countries and in the United Kingdom (Bulkmans et al., 2005; Sasieni & Adams, 1999.)

2.1 Cytological screening

Since the development of cytology-based cervical in the mid-20th century screening using Pap smear test the mortality of cervical cancer has decreased substantially. In the US rates

have fallen by 75 % or more since 1960s. The key aspects of the cervical screening programs based on cytology are the exfoliated cervical cells which are examined to predict the underlying risk of cervical cancer.

The consistently observed substantial reduction of cervical cancer incidence after introduction of cytology screening and the marked difference in cervical cancer incidence between countries with and without screening programs indicates that Pap testing does prevent cervical cancer. (Gustafsson et al., 1997)

Papanicolaou originally introduced cervical cytology with morphological classifications that were based on probability of underlying cancer. However, the current US cytology classification—the Bethesda system—incorporates a view of cervical carcinogenesis that is explicitly based on the natural history of HPV.

For example, the classification of low-grade squamous intraepithelial lesion (LSIL) is based on microscopic signs of an acute HPV infection, whereas high-grade squamous intraepithelial lesion (HSIL) suggests the possibility of an underlying CIN3 (or the more uncertain precancer diagnosis, CIN2) (Smith et al., 2007) The great majority of HSIL and approximately two-thirds of LSIL are associated with carcinogenic HPV types. (Clifford et al., 2005) Very common and equivocal cytological changes, which are classified as atypical squamous cells of undetermined significance (ASC-US), form the boundary between normal and abnormal cytological interpretations; roughly half of changes classified as ASC-US are positive for carcinogenic HPV. In the United States, ASC-US is more common than all other abnormalities combined. Because this finding is common and some represent true abnormalities, a sizeable fraction of CIN3+ cases are detected by ASC-US cytology, despite poor interobserver reproducibility.(Kinney et al., 1998)

With some noteworthy exceptions (Hutchinson et al., 1999; Kitchener et al., 2009) typically a single cervical cytological screen is insensitive for detecting CIN3; sensitivity estimates as low as 50%–60% have been reported in various settings. (Nanda et al., 2000.)

Although a single negative high-quality Papanicolaou test does indicate a substantially lowered risk of cervical cancer lasting multiple years, stronger reassurance of safety (ie, a high negative predictive value) requires repeated rounds of screening to detect growing CIN3 lesions. (Wright et al., 2007.)

In many countries, conventional Papanicolaou smears are still the standard of care. In the United States and a few other countries, liquid-based cytology techniques that create more uniform slides and computer-assisted cytology evaluation systems have been adopted to achieve greater laboratory productivity, but there is no evidence that they detect CIN3 more accurately than conventional cytology (Ronco et al., 2007; Siebers et al., 2009.); therefore, we do not distinguish among cytological techniques when considering the new role of HPV testing.

In Central and South America, coverage may be high in places, but the quality of the cytology programmes and access to treatment are typically poor, and rates of cervical cancer remain some of the highest documented in the world. A notable exception is Chile, where high quality cytology-based screening has had a substantial impact on cancer incidence and mortality. (Sepulveda & Prado., 2005)

Cytology is a subjective test and in programmes without quality control/quality assurance it is virtually impossible to achieve and maintain the clinical performance of cytology.

Cytology is labour intensive and to date has been refractory to high-throughput automated screening. Despite the low cost of consumables and because of the three reasons cited above, high-quality cytology is expensive in absolute terms and may not necessarily be the most cost-effective option for screening. (Goldie et al.,2005) Liquid-based cytology has logistical and operational advantages (interpretation at higher speed, lower rate of unsatisfactory smears and possibility of ancillary molecular testing using remnant fluid), but is more expensive and is neither more sensitive nor more specific than conventional cytology with respect to detection of histologically confirmed high-grade CIN. (Arbyn et al., 2008) We must continue to recognise both the strengths and limitations of cytology for cervical cancer screening. In populations vaccinated against HPV-16/18 we should anticipate that the positive predictive value (PPV) of cervical screening will be reduced because there will be fewer high-grade lesions amongwomen with cytological abnormalities. It is therefore rational to develop multiple, viable modalities for cervical cancer prevention, including methods that achieve similar or better screening performance than cytology alone but also meet the demands of underserved populations, suchas lowcost, the need for fewer than three visits (cytology, diagnostic colposcopy and treatment) in each intervention (screening) cycle and/or fewer interventions in a lifetime due to a greater negative reassurance of a single intervention. It is naive to think that one modality, whether it be cytology-based screening, visual inspection with acetic acid (VIA), HPV DNA testing or HPV vaccination will meet the demands of all populations throughout the world. Importantly, each screening method must be validated for its technical performance and must be cost-effective within the capacity of the region in which it is to be adopted. In other words, the cost-utility of one method *versus* another must be evaluated within the limits of acceptable expenditures and available resources in different settings. Papanicolaou (Pap) test originally introduced cervical cytology with morphological classifications of the cervical cells. However, the current cytology classification, the Bethesda system, incorporated a view of cervical carcinogenesis that is based on the way of HPV infection.

