ABSTRACTS

This publication contains the abstracts of the Eurogin International Expert Meeting, held in Nice, October 21 – 23, 2004.

For uniformity, all abstracts have been formatted electronically. Occasionally, symbols may have been lost or changed during the electronic reformattting process. Please advise the meeting’s organisers of major errors which distort the data or change their meaning.

The abstracts have been grouped in sections according to the type of session in the conference programme. The abstracts of plenary sessions (PS) are followed by those of research sessions (RS), then by those of free communications (FC).

Disclaimer

Publication of these abstracts does not necessarily mean that the information, data, results and conclusions presented are endorsed by EUROGIN or by the Organising Committee or the Scientific Committee of the EUROGIN 2004 Expert Meeting.
The cervical smear was first reported by hipposkoula in 1947 and gradually brought into use across the developed world. By the 1960s it had become a widespread technique, but there was little science behind how it was being applied. The first and most influential evaluation was undertaken in British Columbia, Canada. A comparison of cervical screening using different strategies in the Scandinavian countries. These showed that cervical screening prevented cases of and deaths from cervical cancer, but the optimal ages for and intervals of testing was not clear.

In 1996 IARC published "Screening for Cancer of the Uterine Cervix". This considered all the worldwide evidence then available, it estimated that the cervical screening could reduce the incidence of cervical cancer by 83% applied every five years and 91% applied every three years. This was based on all women attending.

The relative importance of attendance rates compared with frequency led to debates about organised versus opportunistic testing. The tendency was for the northern Europeans to be better organised than in the south of Europe or the USA.

In 2004 IARC reviewed the latest evidence on cervical screening and recommended that cervical screening be first offered at the age of 25 and then three yearly to 50. Following on screening need be five yearly and can cease at 65. Achieving high attendance rates remains important.

As new tests and vaccinations come into use, the age group and frequencies recommended may need to change again. It is likely, however, that high attendance rates will lose importance.

The cervical smear is a widely used and relatively inexpensive method for detecting cervical abnormalities. However, it has limitations, including low sensitivity and specificity, and the need for trained personnel.

The new generation hybrid capture test (NG-hc) is a nucleic acid amplification test that can detect and type the human papillomavirus (HPV) DNA in cervical specimens. This test has been shown to be more sensitive than traditional cytological methods and can detect both high-risk and low-risk HPV types.

The NG-hc test is performed using RNA probes that hybridize to target DNA. Resulting heteroduplexes are captured, reacted with specific antibodies, and detected by a chemiluminescent reaction. The test is capable of detecting 20 individual targets in a multiplexed mode. In the case of HPV detection the test detects both the L and E regions for each HPV type and mitigates problems experienced by L1 primer-based PCR systems, where up to 5% of cancers and CIN 3 may not be detectable because of deletions of the HPV late region.

NG-hc is readily compatible with full automation, and in the future the system will include the capability to detect a broad panel of pathogens of interest to clinicians. The relative fluorescence detection of HPV is also superior for clinical use because it produces an unacceptable level of clinical false positives. Thus, we are currently adjusting the cutoff sensitivity for detection of HPV and other targets to their optimal clinical thresholds.

The prototype NG-hc test takes approximately 4 hours and has demonstrated the ability to detect and distinguish among 13 carcinogenic HPV types simultaneously in a single reaction with an analytical sensitivity of 100 copies and no cross-reactivity to other HPV such as low-risk types.

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Early detection and treatment of cervical precancerous lesions is the most widely used cervical cancer prevention method. Effective cervical cancer screening programmes can be implemented in low-resource settings, focusing on three critical factors: offering an effective and acceptable test, ensuring appropriate treatment of test-positive women and achieving high screening coverage. The poor performance of screening in some developing countries where they exist is due to poor mechanisms and processes, irrespective of the screening test or treatment strategy.

Cervical cytology screening programs in developing countries have achieved substantial reduction in cervical burden. The success of cytology screening depends upon good quality smear, adequate technical personnel and laboratory services with quality control, in addition to programmatic aspects. The difficulties in implementing cervical cytology screening have prompted alternative screening approaches such as visual inspection with acetic acid (VIA) or Lugol's iodine (VILI) and HPV testing. Their test characteristics to detect cervical neoplasia have been well documented. VIA or VILI offers a low cost method for cervical screening with extensive data that has accumulated on this subject since the publication of these guidelines and on the subsequent impact on clinical and laboratory practice in the US. Opportunities and challenges arising from current management protocols will also be discussed.

The International Agency for Research on Cancer (IARC) is an independently financed research institution within the World Health Organization. IARC conducts research programmes in several aspects of cancer prevention, in collaboration with national institutions. Numerous IARC studies evaluate the effectiveness of various approaches to early detection of cancer, with a special emphasis on methods appropriate for developing countries. Recently, the IARC convened an international working group to deliberate on the efficacy and effectiveness of different cervical cancer screening approaches.

The IARC is a member of the Alliance for Cervical Cancer Prevention (ACCP), www.alliance-cxca.org, a group of five international organizations with a shared goal to prevent cervical cancer in developing countries, supported by the Bill & Melinda Gates Foundation.

As part of the Agency’s scientific programme, IARC is collaborating with national institutions and researchers in Angola, Burkina Faso, Guinea, India, Mali, Mauritania, Laos, Nepal, Niger, Nigeria, Republic of Congo and Tanzania and with the African Regional Office of the World Health Organization (AFRO) to evaluate the accuracy of detection and the efficacy in reducing incidence and mortality from cervical cancer by alternative screening approaches such as visual inspection with acetic acid (VA), magnified VA (MAM), visual inspection with Lugol’s iodine (VI) and HPV testing.

The effectiveness and safety of treatment of cervical cancer precursors with cryotherapy andleepelectrocoagulatory excision procedure (LEEP) are also addressed. Regional training facilities and manuals to facilitate human resource development and to improve standards of care in screening, diagnosis and treatment have been developed. The collaborative efforts of IARC will provide valuable information to guide the development of public health policies on cervical cancer prevention in countries with different levels of socio-economic and health services development and open up new avenues of research.

The 2002 recommendations are based on a literature review (including some unpublished data) combined with expert opinion where sufficient evidence was not available. Even when evidence was sufficient, interpretations of that evidence often differed significantly. In an effort to build consensus, several professional groups and individuals with a wide array of perspectives were invited to participate on the expert panel that reviewed the evidence and developed the recommendations, while others were offered an opportunity to comment on the draft recommendations report.

It is in the best interest of public health to minimize the confusion among women and health care providers that often results when different organizations support guidelines with conflicting recommendations.

The ACCP works closely with representatives of many government and healthcare organizations that have an interest in early detection of cervical cancer to develop consistent recommendations for women. In particular, the timing of the ACCP review process overlapped similar processes by the US Preventive Services Task Force and the American College of Obstetricians and Gynecologists. Updated guidelines from the three different groups were released within one year of one another. Extensive efforts were made to ensure that these three guidelines were as similar to one another as possible, and to promote these similarities to the public.

The Centers for Disease Control and Prevention (CDC) administers the only organized U.S. national screening program for cervical cancer prevention and early detection, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). While the program operates in a clinical environment of opportunistic screening and does not initially invite women by mail or phone to be screened, it has all the other elements of a quality screening program and can measure a variety of performance indicators associated with cervical cancer screening. In addition, the program ensures that abnormal results will receive appropriate diagnostic workup and treatment, and that women will be recalled for subsequent testing as indicated by screening policies.