2.2 HPV DNA test

Human papillomavirus (HPV) infection is very common in young women after the onset of sexual activity and, when it persists, the viral oncoproteins produce perturbation of the cell-cycle controls resulting in cervical intraepithelial neoplasia (CIN). At their mildest (CIN1), these lesions are generally no more than manifestations of HPV infection, but at their most severe (CIN3) the risk of progression to cancer is higher if not detected and treated. Fortunately, the transition to cancer usually takes years or decades, thus allowing the opportunity for detection by exfoliative cytology. The peak incidence of HPV infection occurs at about age 20, the peak incidence/detection of CIN3 occurs at about age 30, and the peak incidence of cancer occurs in the 40 s. It is estimated that without secondary prevention, cervical cancer would occur in around 3–5% of women who acquire a high-risk HPV infection, although for every cancer that occurs a far larger number of CIN lesions develop, of which the majority will spontaneously regress. Most of the pre-malignant and malignant lesions are of the squamous type, but around 15% are of the glandular type. HPV types -16 and 18 are the dominant oncotypes in squamous lesions but type -18 is relatively more important in glandular lesions. The recognition of the strong causal relationship

between persistent infection of the genital tract with high-risk HPV types and occurrence of cervical cancer has resulted in the development of a number of HPV DNA or RNA detection systems for screening.

Here I briefly summarize the update results of the meta-analysis trials.

There is now overwhelming evidence from randomized clinical trials that high risk HPV DNA screening is more sensitive than cytological screening for detecting histological proved CIN3. (Cuzick et al., 2008.)

Based on the central role of persistent infections with carcinogenic human papillomavirus (HPV) in cervical cancer, DNA testing for carcinogenic genotypes of HPV has recently been introduced into cervical cancer screening. HPV testing is more reliable (Carozzi et al., 2005; Castle et al., 2004.) and more sensitive but less specific than routinely performed cytology for detection of cervical intraepithelial neoplasia grade III and cancer (grade III+) or grade II+. (Arbyn et al., 2006; Bulkmans et al., 2007; Cuzick et al.,2006; Mayrand et al., 2007; Naucler et al., 2007.) HPV testing might soon be widely accepted as an alternative to routine cytology for cervical cancer screening.

In Castle's trial the aim was to evaluate the cumulative incidence of cervical intraepithelial neoplasia II or worse (grade II+) or cervical intraepithelial neoplasia grade III+ after short term persistence of prevalently detected carcinogenic human papillomavirus (HPV) (Castle et al., 2009).

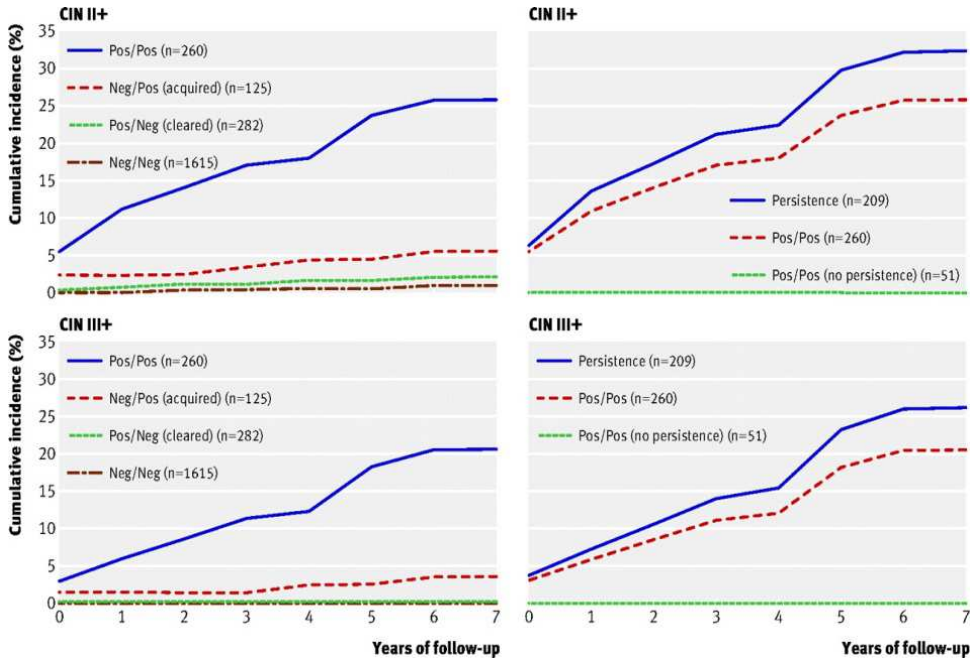

Fig. 1. Cumulative incidence of cervical intraepithelial neoplasia (CIN) grade II or worse (II+) and grade III+ after repeat measurements of carcinogenic human papillomavirus (HPV) at about one year (Castle et al., 2009)

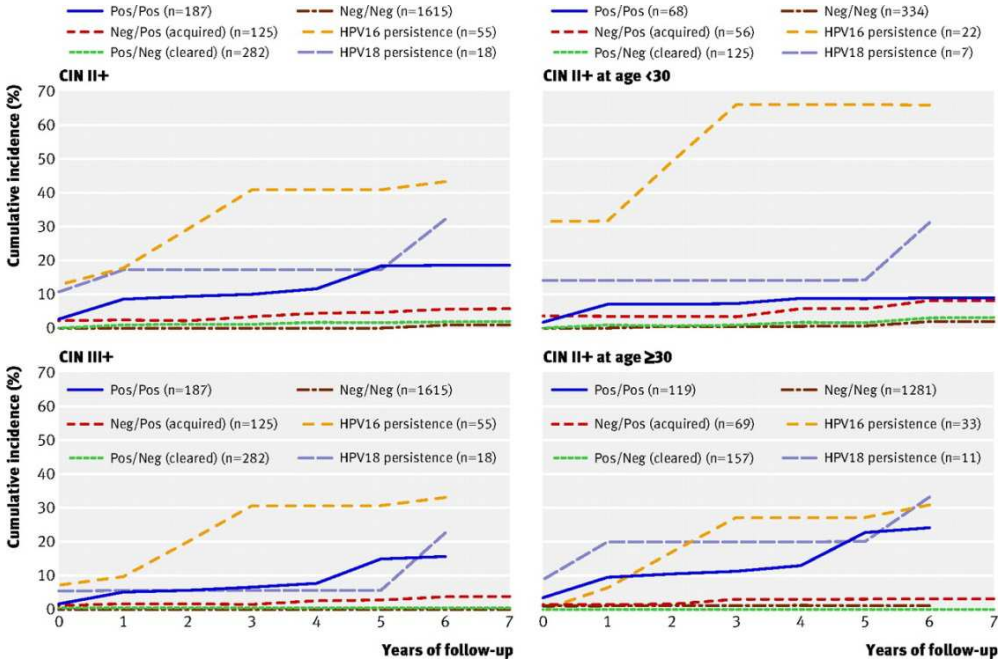

Fig. 2. In figure 2 The cumulative incidence of cervical intraepithelial neoplasia (CIN) grade II or more severe (grade II+) or grade III+ after repeat measurements of human papillomavirus (HPV) at about one year interval (9-21 months) in women who had persistent HPV 16, had persistent HPV 18, tested positive for carcinogenic HPV twice (Pos/Pos), tested positive for carcinogenic HPV at enrolment but negative at follow-up ("cleared"), tested carcinogenic HPV negative at enrolment but positive at follow-up ("acquired"), and tested negative at both time points (Neg/Neg). In right panels same groups are stratified by age. Time 0* indicates start time of analysis, 9-21 months after enrolment (Castle et al., 2009)

Among women aged <30, short term persistence of HPV 16 was highly predictive of a subsequent diagnosis of cervical intraepithelial neoplasia grade II+ (CIN2+), with a three (and five) year risk of 65.9% (40.4% to 91.5%). By comparison, among women aged ≥30, the three (and five) year risk after short term HPV 16 persistence was 27.2% (11.1% to 43.3%). There was no significant difference in the intensity of follow-up (median number of days between visits) by HPV status, although women who were in higher risk HPV groups (such as persistent HPV 16) naturally had fewer follow-up visits on average because of censoring treatments for diagnoses of grade 2+. In the summarise of Castle's trial I can allocate that women who tested positive twice for carcinogenic HPV had an increased risk of CIN2+ and CIN3+, while the risk in women who test negative for carcinogenic HPV at either or both time points was low. They did not observe any appreciable differences in the risks between those women with a shorter and longer time intervals between the enrolment and follow-up visit, suggesting that these findings are robust to variability in which women return for follow-up testing. Among those who tested positive twice for carcinogenic HPV, all subsequent diagnoses of cervical intraepithelial neoplasia grade II+ were linked to

persistence of a specific HPV genotype. With the exception of HPV 16 and possibly HPV 18, however, detection of persistence of a specific genotype did not differentiate women at risk for CIN2+ qualitatively better than repeated detection of an aggregate of carcinogenic HPV types (Castle et al., 2009).

Some trials' results, which were highlighted at a press briefing held in advance of the annual meeting of the American Society of Clinical Oncology (ASCO), confirmed that for women with a negative HPV test and normal cytology, a 3-year follow-up appears to be safe and appropriate. Women who tested negative for HPV had a 5-year cancer risk that was similar to those who tested negative for HPV and had normal cytology (3.8 vs 3.2 per 100,000 women per year; $P = .8$). This was half the cancer risk of women who had a negative result on Pap testing only (3.8 vs 7.5 per 100,000 women per year; $P = .3$). Concurrent HPV testing and cervical cytology (cotesting) is an approved and promising alternative to cytology alone in women 30 years and older. Screening guidelines from organizations such as the American College of Obstetricians and Gynecologists and the American Cancer Society have endorsed the use of cotesting in this age group as a safe alternative to Pap testing alone. The summarize of the results is shown at the 1. table. (Annual Meeting of the American Society of Clinical Oncology, 2011).