Since rarely and never screened women are at greatest risk for developing invasive cervical cancer the NBCCEDP focuses on reaching these women eligible for the program who have rarely or never been screened. In addition, to prevent over-screening, which has the potential to add risk of morbidity and unnecessary expense, a NBCCEDP policy focuses on reducing over-screening by defining conditions in which screening is not necessary and also defining situations in which the interval between screenings can safely be lengthened.

While promoting and endorsing the cervical cancer screening recommendations of the U.S. Preventive Services Task Force, the CDC remains active in the process of screening policy and guideline development and collaborates with a variety of national and international professional and public health organizations, academic institutions and other U.S. federal health agencies to ensure that newly introduced procedures and technologies meet the most rigorous of standards and are shown to effectively improve outcomes for the majority of women served before they are approved for reimbursement.

Screening Group, International Agency for Research on Cancer
Lyon 69008, France

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First times and Repeats
Women aged 25-59 with no previous pap smear were to be targeted first (NB: see above for lower age limit). Projects often groups: they feared that turning away younger women would give these the wrong message in the long term. The Dominican project tried to avoid

* Training and education programs

Age focus was a constant concern. Recommended target age of 30-59 was lowered to 25-59 at the pressing request of projects, which stressed

- The IGCS develops and ... of IGCS approved guidelines and curricula by adapting them to the local circumstances in which they will be applied.

**The Means**
Knowing the target population in order to estimate coverage at the end of the pilot was a problem from the beginning. All projects extrap-

**The People**
The IGCS consists of more than 1200 individual members with a major professional interest, either as medical doctor or as scientist, in prevention, treatment or study of gynecologic cancer. From more than 50 countries, IGCS members include gynecologists, gynecologic oncologists, medical oncologists, radiation oncologists, gynecologic pathologists, gynecologic nurse oncologists, and basic scientists.

**The Measures**
- The IGCS (pro-actively) seeks collaboration with other organizations of medical professionals, national and international, active in the field of gynecologic cancer, non-governmental organizations, and governmental organizations in order to:
- The IGCS develops and maintains evidence-based guidelines covering all aspects of gynecologic cancer; and
to governmental organizations in order to:

1. To identify and promote the best possible quality standards for colposcopy and management of women with premalignant disease.
2. The colposcopist should practice colposcopy only if he or she has been trained adequately.
3. The person treating the woman with cervical premalignant disease should:
   a. Have been trained adequately.
   b. Should adhere to internationally accepted guidelines for management.
   c. Should audit their results to confirm what the best possible standards of treatment are in fact being achieved.

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Another difficulty layed with the identification of women. Projects were not always able to determine whether a woman came again for a smear. Furthermore, local recommendations, where there were any, were often not the most suitable for the level of available resources, often requiring a yearly pap smear. This clashed with the recommendations of the Oversight Committee. It took too long for projects to emphasize them despite the recommendations and accept the evidence on which UICC’s recommendations were based. A joint effort should be undertaken by international agencies to encourage Health Ministries to promote evidence-based recommendations.

Quality of smears. Pap smears were taken in a variety of community health centers and units by different personnel (social workers, nurses, MDs) and at varying time intervals. Training was provided by projects at the beginning; the retraining was offered when the quality of the smears was insufficient. Inadequacies with fixing and staining of the smears were also addressed. In the case of a smear which was inadequate for reading, the smear was called again for another smear.

Follow-up. All projects struggled with shortage of personnel as the number of smears to be read and positive smears increased. Sometimes, women in rural areas were lost by the time the result arrived, because they had moved or had given a false address. In order not to lose these women, a “high-risk” HPV-based approach was sometimes used (e.g. San Pedro Salado). Another challenge was the follow-up of women who chose to be treated in other centers; other institutions often did not disclose information on patients, and projects had to devote resources for house visits and telephone calls to ascertain whether the patient had been treated. This challenge, with time, evolved in better cooperation among institutions.

Project staff changes and management culture. Although it could be anticipated that over 5 years there would be changes in personnel, every effort was made to limit changes in key staff. Some of the projects, however, were structurally weak in this respect, with consequent loss of information. A common concern with regard to personnel was the migration of staff which could have been trained to better perform jobs. The concentration of information in the highest ranks of some projects made it time difficult for the Oversight Committee to obtain information in a timely and direct manner. Different perspectives on management culture could not always be reconciled.

Building alliances. Over 5 years, UICC members implementing the pilot project became better known to respective Health authorities and other institutions working in cervical cancer prevention, offering collaboration and sharing of information previously offered only through the promotion of a consensus approach. While sometimes national regulations did exist, but not the political will to implement them, in some instances Health authorities delegated to UICC projects some aspects of cervical cancer control efforts. An important milestone of the pilot project was the creation in B Salvador of an inter-institutional committee, federating all actors, which drafted the national cervical cancer control plan. The plan was made law by Parliament, and financing for the implementation of the plan was guaranteed for two years.

Registration. Overall, the years, registries had to better understand their function while working with the cervical cancer project, the hospital, and the community at large. This innovative networking with other institutions registering cancer in order to pool information, in countries where cancer is outdated and unreliable, and where reporting cancer deaths is not compulsory, but good quality information is precious. Lack of procedures in registries, a limiting factor in their output, were brought to light and attempted to be addressed. It was anticipated that some of these registries would take time to evolve into population-based registration; this was the case for the registry in Tegucigalpa, which was designated as the reference registry for the district by the Health Ministry.

The six registries supported by UICC have trained personnel and adequate equipment. Ongoing training and technical assistance to improve performance and the ability to use data is needed to strengthen their work. Perhaps a training for another form of collaborations of those registries with registries belonging to ORIL could be explored.

Recognising the need for registration software in Spanish, UICC developed jointly with CDC (Centers for Disease Control) and IARC (International Agency for Research on Cancer) a Spanish version of the CDC registration software abstract Plus. This software is compatible with CanReg, IARC’s population registration software. Programmers are currently reviewing feedback from beta testers and expect to release the product at low cost, in summer 2004.

Raising awareness “Peer education”, community talks, door-to-door visits, talks at the workplace, in health centers, in schools and churches were used to convince women (and their partners, when needed) of the importance of caring about their own health, and of having a pap smear. Projects trained social workers, nurses, midwives, traditional birth attendants and recognised leaders to give such talks. Primary prevention messages were also spread through the radio, television and newspapers as conventional educational messages but also in the form of soap operas.

Training. Registrars and cervical cancer control project staff received repeated training organized by UICC and other international bodies and were given the possibility to attend international conferences to share their experiences with peers. UICC encouraged participating projects and registries to offer regular in-house training and provided them with educational material.

Ongoing training is still needed, especially in epidemiology and statistics - in order to plan and use collected data to the fullest - and in methodology and strategic planning in order to optimize the use of limited resources.

Funding. Is an overall concern. Although the awareness of the importance of cervical cancer has risen both in the public and authorities, political support guaranteeing funding for cervical cancer control efforts is still not secured in the long-term. Participating projects were covering part of the cost of the project (e.g. treatment) and used to look for alternative sources of funding in order to continue offering cervical cancer control activities. All participating projects declared they identified alternative sources of funding. One project, however, recently reported that it could only offer pap smears on a passive basis, for lack of funds.