Test Results	5-Year Risk (%)	Excess Risk (%)
HPV positive	7.6	7.4
HPV negative	0.2	
Pap positive	4.7	4.3
Pap negative	0.4	
HPV positive/Pap positive	12.0	
HPV positive/Pap negative	6.0	
HPV negative/Pap positive	0.9	
HPV negative/Pap negative	0.2	

Table 1. 5-Year Risk for Cancer/Precancer by Test Results

3. HPV DNA screening in triage of women with equivocal or low grade cytological alterations

In seven studies, where also repeat Pap smear was taken, the sensitivity of HPV DNA test was on average 14 % higher than repeat cytology, considering ASCUS or worse as a positive result for detection of CIN2+. The HPV DNA test and cytology triage showed similar specificity(Cuzick et al., 2008). The sensitivity of HC2 triage of women with an index smear showing low-grade squamous intraepithelial lesions (LSIL) was very high: 97.2% (95% CI: 95.6–98.8%), pooled from 11 studies for the outcome of CIN2+ and 97.1% (95% CI: 94.0–100%), pooled from six studies for CIN3+ (Cuzick et al., 2008; Kulasingam et al., 2002; Sherman et al., 2002; Schneider et al., 2000). However its specificity was very low: 30.6% (95% CI: 22.7–38.6%) for CIN2+ and 26.1% (95% CI: 15.1–37.1%) for CIN3+. Histologically confirmed CIN2+ and CIN3+ were present in respectively 17.6% (95% CI: 11.8–23.3%) and 7.4% (95% CI: 2.9–12.0%). The very large majority of women with LSIL had a positive HC2

result: pooled estimate of 74.4% (95% CI: 67.0–81.9%; range: 58–85%). However, Cuzick's overview trial found that for women aged 35 or more, the HPV positivity rate was much lower than for younger women and that the potential value of HPV DNA testing as an adjunct to cytology in this group was substantially better than for younger women (Ronco et al., 2007). Similar observations were made in the HPV in Addition to Routine Testing (HART) study (Cuzick et al., 2003). However, another study found a high rate of HPV positivity in women older than 35 with only a small decreasing gradient with age, suggesting that specificity may not be improved very much in this group by using HPV DNA testing before referring to colposcopy (Moss et al., 2006). Furtherwork is needed to synthesise all the data on HPV triage of LSIL according to age. Even more important, a negative HPV test provides long- term risk stratification: 5-10 years of reassurance, due to the high negative predictive value of the HPV DNA test, of not developing CIN3 and even more stronger reassurance of not developing invasive cancer among HPV DNA negative women. Because the vast majority of HPV infections represented acute HPV infection what are disappeared without causing cancer, HPV DNA testing has mediocre specificity and positive predictive value for cervical cancer screening. (Figure 3.)

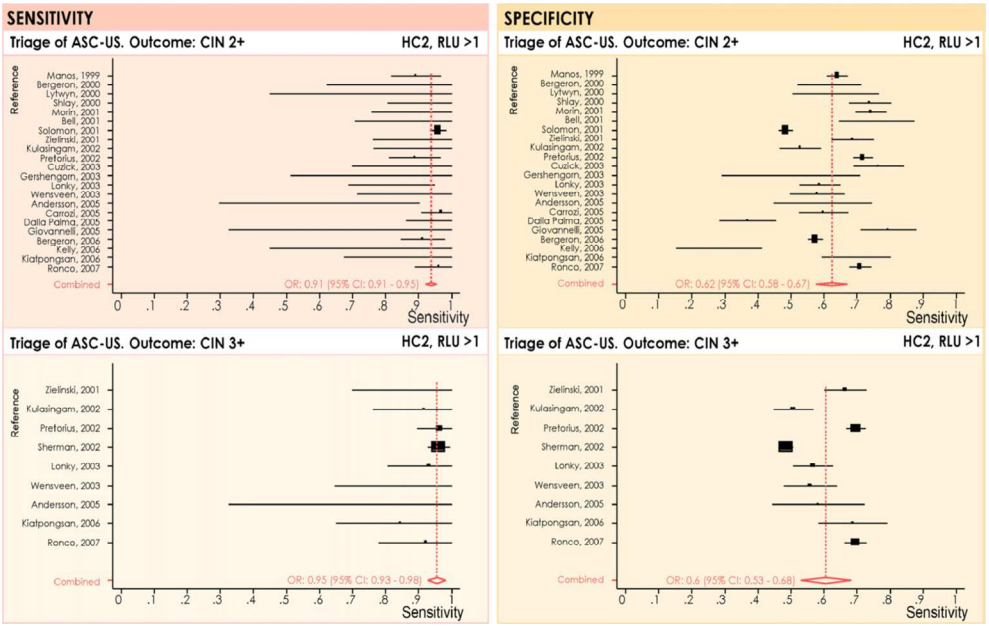

Fig. 3. Meta-analyses of the sensitivity (left) and specificity (right) of triage of women with cytological findings of ASC-US using the Hybrid Capture® 2 assay (RLU > 1) for identifying underlying CIN2 or worse (upper) or CIN3 or worse (lower). ASC-US: abnormal squamous cells of undetermined significance; CI: confidence interval; CIN2+: CIN grade 2 orworse; CIN3+: CIN grade 3 orworse; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA (previously Digene Corp.); OR: odds ratio; RLU: relative light unit.(Castle et al., 2009; Pretorius et al., 2002)

4. Primary screening HPV test, lonely and combination with traditional Pap smear to detect the precancer lesions

Successful risk stratification based on HPV screening depends on whether the infection found are persistent (high risk for CIN) or new (low risk for CIN), especially in elderly women.

Women aged 30 years or older, who test positive for high risk HPV DNA, especially the first time they are tested (when the infections might already be persistent), are at sufficiently high risk of CIN3+ to merit intensified follow-up.

There is now overwhelming evidence from randomized clinical trials that carcinogenic HPV DNA screening is more sensitive than cytological screening for detecting histological CIN3 (Mayrand et al., 2007; Ronco et al., 2010). Even more important, a negative HPV test provides long-term risk stratification: 5–10 years of reassurance (ie, a high negative predictive value) of not developing CIN3 and even stronger reassurance of not developing invasive cancer among HPV DNA–negative women. High negative predictive value permits safe and cost-effective lengthening of the cervical screening interval when HPV testing is used (Dillner et al., 2008; Khan et al., 2005) (Figure 4).

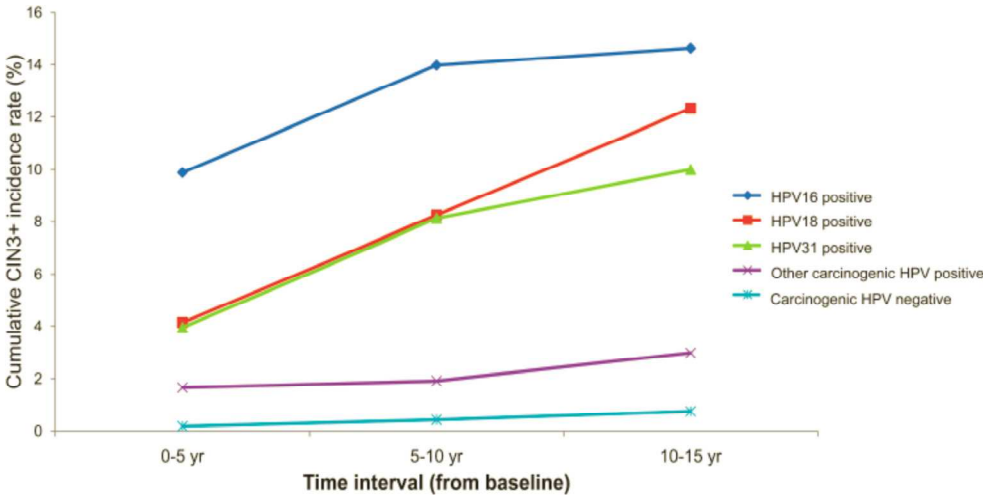

Fig. 4. Cumulative incidence rate of cervical intraepithelial neoplasia grade 3 or invasive cervical cancer (CIN3+) over 15 years following a single human papillomavirus (HPV) test. A cohort of 20 000 women from Kaiser Permanente (Portland, OR) was followed up by conventional cytology screening for approximately 15 years (78). Archived cervical specimens obtained from the women at enrollment (baseline) were tested for carcinogenic HPV types. The risk estimates, adjusted for loss to follow-up, show primarily that in this older cohort (average age approximately 35 years), a negative HPV test predicts very low risk of subsequent CIN3+. Baseline test positivity for HPV16, HPV18, or HPV31 was most strongly linked to subsequent CIN3+. (Schiffman et al., 2011)

Overall, the sensitivity of HC2 for finding underlying high-grade intraepithelial neoplasia was 89.7% (95% CI: 86.4–93.0%)) but varied over a large range between 50% (Clavel et al., 2001; Sankaranarayanan et al., 2004) and 100%. In North America and Europe, the pooled specificity was higher: 91.7% (95% CI: 90.3–93.1%; range: 85–95%).