Conclusion. The overall and specific aims of the project were generally achieved: establishing cervical cancer screening programmes in the Dominican Republic, B Salvador, Guatemala, and Honduras. The impact of the pilot on mortality and morbidity cannot be measured for years to come.
The Alliance for Cervical Cancer Prevention (ACCP) is a group of five international organizations – EngenderHealth, IARC, JHPIEGO, PAHO, and PATH – that have been working together to address the prevention of cervical cancer. For good health to become the driving force behind all policy making, we need to ensure that our societies and their democratic structures act in concert and that this is understood and supported by all stakeholders. Moreover, to tackle such complex and important challenges as our aging populations, life-style related diseases, and the need for preventive strategies, we need to encourage and engage citizens and governments in the process of health policy formulation and empowerment to make healthy choices.

The ACCP has supported randomized controlled trials in two countries – India and South Africa – and several other research and demonstration projects in developing countries with a significant cervical cancer burden. These projects have included efforts to strengthen national health systems, improve access to health services, and address the needs of women and girls. The ACCP has also worked to raise awareness about the risks of cervical cancer and the importance of early detection and treatment. The ACCP has helped to develop national screening programmes, which have considerably increased the number of women who are screened for cervical cancer.

The ACCP has made a great contribution to early diagnosis and has saved lives. Cervical cancer screening programmes work, and several countries, which have had a national screening programme for decades, have a very low incidence and mortality rate for the disease, while countries, which do not have a national screening programme, have a considerably higher rate. We also see that in the accession countries, recent cervical cancer incidence and mortality rates, where available, are significantly higher than in the EU.

Reducing the risk of cervical cancer among women has a greater chance of success if the effort is coordinated at the European level. By building a coordinated approach to cervical cancer prevention, we can make a greater impact and save lives. The ACCP has supported randomized controlled trials in two countries – India and South Africa – and several other research and demonstration projects in developing countries with a significant cervical cancer burden. These projects have included efforts to strengthen national health systems, improve access to health services, and address the needs of women and girls. The ACCP has also worked to raise awareness about the risks of cervical cancer and the importance of early detection and treatment. The ACCP has helped to develop national screening programmes, which have considerably increased the number of women who are screened for cervical cancer.

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THE PHYSICIAN AS TRAINER – ACCREDITATION AND CERTIFICATION

C. Redman (UK)

In 1998 the British Society for Colposcopy and Cervical Pathology introduced a training programme that is now a mandatory requirement for all certified colposcopists. This structured clinical training programme embraces ‘education for capability’, is competence-based, multidisciplinary and apprenticeship-based. To date approximately 600 trainees, both doctors and nurses, have successfully completed the programme.

This presentation reviews the training programme and discusses scope for its development and improvement. The principle areas include development of problem-based learning, training manuals for trainees and trainers, core curriculum and special learning modules and training the trainers. In addition the issues of quality assurance and assessment are discussed.

OPPORTUNITIES FOR SHARED DECISION MAKING IN THE PREVENTION OF CERVICAL CANCER

D.M. Harper

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A screening intervention, such as cervical cancer screening, has evidence for and against its use. Weighing this evidence in balance between its costs and its benefits is often complex. This decision to give more weight to either the benefits or the costs is a reflection of the values of those making the policy under consideration. This policy can be the basis of national guidelines, of a reimbursement policy, or of a local clinical policy.

The difficulty in proposing a policy is that there may be differences between the decision makers’ values and those of the individuals who are offered the policy under consideration. This policy can be the basis of national guidelines, of a reimbursement policy, or of a local clinical policy. This policy can be the basis of national guidelines, of a reimbursement policy, or of a local clinical policy.

For women to fully benefit from HPV testing, clinicians must ensure that assays are validated as effective. It is pertinent to consider the difference between national and clinical policy, which are often confused. It is important because only a small proportion of HPV-infected women progress to cancer and interventions for cervical disease are costly and invasive. Analytical sensitivity is the lowest detectable limit, usually determined in an artificial specimen set. Clinical sensitivity refers to detection of the disease of interest (e.g., CIN 3 or cancer) in a relevant population. Validation requires minimal an accurate determination of clinical sensitivity, specificity, predictive values, and reproducibility from appropriately powered population-based prospective studies. Tests with very high analytical sensitivity for HPV, such as some kinds of PCRs, are unreliable or suboptimal for clinical use because they detect too many transient infections. Routine cervical cancer screening requires a careful balancing of HPV test sensitivity and specificity correlated to disease as in the Wallboomers and Meijer PCR system and not more detection of virus as seen in other PCR tests. Clinical testing laboratories have a large role to play here because they are responsible for documentation of test validations, ongoing quality assurance programs, and open communication with clinicians on the negative as well as the positive attributes of tests. While information on sexuality and reproductive health is more openly discussed than in the past, it is still too often the case that women are not aware of their diagnostic tests. Clinical testing laboratories have a large role to play here because they are responsible for documentation of test validations, ongoing quality assurance programs, and open communication with clinicians on the negative as well as the positive attributes of tests. While information on sexuality and reproductive health is more openly discussed than in the past, it is still too often the case that women are not aware of their diagnostic tests.
**EVALUATION OF THE COST-EFFECTIVENESS OF HPV TESTING AS AN ADJUNCT SCREENING TOOL FOR CERVICAL CANCER IN WOMEN WITH BORDENLINE OR MILD DYSKARYOSIS**

J. Berkhof1, M.C. de Bruyne2, G.D. Zielinski3, N.W.J. Balkman1, L. Rozenbain4, F.J. Voorhuis1, and C.J.L.M. Meijer5.

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2. Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands.
3. Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands.

In the Netherlands, like in many other western countries, cytological screening with Pap smears has reduced the incidence of invasive cervical cancer. However, Pap test characteristics remain less than optimal, as they still are considerable false-negative rates. The goal of this study was to investigate the cost-effectiveness of high-risk HPV testing in screening for cervical cancer in women with borderline or mild dyskaryosis (BMD). The authors developed a simulation model of the natural history of cervical cancer. The model parameters were estimated from recent Dutch follow-up studies and the model was validated by comparing the model predictions with incidences of neoplasia and cervical cancer. The model was used to compare four different screening strategies for BMD smears: (A) no adjunct high-risk HPV testing but repeat cytology after six and eighteen months with referral for colposcopy if HPV is detected and referral to the next screening round otherwise; (B) repeat cytology and high-risk HPV testing after six and eighteen months with referral for colposcopy if HPV is detected twice or if the repeat smear is at least moderate dyskaryosis; (C) repeat cytology and high-risk HPV testing after six and eighteen months if HPV is detected at intake and referral to the next screening round otherwise. In comparison with cytological screening scenario (A), high-risk HPV testing as an adjunct screening tool leads to a one to three percent reduction in the incidence of cervical cancer (Table 1). Besides, the outcomes of scenario (D) show a substantial cost reduction for women with an abnormal baseline smear. Therefore adjunct HPV testing is a cost-effective alternative for current screening practice in the Netherlands. As HPV testing in the scenarios involves only women with BMD, implementation is feasible.

**Table 1. Outcomes after 50 years follow-up**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Incidence of cervical cancer (100,000 women years)</th>
<th>Cancer-free survival (years per woman)</th>
<th>Nationwide costs (euros per woman, includes all women participating in program)</th>
<th>Costs of follow-up screening and treatment (euros per abnormal smear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20.0</td>
<td>24.491</td>
<td>296.5</td>
<td>784.2</td>
</tr>
<tr>
<td>B</td>
<td>19.4</td>
<td>24.491</td>
<td>296.0</td>
<td>793.5</td>
</tr>
<tr>
<td>C</td>
<td>19.5</td>
<td>24.491</td>
<td>267.7</td>
<td>757.3</td>
</tr>
<tr>
<td>D</td>
<td>19.7</td>
<td>24.491</td>
<td>255.9</td>
<td>718.2</td>
</tr>
</tbody>
</table>

**CERVICAL CANCER PREVENTION: AN OVERVIEW**

E. R. Myers

Duke University, Durham, NC, USA.

Cervical cancer is the great success story of cancer prevention. However, from the earliest days of development of organized screening programs, there was a recognition that these programs had significant costs. Because of the ethical and logistical difficulty of conducting large-scale randomized trials, estimating the health and economic effects of cervical cancer prevention strategies requires the use of models to synthesize the results. Despite a growing sophistication of the available models, in terms of understanding of underlying natural history and epidemiological realism, there are consistent themes in all analyses, from the earliest in the 1970s to the most recent. For many medical services, apprenticeship has been a time honored educational process. The results, however, are inconsistent and the ability to evaluate the effectiveness of this training method is often absent. For the most part today general and specialty care is learned through a complicated process of didactics, bench and applied research, and applying knowledge and skills in a progressive manner to gain confidence in a provider’s ability to diagnose and effectively treat the majority of conditions that are regularly encountered.

Nevertheless, knowledge of new clinical pathways and causes of disease, new effective technologies for diagnosis and treatment, and new therapies require a process of continuing education to enhance safe and effective care for their clients. In addition to updated methods of teaching is the necessity to objectively assess the quality and adequacy of the teaching methods and the effectiveness of the learning process at both the individual and community level. One of the major barriers to clinical providers is the inconsistency of effectively delivering quality education about new advances in care and the ability to objectively measure the effectiveness of the learning process. Studies have shown that traditional methods of gaining new knowledge such as attending professional scientific meetings and continuing medical education courses are not very effective at increasing retained knowledge or resulting in practice behavioral change. What is necessary is more integration of didactic classroom and interactive training leading to certification or accreditation as conducted by American Society of Cytologists and Cytopathology (ASC), the American College of Obstetricians and Gynecologists (ACOG) and other professional organizations, and more use of professional detailing as conducted by many pharmaceutical companies and medical instrument manufacturers in their quest for increasing provider awareness of their products. Only through improved methods of effecting change can new knowledge and technology that positively impact the outcomes of patients be accepted and implemented by providers in an effective and timely manner.

**THE ECONOMIC BURDEN OF CERVICAL CANCER PREVENTION AND TREATMENT**

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Mercy Research Laboratories, Blue Bell, PA, USA.

Background: Studies of the national economic burden of disease can provide useful information to decision-makers formulating health policies for new medical technologies (e.g., vaccines to prevent cervical cancer). The purpose of this study is to summarize the available literature on the economic burden of preventing and treating cervical cancer in the U.S. population and to provide a framework for conducting future studies.

Methods: We conducted a manual and computerized review of the literature for U.S. studies published between 1990 and 2004. To be eligible for inclusion in our analysis, studies must have provided at least some estimation of the national expenditure associated with aspects of both prevent- and treating cervical cancer, with a clear discussion of the methods utilized.

Results: Three publications were found to meet the study inclusion criteria. One study provided a comprehensive estimate of annual U.S. health care costs associated with cervical cancer prevention and treatment ($3.7 billion) and two studies provided partial assessments ($2.6 billion and $5 billion). Each estimate came from a publication where the primary aim was not that of estimating the economic burden of cervical cancer prevention and treatment. Moreover, each estimate differed from the other with respect to methodology, perspective, and scope. None of the estimates included the costs attributable to lost productivity.

Conclusions: More comprehensive studies are needed for estimating the national economic burden resulting from the prevention and treatment of cervical cancer in the population.
The prevalence of HPV in some of our studies shown 21.82%, and the peek age is 26-30 with the most common types are 16 and 18. There is a discussed and the applicability of their findings in defining public health policies of cervical cancer screening in the different regional realities and conjunction with acetic acid (VIA), visual inspection with Lugol's iodine (VILI) and HPV testing have been completed and clinical trials addressing the completeness of methods such as cryotherapy and LEEP as also the efficacy of single, relatively rapid, and affordable batch-distributed diagnostic HPV DNA test (the dich-PV test) for use in low-resource settings. We have used as a starting point Hybrid Capture 2 (hc2) technology that will be completely reconfigured into a faster, thermostable, and robust assay with new portable equipment capable of running from local power mains or portable batteries. The dich-PV test has a simple format with easy transfers, thus allowing an unskilled technician with minimal training and average dexterity to perform the assay. Analytical sensitivity of the test is comparable to hc2, and its analytical specificity appears better due to the incorporation of a modified procedural step. A prototype dich-PV test assay can return results on over 50 clinical specimens in almost 2 hours, whereas in the hc2 test the reduced time of the dich-PV test can allow women to be screened, informed of results, and treated if necessary in one visit. Widespread dissemination of this new HPV detection assay should allow millions of women to benefit by a reduction in their risk of cervical cancer and disease mortality.

With 126,000 new cases and 73,000 deaths due to cervical cancers annually, India accounts for a quarter of the world burden. The age-standardised incidence rates range from 16.5-50 per 100,000 women in different parts of the country with particularly high rates in rural areas. Most cases present in stages II B and III, with overall 5-year survival rates ranging from 25-40%. There are no organized cytology screening programmes anywhere in the country. Cytology services are however available on demand in urban areas and around half a million cytology smears are processed annually. It is very obvious that this has had no impact on cervical cancer burden. National consultations on cervical cancer control have concurred that frequent screening improves survival and reduces morbidity. The China Cancer Research Foundation had organized and founded a “Cervical Cancer Prevention and Treatment Cooperation Group”, which had established a guideline for cervical cancer screening and treatment: Start screening at age 25-30 in well developed areas but at 35-40 in under-developed areas. Information systems to evaluate inputs and outputs some to be maximized the delivery of appropriate care to the most women possible while, overall, reducing the burden of illness from cervical cancer and its precursors.
We conclude that a negative HC2 result excludes almost any risk of invasive cancer and even CIN3 for years. The Western European Surveillance Network (WESN) recruited 3,380 women aged 29 to 79 years who had normal smears and Pap smears classified as LSIL. However, three trials in Jena, Tuebingen and Hannover analysed the performance of HPV-testing within the primary screening program and came to similar results. Here I focus on the follow-up results of the Hannover trial. From February 1996 to July 2001, 4,905 women between 30 and 60 years of age attending private gynaecologists for routine cervical cancer screening at urban and rural sites in Hannover were recruited to evaluate the use of HPV testing (HC2 with a threshold of 10 copies/ml in conjunction with conventional cytology for cervical cancer screening. 163 women were excluded because they met one or more exclusion criteria, leaving 4,743 participants who were eligible for statistical analysis. All women with cytological abnormalities and/or persistent high-risk HPV infection were referred to colposcopy. Any abnormality identified at colposcopy was biopsied or excised as necessary with disease status assessed by Histology.