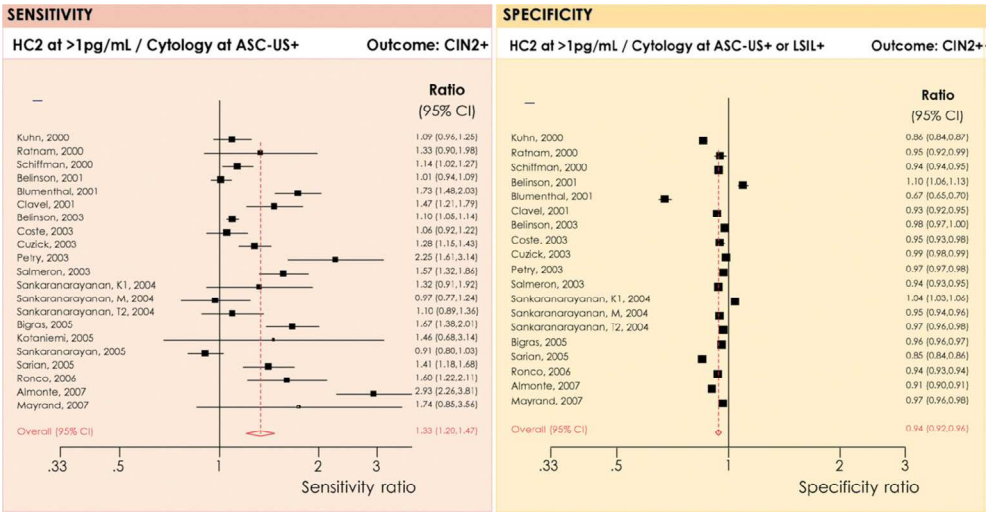

Fig. 5. Relative sensitivity (left) and specificity (right) of HPV testing using the Hybrid Capture® 2 assay compared to cytology in primary screening studies. ASC-US: abnormal squamous cells of undetermined significance; CI: confidence interval; CIN2+: CIN grade 2 or worse; HC2: Hybrid Capture® 2 (Qiagen Gaithersburg, Inc. MD, USA (previouslyDigene Corp.); LSIL: low-grade squamous intraepithelial lesion (Cuzick et al., 2008).

Because the vast majority of HPV infections represent acute HPV infections that are destined to clear without causing cancer, HPV testing has mediocre specificity and positive predictive value for cervical cancer screening. The women who test HPV positive 3 years after a negative HPV test [the current recommendation for cotesting are at much lower risk of CIN2 or CIN3+ than women who are HPV positive at their first screen and, therefore, may already have a persistent infection (Schiffman et al., 2011).

This important fact mandates much longer HPV screening intervals than current cytology screening intervals of every 2 years and suggests that the current 3-year interval for cotesting will still be too frequent. The corollary of high sensitivity of HPV testing for incipient as well as prevalent CIN3+ is a high negative predictive value that lasts for years (Schiffman et al., 2011). Several studies have shown that HPV negativity alone or in combination with negative cytology signifies a longer disease free interval against CIN2+ than being negative for cytology alone.

Early studies measured HPV retrospectively and did not use it for management. Sherman ME et al. followed 20,810 women for 10 years and found that in cytologically negative

women lesions were diagnosed much more rapidly in those who were HPV-positive compared to women who were HPV-negative (Sherman et al., 2003). In two Danish cohorts of women aged 22–32 years and 40–50 years HPV DNA was measured retrospectively and again not used for triage. The authors concluded that HPV DNA testing at five-yearly intervals offers protection similar to cytology testing at three-yearly intervals (Kjaer et al., 2002). Clavel C et al. reported that 5 of 4,401 women with negative cytology and HPV DNA tests and followed-up for a median of 34 months developed high-grade lesions, compared to 29 of 501 women who were initially cytology-negative but HPV-positive and concluded that a screening interval of three to five years was safe in double negative women (Clavel et al., 2004). Similar conclusions were obtained by Bulkmans NW et al. in a cohort of 2,810 cytology-negative women followed for five years, where 4 of 62 HPV-positive women developed CIN3+ compared to 1 of 2,175 HPV-negative women (Bulkmans et al., 2005). Long-term follow-up of the Hammersmith cohort and two large recent randomised trials in Sweden and The Netherlands have all shown that the higher detection rate for CIN2+, when HPV DNA testing was used as part of the initial screening process, led to lower rates of CIN3+ at the subsequent screening round and indicates that HPV DNA tests are highly sensitive to detect prevalent cases(Cuzick et al., 2008; Naucler et al., 2007). In the Hammersmith study, the cumulative proportion of CIN2+ within five-years after a negative HPV DNA test, when most women would have had at least one routine repeat smear was about half as high as for women who were originally cytology negative (0.6% versus 1.2%), and only after six or more years do the CIN2+ rates in women originally HPV-negative approach those seen after three years in women who were originally cytology-negative. In the Swedish study of women aged 32–38, the detection rate for CIN2+ associated with the addition of HPV DNA testing was increased 51% percent at the initial screen, but 42% lower in the follow-up period (mean: 4.1 years). For the Dutch study, the detection rate of CIN3+ was 70% higher initially but 55% lower in the 6.5 year mean follow-up period. The fact that the higher detection rate for CIN2+ when HPV DNA testing was used as part of the initial screening process led to lower rates of disease at the subsequent screening round (Bulkmans et al., 2007; Naucler et al., 2007). It also suggests that there is minimal over-diagnosis for women aged over 30, as the cumulative CIN2+ rates over two rounds were similar in all three studies, and also that the screening interval can be safely extended to at least 6 years with HPV DNA testing.

Although the ability to lengthen screening intervals is a great advance, it poses a major challenge for transitioning from cervical screening programs that are based on repeated cytology. In particular, in the United States, the considerable general reluctance to move to long-interval screening is due at least in part to reasons unrelated to theoretical best public health practice. By contrast, in some European settings, where cervical cancer screening practices are dictated more directly by public health considerations, detailed planning is underway for a transition to long-interval HPV testing (Naucler et al.,2009).

The limited data on follow-up beyond six to seven years does not allow evaluation of longer screening intervals at this time and further work is needed to see if even longer intervals might be safe, particularly for women with two or more negative HPV tests (Cuzick et al., 2008).

Some professional organizations now recommend the routine use of HPV DNA testing for screening women aged 30 years and older.

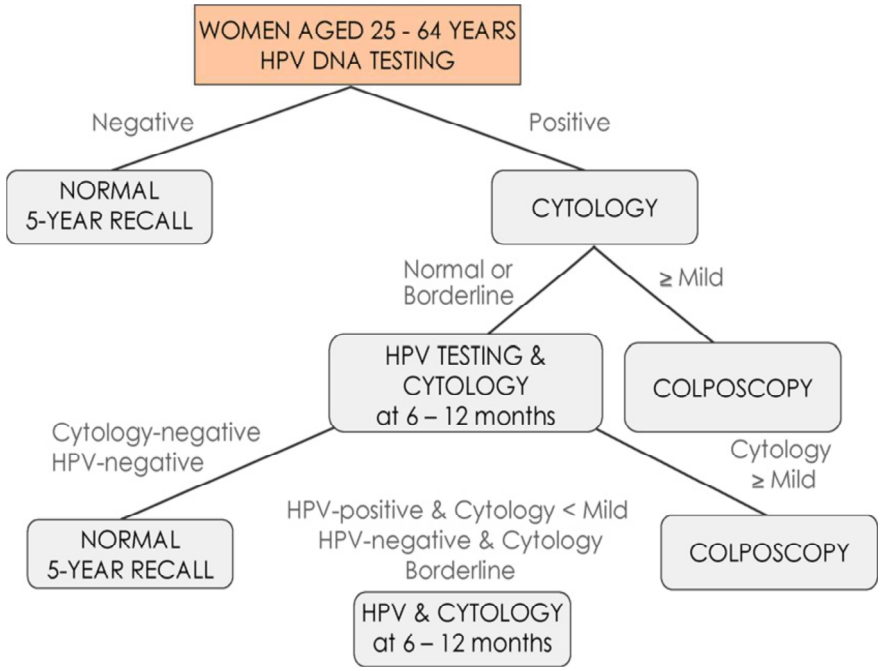

Fig. 6. Proposed new screening algorithm which employs HPV DNA testing as the primary screening test and uses cytology to triage HPV positive women (Cuzick et al., 2008).

5. HPV screening with triage by novel biomarkers

Most of the biomarkers identified thus far are markers of HPV related transformation , which reveals HPV infection. These biomarkers are more prevalent in CIN3 than in acute HPV infection.

Currently developed and used biomarkers can be shared as follow:

a. markers of increased HPV oncogene expression, such as HPV mRNA,
b. markers of increased cell proliferation, such as Ki-67, p16
c. markers of chromosomal instability, such as HPV DNA integration

At present, the most promising candidate as a biomarker for triage after a positive HPV test is immunocytochemical staining of cytology slides for p16 (Denton et al., 2010; Tsoumpou et al., 2009; Wentzensen et al., 2007).

The p16 overexpression is associated with the disruption of the retinoblastoma cell cycle pathway by HPV E7 (Denton et al., 2010; Tsoumpou et al., 2009). A combined stain for p16 and Ki-67 that was recently introduced into the diagnostics market can highlight rare transformed cells (Denton et al., 2010). Because its sensitivity for CIN3 is far higher than cytology's and almost equal to that of HPV testing and its specificity is comparable to cytology's, this stain could be used as a triage following primary HPV testing if it proves reliable and the cost for routine use is low (Denton et al., 2010).

6. HPV DNA test as a subsequent management after negative biopsy and/or colposcopy

Historically, colposcopically directed biopsies have been the clinical reference standard for diagnosing and grading pre-cancer into CIN1, 2, or 3. However, the choice of biopsy site and the histopathological diagnosis of resultant biopsies tend to be variable and subjective. Clinicians rely on colposcopy to determine the presence or absence of epithelial lesions, find the area of the cervix with the highest degree of the lesion and direct biopsy for histological diagnosis. Unfortunately well -trained gynecologists have false negative colposcopy rates as high as 20-40 % in patients with histological diagnosed pre-cancer lesion(Schiffmanet al., 2007).The use of HPV DNA testing related to triage is in women who are referred for colposcopy, because of alteration smear, but no visible lesion on colposcopy allowable. For these women, a negative HPV test provides additional reassurance, that there is unlikely to be any undetectable disease, while being HPV positive (especially for types -16 and 18), indicates a continuing risk needing for short–term repeat testing(Gravittet al.,2008). Especially for type -18, the possibility of an adenocarcinoma or its precursor lesion, adenocarcinoma in situ, should be excluded by careful examination of the endocervical canal.