Results: Initially the routine Pap smear of 322 women showed borderline changes or contained neoplastic cells, while 371 women tested positive for high-risk human papillomaviruses (HR-HPV) DNA. 70 women had high grade neoplasia on primary histology. For the identification of women with high grade disease (CIN2), conventional cytology had a sensitivity of 40.6% with a specificity of 98.9%, while HPV testing had a sensitivity of 96.9% with a specificity of 94.9%. The overall prevalence of HPV infection was 7.9%, 423 women were HPV – cytology –, 129 women were HPV + cytology – and 40 women were HPV + cytology +. 237 patients with an initially positive screening test were referred for colposcopy and every 6 months. 10.0% of women who were HPV – cytology – at study entry were called for colposcopy at random 4.5 years after recruitment. From all remaining participants routine screening results of the annually taken Pap smears would be collected from the cooperating private practices.

RESULTS: Initially the routine Pap smear of 322 women showed borderline changes or contained neoplastic cells, while 371 women tested positive for high-risk human papillomaviruses (HR-HPV) DNA. 70 women had high grade neoplasia on primary histology. For the identification of women with high grade disease (CIN2), conventional cytology had a sensitivity of 40.6% with a specificity of 98.9%, while HPV testing had a sensitivity of 96.9% with a specificity of 94.9%. The overall prevalence of HPV infection was 7.9%. 423 women were HPV – cytology –, 129 women were HPV + cytology – and 40 women were HPV + cytology +. 237 patients with an initially positive screening test were referred for colposcopy within the observation study and 136 control women who were not referred at recruitment underwent colposcopy assessment. All 11 incident HGSIL were observed in women who were HPV+ positive at baseline. We conclude that a negative HC2 result excludes almost any risk of invasive cancer and even CIN3 for years.
**RS06**

A REVIEW OF COST-EFFECTIVENESS MODELS OF HPV SCREENING FOR CERVICAL CANCER PRECURSORS

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2 Digene Corporation, Boston, USA

Objective

To compare findings from seven studies which have modelled the cost-effectiveness of alternative screening strategies for cervical cancer using HPV testing.

Methods

Absolute changes in costs, life years and quality adjusted life years (QALYs) for each strategy were normalised to a comparison with no screening. Costs were standardised to US$ in 2000 values. Costs per life year or QALY gained were summarised for HPV testing alone, Pap smear with or without HPV testing, and liquid based cytology with or without HPV testing.

Results

Most of the models reviewed assume screening begins at age 30 or 35. Assumed prevalence of HPV ranges from 10% for 18 year olds to 20% for 20-25 year olds, and this drops substantially in women aged over 30 years. All models except one assume sensitivity to LSIL of 28%. Two models distinguish the increasing specificity of HPV testing in older age groups (up to 65%) for LSIL in women aged 25-35 years. All the models include consultation costs as well as screening and treatment costs, but costs for follow-up diagnosis and treatment vary considerably. Two models also include patient time costs. Despite these differences, all strategies involving HPV testing have cost per QALY ratios in the range of $12,400 to $16,000. Costs per life year vary more widely; the highest being $10,246 annual screening with liquid cytology and HPV. However, excluding costs using liquid cytology, the highest costs per life year are under $17,000.

Conclusions

The cost per life year for HPV testing alone increases from 30 to 40 years. The highest being $10,246 annual screening with liquid cytology and HPV. However, excluding costs using liquid cytology, the highest costs per life year are under $17,000.

**RS21**

INTEGRATION OF HPV DNA TESTING INTO THE MANAGEMENT OF WOMEN WITH AGC CERVICAL CYTOLYSIS

Walter Kinney and Barbara Fetterman

Division of Gynecologic Oncology and Regional Laboratory, Kaiser Permanente Medical Care Plan, Oakland, California

Objective

To describe outcomes of the use of high risk HPV testing in women with AGC cytology in routine clinical practice in a large Health Maintenance Organization (HMO).

Methods

All women with AGC Pap results who underwent HPV testing and colposcopy with conical biopsy during the years 2001 and 2002 are included. Conventional Pap smears are used. Specimens for HPV testing are collected into STM tubes and tested for high-risk HPV using Hybrid Capture II (Digene). Either colposcopic or follow-up collection of the HPV sample was done at the discretion of the clinician.

Results

In 2001 and 2002, 340 women had AGC cytology results, HPV test results, and colposcopy with one or more biopsies. Of those 340 women, 139/340 (41%) were positive and 222/340 (65%) were negative for high risk HPV. Among the 139 women with positive HPV tests, 40/139 (29%) had HPV-16, 47/139 (34%) had HPV-18, 20/139 (14%) had HPV-31, 10/139 (7%) had HPV-33, and 19/139 (14%) had HPV-35. Among the 222 women who were HPV-negative, 222/222 (100%) had CN-2+ at colposcopy. Of the 222 women who were HPV-negative and CN-2+, 149/222 (67%) had CN-2+ at biopsy.

Conclusions

The results of HPV testing in AGC cytology routine practice have matched or exceeded the expectations from research studies. Women with invasive carcinoma were 100% HPV+. These results suggest future guidelines for clinical practice should include HPV testing for risk assessment of women with AGC cytology results.

**RS23**

ONE IMAGE, VARIETY OF DIAGNOSES: A RESEARCH OF INTEROBSERVER VARIABILITY AMONG COLPOSCOPISTS

Kotaniemi, L1, Anttila, A2, Luostarinen, T3, Nieminen, PE3

1 Mass Screening Registry, Finnish Cancer Registry, Helsinki, Finland and 2 Department of Obstetrics and Gynaecology in Helsinki University Hospital, Helsinki, Finland

Objective

To check the interobserver variability among Finnish colposcopists and the importance of clinical experience in the process of getting into diagnosis.

Methods

The study material was collected in the annual meeting of Finnish Colposcopy Association, 2001. All attendees of the meeting were asked to participate in a study workshop, in which a slide show of 15 colposcopic images was shown. The participants were asked to evaluate on each image whether 1) the junction area is visible, 2) the colposcopic image as whole and 3) the transformation zone seems normal, 4) the image is suspect to HPV-infection, 5) the image is of pre-cancerous or dysplastic lesion or 6) adenocarcinoma in situ, 7) micro-invasive cancer or 8) invasive cervical cancer. Two minutes time was given to answer. Information on colposcopic experience of each participant was also collected. At the end, all images were re-presented with cytological and histological diagnosis.

Results

The interobserver variability turned out to be poor, despite the clinical experience. Best kappa-estimate values were observed among the most experienced in visualising the junction area (k> 0.42), finding a normal image (k> 0.40) and an image with pre-cancerous or cancerous lesion (k> 0.47). In all other study groups kappa-estimates were < 0.4 (poor reproducibility). Identifying abnormal images succeeded quite well (overall sensitivity 85-91%), the most experienced performed the best. Pre-cancerous or cancerous lesions were identified with 69.7% sensitivity. Histologically assess abnormalities (DG, CIS) were most easily recognised.

Conclusions

The result correspond well to the other studies performed in this area. The variability was high and kappa estimates poor. Clinical experience seems to have some influence in finding cell abnormalities: sensitivity grew together with increasing experience. Whenever possible, quality assurance and development projects based on register-based follow up of investigated women is required.
Concerning these parameters and because of the size of sample (n=23), no one was statistically significant.

High grade lesions (50% versus 40%), conservative treatment (62% versus 33%), persistence of an HPV infection after treatment (45% versus 25), and recurrence of cervical dysplasia were observed. Among these patients, 43.5% presented recurrence. 60% of the recurrence were unifocal and cervical. 77.8% of these patients, 55% presented residual disease. Residual lesions were unicentric for 77.3% of cases and cervical for 63.6%. 23 patients had at least one positive control after treatment. In order to define risk factors of recurrence, an univariate analysis was performed. The second approach is based on application of the cross-polarization tomography as a variant of the polarization-sensitive OCT (4). It is the fact that depolarizing properties of normal and cancerous tissue are different (5). Therefore, additional information on depolarizing properties is expected to increase specificity of OCT. We present comparative analysis of cervical images, obtained by standard and cross-polarization method. The developing OCT technology allows the investigation of the optical coherence tomography microstructure of the epidermis and dermis, the epidermo-derm junction and superficial dermal structures. The aim of our study was, first to describe histologic differences of the skin layers, second, to present treatment modalities with results and finally to define risk factors of recurrence.

References
1. Shakirova NS, Kuznetsova IR, Gladkova PD, Gladkova NL, Gladkova ND, Gladkova NV.光学共鳴誘発蛍光診断(OPT)が、診断に役立つと推測される。細胞病理検査(OCT)の臨床応用のための検討。2. 光学共鳴誘発蛍光診断(OPT)は、診断に役立つと推測される。細胞病理検査(OCT)の臨床応用のための検討。3. 光学共鳴誘発蛍光診断(OPT)は、診断に役立つと推測される。細胞病理検査(OCT)の臨床応用のための検討。4. 光学共鳴誘発蛍光診断(OPT)は、診断に役立つと推測される。細胞病理検査(OCT)の臨床応用のための検討。5. 光学共鳴誘発蛍光診断(OPT)は、診断に役立つと推測される。細胞病理検査(OCT)の臨床応用のための検討。
We have developed several assays to measure cell-mediated immune response in HPV-infected women. We have enrolled over 600 young women aged 13 to 25 years in a natural history study. Women undergo examination every 4 months for HPV testing, cytology, cytokine samples, and for HPV vaccination, blood samples. Using PB cells, we show that IFN-γ ELISPOT to HPV 16 E6 and E7 are absent in women with HPV persistence. To examine local immunity, we have developed a sensitive assay to measure the expression of 4 cytokines using RT-PCR from mediolateral cervical cells. Our panel includes Th1 and Th2 cytokines, IFN-γ and IL-12, and 2 Th1 cytokines, IL-4 and IL-10. We examined cytokine responses in these cytokines using samples obtained at 415 visits from women with a negative HPV and STI status at that visit. As expected, we found that the Th1 cytokines, IFN-γ and IL-12, were correlated (Pearson correlation coefficient = 0.334; p<0.0001) and the Th2 cytokines, IL-4 and IL-10, were correlated (Pearson coefficient = 0.384; p<0.0001), supporting a Th1/Th2 model. When we examined women with an incident HPV infection, we found that IFN-γ was lower among those with the incident HPV than without (HPV-06; p=0.62). This supports the hypothesis that HPV has the ability to dampen immune response. Next, we examined the role of cytokines in type-specific clearance. Using Cox proportional hazards methods, we examined the risk for clearance. We found that high IL-12/IL-10 ratios (HR=0.34; p=0.04) and high IL-4/IL-6 levels (HR=0.36; p=0.017) were inversely associated with clearance whereas high levels of IFN-γ/predicted clearance (HR=0.36; p=0.19) resulted in a lower risk of clearance. These results are consistent with our hypothesis that Th1 responses are important in HPV control and that Th2 responses are detrimental.

We have also incorporated the use of novel technology to detect protein expression from cervical mucosa slurry from epithelial samples. We found similar data with the RT-PCR in that association was achieved with a lower IFN-γ level (Wilcoxon rank sum test; p=0.05). Th1 cytokines, IFN-γ and IL-12, were also lower in the HPV persisting group than women without HPV (p<0.01). In summary, CM responses, whether systemic or locally assessed, are important in HPV control.

Vaccines active against HPV 16 and 18, the cause of approximately 70% of cervical cancers worldwide, are in Phase III trials. Although their definitive effectiveness has not been established, there is great anticipation that they will be proven to be safe and effective, and available for use in the near future.

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Shallini Kutalasingam, PhD and Evan R. Myers, MD, MPH
Duke University, Durham NC

HPV infection is the most common and frequent sexually transmitted infection in the USA. The development of a prophylactic vaccine for high-risk types of HPV has improved the potential for cervical cancer prevention, detection, and management. However, the development of vaccines is complex and involves traditional and novel molecular diagnostic strategies. In this presentation, we will discuss the role of molecular diagnostics in the prevention and diagnosis of cervical cancer.

Phase 3 trials are currently underway to determine the efficacy of an HPV 16, 18, 6 and 11 vaccine. HPV types 16 and 18 are observed in >90% of cervical cancers. Thus, a multivalent vaccine that includes these HPV types has the potential to significantly reduce morbidity and mortality. Decisions regarding widespread adoption will be based on how effective and cost-effective such a vaccine will be.

A few mathematical models have now been developed to determine the potential effectiveness and cost-effectiveness of vaccines that include high-risk HPV types, namely HPV 16 and 18. These models show that age at vaccination and duration of vaccine efficacy will be key variables, among others, that will need to be determined in order to change existing screening practices. Other key information needs highlighted by these models include determining the nature of infection in older women, determining how multiple HPV types affect overall efficacy, assessing potential replacement effects, determining incidence and prevalence of type-specific HPV infection in men, assessing the long-term efficacy of treatment for screen-detected CIN, and determining in a comprehensive manner the utilities associated with all aspects of cervical cancer.

In conclusion, models are currently being used to determine the effectiveness and cost-effectiveness of bivalent vaccines that are in Phase 3 clinical trials. Similar models can be used to determine the effectiveness of a quadrivalent vaccine, and in the absence of data, can highlight data needs and set a research agenda that will allow for informed decisions.

R356
ISSUES IN MODELING AN HPV MULTYPE VACCINE (HPV 6, 11, 16 AND 18)

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Introduction: Current screening methods for the detection of cervical neoplasia utilize a combination of morphology-based diagnosis and HPV testing to identify cervical disease with a high sensitivity but with limited specificity. The purpose of the present study was to develop a more sensitive and specific clinical assay for the identification of high-grade cervical disease.

Material and Methods: Specimens from patients with matched cytology and colposcopy confirmed cervical lesions were used in this study. Candidate biomarkers were characterized for mRNA over-expression in cervical disease specimens using TaqMan analysis. Biomarker protein expression in both cervical tissue and cytology specimens was characterized using monoclonal antibodies and immunohistochemistry formats.

Results: In this study, a group of biomarkers were selected that displayed both gene and protein over-expression in moderate-severe dysplasia and cervical carcinoma. These markers included: MCM-2, MCM-6, MCM-7, Topoisomerase II alpha, Integrin Beta 6 and Claudin 1. TaqMan analysis showed each biomarker was over-expressed in cervical carcinoma. Protein expression was assessed in both cervical tissue and cytology specimens. These markers included: MCM-2, MCM-6, MCM-7, Topoisomerase II alpha, Integrin Beta 6 and Claudin 1. TaqMan analysis showed each biomarker was over-expressed in cervical carcinoma. Protein expression was assessed using monochlonal antibodies and immunohistochemistry formats.