7. HPV testing after treatment of cervical intraepithelial neoplasia

CIN is a very common disease especially in women of reproductive age and a balance is needed to maximize the prevention of cervical carcinoma and the same time avoid overtreatment. Management strategies of CIN include decision-making regarding the appropriateness of conservative approach versus treatment. Conservative strategies are appropriate for women with low-grade CIN, particularly in the younger age range. High-grade CIN (CIN2 or CIN3) should be treated. Conservative methods reduce overtreatment as low-grade CIN lesions may regress spontaneously. When HG-CIN is detected the treatment is mandatory. CIN 3 which is the true precursor of cervical cancer will progress to cancer if left untreated at a rate of around 30 % over 2 years (Kitchener& Stern,2008). CIN 1 has been reported to progress to CIN 2/3 at a rate of 15 % over 2 years but some of these cases may harbour undetected CIN2/3 (Castellsague et al., 2006; Kitchener& Stern,2008). Screening programs that exploit the extra sensitivity for CIN3+ conferred by HPV testing must still minimize treatment of women that is unnecessary on both public health and individual grounds. In the United States, the predominant mode of treatment for CIN2 or CIN3 is the excision of the transformation zone using a wire loop cautery, commonly known as loop electrosurgical excision procedure (LEEP) or large loop excision of the transformation zone. This office-based procedure has two advantages: it can be performed under local anesthesia and it produces a tissue specimen. The concern over the risk of premature delivery following this treatment motivates recent efforts to reduce overscreening and overtreatment, especially among young women(Kyrgiou et al.,2006). However, the societal trade-offs that come from trying to prevent every case of cervical cancer, vs the desire to prevent overtreatment of many women , should and will be debated. HPV testing following treatment with LEEP can identify women who remain at high risk of recurrence (Kreimer et al., 2006). Successful treatment of the transformation zone often leads to HPV negativity in cervicovaginal specimens for the causative HPV type (Kreimer et al., 2007)., although HPV infects the vagina (and vulva and anogenital skin) and not just the cervix. The reason for viral clearance even when the excision heals, thus creating a new

transformation zone, is not certain. The pre-reconisation HPV testing might be useful in reducing the number of reconisations in those cases where high-risk HPV test is either negative or does not confirm the same HPV type, as before (Koiss et al., 2001). Nonetheless, negative HPV tests after LEEP predict a high probability of cure (Kreimer et al., 2006). The HPV test can be useful to replace cytology for the follow up due to the high negative predictive value.

8. Conclusions

In conclusion, much has been achieved during the last 10 years from research on prevention of cervical cancer through vaccination and screening. It is imperative that planning for future prevention guidelines does not address vaccination and screening separately. Implementation of all components of an organized prevention would increase the efficiency of the process. Increased coverage of prevention activities, both vaccination and screening, will be of utmost importance (Koiss et al., 2010). It is abundantly clear that HPV DNA testing is substantially more sensitive than cytology at detecting high-grade CIN. However, HPV testing is somewhat less specific than cytology due primarily to the detection of transient infections that have not produced cytologic alterations. Basic principles suggest that in such circumstances the more sensitive test should be applied first (i.e., HPV DNA testing) and the more specific test (i.e., cytology) should then be used only for HPV-positive women to determine management. Management of HPV-positive, cytology-negative women presents a new challenge. Management of HPV-positive, cytology-negative women presents a new challenge. Results from the HART, Swedish and the Amsterdam (POBASCAM) studies suggest they can safely be managed by repeating the testing with both cytology and HPV after one year and this is being further explored in several ongoing studies (Bulkmans et al., 2007; Cuzick et al., 2003; Naucler et al., 2007). Women double negative at that time could be returned to routine screening while positives could be referred to colposcopy. This approach of using HPV DNA testing as the sole primary screening modality has several advantages: HPV DNA detection assays provide an automated, objective and very sensitive test. Implementation projects of the HPV/Pap triage screening strategy to demonstrate what could be acceptably safe intervals for both vaccinated and unvaccinated women should be initiated. We will also need to determine the best follow-up algorithms for HPV-positive/Pap-negative women. Genotyping tests, which specify the exact HPV types present on the cervix, and molecular markers of HPV targeting oncogene mRNA or proteins associated with deregulation of the cell cycle may prove to be useful for this purpose. If second-generation HPV vaccines targeting most hrHPV types are included in vaccination programs, screening activities will need to be reevaluated and algorithms modified. These prospects provide hope for a further decrease in cervical cancer incidence and mortality in the coming decades.

9. References

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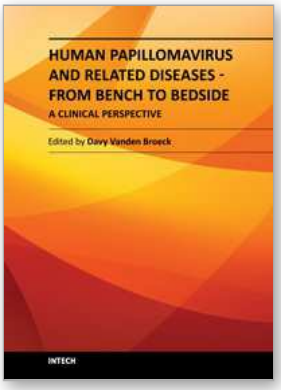

Human Papillomavirus and Related Diseases - From Bench to Bedside - A Clinical Perspective

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Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on the clinical aspects of HPV and related disease, highlighting the latest developments in this field.

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