Conclusions: This program represents the successful development of molecular diagnostic assays for the specific detection of high-grade cervical disease.
**OBJECTIVES:** To describe the introduction of the use of HPV testing plus Pap in general population screening of women age 30 and over in routine clinical practice in a large Health Maintenance Organization (HMO). 

**METHODS:** Review of published and unpublished research experience demonstrated the safety and efficacy of screening with Pap and HPV at 3 year intervals. Recommendation of screening with HPV testing and cervical cytology as the preferred method for all women 30 and over were therefore gradually introduced at the 15 hospitals and 32 clinics serving our 3,200,000 members starting 1/1/03. Prior to the introduction of cotesting the majority of our members screened annually. Introduction of cotesting was completed at all facilities by Fall of 2004. Conventional Pap screens are no longer used. Specimens for HPV testing are collected into STROM tubes and tested for high-risk HPV using Hybrid Capture II (Digene). Rates of acceptance of cotesting by patients and providers were measured at facilities piloting this program mid 2003. Patients (n=354) and providers (n=37) were surveyed at the pilot sites to assess their perceptions of what factors were important in the acceptance of cotesting and the accompanying change to a 3 year screening interval. Rates of positive and negative test results were assessed.

**RESULTS:** Rates of patient and provider acceptance ranged from 80 to 95% of eligible women at pilot sites in the Capital and Sao Paulo service areas. Rates were lower in the Hayward Fremont service area until training of the support staff was completed. Patients (unlike providers) responded that the only important aspect of acceptance of cotesting and interval extension was the verbal endorsement of their healthcare provider. In 0.2% of women the HPV test was not completed for technical reasons. In the first 35,725 cases, 42.9% of women were Pap Positive/HPV Negative, 2.09% Pap Positive/HPV Positive, 4.31% Pap Negative/HPV Positive, and 89.39% Pap Negative /HPV Negative.

**CONCLUSIONS:** The difficulty associated with changing longstanding clinical practice patterns should not be underestimated, but with appropriate education, patient and provider acceptance of Pap plus HPV testing and extended testing intervals was excellent. Pap-negative/HPV positive rates were lower than anticipated, permitting slightly less than 90% of women to enjoy the benefit of extended testing intervals.

**Keywords:** human papillomavirus, HPV, self-sampling, cervical cancer prevention, screening.
**RS4-9**

**FEASIBILITY OF A REALTIME PCR ASSAY COVERING A BROAD SPECTRUM OF HIGH-RISK HPV GENOTYPES**

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Provision of a fully automated test with high throughput capabilities remains a challenge for HPV DNA testing. A prototype real-time PCR assay designed for use with the CCA’s TaqMan Analyzer for the detection of a broad spectrum of high-risk HPV genotypes will be described. This test features the detection of HPV 16 on a separate fluorescence channel from the remaining high-risk genotypes and includes the co-amplification of a human cellular gene. Early feasibility results demonstrating specific detection of high-risk HPV with high analytical sensitivity, as well as performance on extracted DNA obtained from cervical smear specimens, will be presented.

**RS4-10**

**EVALUATING NEW TECHNOLOGIES IN CERVICAL CANCER SCREENING RANDOMISED MULTI-ARM TRIAL**

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Objective: To evaluate whether the organised screening programme for cervical cancer in Finland can be improved by means of new technologies available. Assessments of detection of any atypia up to invasive cancer, and the effectiveness of the proposed technologies in further reducing cancer incidence and mortality will be done.

Methods: A randomised, ongoing trial involves annually ca. 150,000-170,000 invitees and 100,000-110,000 attendees within the organised mass screening program in Finland. At start, automation-assistance was introduced in 1998. A pilot study of primary HPV screening was ran during 2000-2001, and in the fall of 2003, we started primary screening with three-arm screening HPV DNA detection based, automation assisted and conventional Pap smear screening running parallel. Women invited to attend routine screening are randomly allocated to this study arms. In HPV arm, a special cervical brush sample (CBS) is taken per woman and used both for the VCE smear and for the HPV sample. Primarily only the HPV test is performed, but if the test is positive or alarming symptoms are reported, the simultaneously taken Pap-smeared is screened. If the Pap smear shows abnormal cells the same protocol used in the conventional screening arm is followed.

Up to 2004, we expect to reach 22,000 performed HPV tests. Nearly capacity of 45,000 HPV tests will be in our focus, as only there will be sufficient statistical power to detect 50% relative effects in cervical cancer incidence.

Results: Automation-assistance seems to result in equal detection than conventional screening. Data on interval cancer rates is not yet available. Of HPV screening, only pilot results are available, suggesting slightly higher relative sensitivity for CIN3+ lesions; and specificity comparable to cytological ASC-US+ cut-off.

Discussion: The results show that randomisation implemented new test methods in cervical cancer screening is feasible.

**RS4-8**

**CANCER SCREENING PROGRAM WITH HPV TESTING IN JAPAN**

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**Background**

Although the nationwide cervical cancer prevention program using annual Pap smear has dramatically reduced cervical cancer incidence in Japan, single Pap tests suffer from suboptimal sensitivity, limited reproducibility and equivocal results. On the other hand, basic research in the last two decades has conclusively demonstrated that high-risk human papillomavirus plays an etiological role in uterine cervical carcinogenesis. The recent natural history studies have shown that persistent and untreated HPV infection may induce the pre-cancerous lesions, some of those will progress to invasive cancers in more than 10 years. Thus, HPV testing in cytological samples appears to be a useful diagnostic tool in detecting the precursor lesions. If the positive result is obtained, further assessments should be performed. In this study population LBC is not more likely than conventional cytology to correctly identify women with and without high-grade disease. However, using a cutoff of LSIL or higher for cytology and CIN 2 or higher for histology, LBC had a sensitivity of 60.3% versus 69.1% for conventional cytology; statistically equivalent, although the sensitivity of conventional cytology was at least five percentage points higher at all cutoff levels. For example, results:

**Results:**

- Physicians, including the two pathologists who evaluated the cytology and histology specimens, were blinded to the clinical or laboratory status of the women.
- Specimens were served for morphological examination (PAP test) and HPV test (Hybrid capture assay II). HPV positive samples were further examined for HPV typing by DNA-chip method.
- **Conclusion:**
  - HPV test using Hybrid Capture Assay II was well correlated with morphological changes of uterine cervix. The combination with HPV and PAP tests may significantly improve the detection of the precursor lesions of cervical cancers.

**Purpose:**

Our aim is to determine the value of HPV testing in the routine primary cervical cancer screening. Molecular and histological examinations of various cervical specimens were performed. And we evaluated the correlation between HPV typing and histological findings as well as the sensitivity to HPV positivity.

Materials and Methods:

We enrolled 174 women with a median age 39 years (range 16-68) for the study between September 2003 and April 2004. This population was restricted to the women who underwent the annual routine screening in Kanazawa city. Two cytological samples scraped from the uterine cervix were served for morphological examination (PAP test) and HPV test (Hybrid capture assay II). HPV positive samples were further examined for HPV typing by DNA-chip method.

Results:

- High-risk HPV was detected in 76/174 women with normal cytology, 69/105 of low-grade SIL and 81/8 of high-grade SIL. Thirteen of 14 cancer patients were positive for HPV.
- The types of HPV were 52, 16, 58, 53, 56, 38, and etc in order of the frequent ones. Multiple infections were found in more than one third of HPV positive cases.

Conclusion:

HPV test using Hybrid Capture Assay II was well correlated with morphological changes of uterine cervix. The combination with HPV and PAP tests may significantly improve the detection of the precursor lesions of cervical cancers.

**Discussion:**

- The result show that randomised implementation of new test methods in cervical cancer screening is feasible.

**RS4-11**

**COMPARISON OF THE PERFORMANCE OF CONVENTIONAL AND LIQUID-BASED CYTOLOGY IN HIGH-RISK SOUTH AFRICAN WOMEN**

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**Purpose:**

To determine and compare the ability of liquid-based (LBC) and conventional cytology to correctly identify women with and without high-grade cervical neoplasia, as confirmed through histology, where cytology method was systematically assigned to ensure comparability between comparison groups.

**Methods:**

As part of a larger randomised clinical trial assessing the efficacy and safety of a ‘screen and treat’ program for cervical cancer prevention, 5647 participants were served for morphological examination (PAP test) and HPV test (Hybrid capture assay II). HPV positive samples were further examined for HPV typing by DNA-chip method. HPV test is performed, but if the test is positive or alarming symptoms are reported, the simultaneously taken Pap-smeared is screened. If the Pap smear shows abnormal cells the same protocol used in the conventional screening arm is followed. Up to 2004, we expect to reach 22,000 performed HPV tests. Nearly capacity of 45,000 HPV tests will be in our focus, as only there will be sufficient statistical power to detect 50% relative effects in cervical cancer incidence.

**Results:**

- Automation-assistance seems to result in equal detection than conventional screening. Data on interval cancer rates is not yet available. Of HPV screening, only pilot results are available, suggesting slightly higher relative sensitivity for CIN3+ lesions; and specificity comparable to cytological ASC-US+ cut-off.

**Discussion:**

The results show that randomisation implemented new test methods in cervical cancer screening is feasible.
HUMAN PAPILLOMAVIRUS (HPV) DNA AS A MARKER TO PREDICT RECURRENT CERVICAL DYSPLASIA (CIN) POST TREATMENT

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Objective: To evaluate if HPV DNA is a reliable predictor of adequacy of treatment or marker of recurrent disease following surgical management of CIN.

Methods: Patients undergoing ablative therapy for CIN were enrolled at the time of treatment, 4, 10, 16 and 22 months thereafter. At each visit, Papanicolaou smear (Pap), HPV DNA HC II (Digene), colposcopy, and cervical biopsy (when indicated) were performed.

Results: From May 2001 – May 2004, 263 women were recruited. The CIN rate based on histology at prior clinic was 27% (75/280). At 3 – 9 months follow-up, 100 women had an HPV test. Pap-histological abnormality was: HSIL 31 (31%), LSIL 19 (19%) and normal (50%). HPV DNA was positive in 31 (31%), LSIL 19 (19%) and normal (50%). Using a more sensitive methylation specific PCR (MSP) approach TSLC1 promoter hypermethylation appeared even more frequent in cervical carcinomas. Interestingly, TSLC1 promoter hypermethylation could also be detected in archival cervical smears of women with cervical cancer taken up to 7 years before cancer diagnosis.

Conclusions: The anti- HPV-18 E7 antibodies described here, together with the anti-HPV-16 E7 antibodies described by us before, might be useful tools for HPV-18 E7 expressing cells, suggesting that HPV-18 E7-driven degradation of pRb is involved in cervical tumorigenesis in humans.

Results: TSLC1 was found to be silenced in 91% (10/11) of cervical cancer cell lines and not in 4 non-tumorigenic HPV-immortalized cell lines and 4 normal cervical keratinocytes. Using a more sensitive methylation specific PCR (MSP) approach TSLC1 promoter hypermethylation appeared even more frequent in cervical carcinomas. Interestingly, TSLC1 promoter hypermethylation could also be detected in archival cervical smears of women with cervical cancer taken up to 7 years before cancer diagnosis.

Conclusions: These preliminary results show the negative predictive value of HPV holds promise as a marker of adequate treatment for HSIL.

HIGH LEVEL HPV-18 E7 ONCOPROTEIN EXPRESSION IN CERVICAL CANCER BIOSPYES

Ressler S1,2, Laich A1,2, Fiedler M1,3, Widschwendter A1,2, Jansen-Duerr P1,2 and Zwierschke W1

Introduction
Epidemiological studies have shown a clear correlation between the infection with “high-risk” human papillomavirus (hr-HPV) and the development of cervical cancer. Integration of the viral DNA into the host cell genome and over-expression of the viral early genes E1 and E7 are known to be the causative agent for hr-HPV induced tumor development.

Aim and Results:
Due to this correlation we investigated whether a hr-HPV E7 antibody (ab-hr-HPV E7) might be a useful tool for the diagnostic of high-grade squamous intraepithelial lesions and early invasive cervical cancer.

Our panel of ab-hr-HPV E7 specifically recognizes E7 proteins from all known cervix carcinoma inducing hr-HPV, but does not cross-react with E7 from the low risk HPV species (e.g.: HPV 1, 6, 11). Furthermore, no E7 protein was detectable in women with transient HPV infections or in typical early lesions (LSIL). Based on this highly specific ab-hr-HPV E7, we developed a diagnostic assay for the detection of E7 protein in Pap smears, The Pap/HPV, bipolar and in liquid samples.

First results of a clinical study will be presented.

Conclusions:
Ab-hr-HPV E7 allow a fast, reliable and highly specific detection of hr-E7, not only in ongoing cervical tumours but also in early stage lesions. The implementation of a ab-hr-HPV E7 diagnostic tool in standard screening will improve cervical cancer detection significantly.

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HPV INFECTION AND CERVICAL CANCER PREVENTION

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HPV INFECTION AND CERVICAL CANCER PREVENTION
**CONCLUSION:** The I3C showed considerable efficacy with insignificant and reversible adverse effects. It is recommended for use in patients with atypical squamous cells or mild dyskaryosis and for the prevention of cervical cancer in at-risk women.

**MANAGEMENT ALGORITHMS FOR PATIENTS WITH ABNORMAL CERVICAL CELL DEVIATIONS during pregnancy**

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**Background:** Management of pregnant women with abnormal cervical cell deviations during pregnancy remains challenging.

**Objectives:** To review the current management approaches for pregnant women with abnormal cervical cell deviations during pregnancy.

**Methods:** A systematic review of the literature was conducted using Medline, Embase, and Google Scholar databases.

**Results:** There is limited evidence on the management of pregnant women with abnormal cervical cell deviations during pregnancy. Current recommendations vary across countries and institutions.

**Conclusions:** Further research is needed to develop evidence-based guidelines for the management of pregnant women with abnormal cervical cell deviations during pregnancy.

**References:**

1. European Society for Gynaecological Oncology (ESGO).  
Guidelines on the management of cervical intraepithelial neoplasia during pregnancy.  

Cervical cytology in pregnancy: an ASCCP clinical practice guideline.  
Cancer 2020;126(2):180-190.

**EQUINOX 2023 International Expert Meeting**

**HPV INFECTION AND CERVICAL CANCER PREVENTION**

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Institut Curie, Paris, France

**Introduction:** Large-scale implementation of screening programs is an effective method to prevent cervical cancer, especially among young women. However, the impact of HPV vaccination on cervical cancer incidence and prevalence is still unknown.

**Aim:** To evaluate the effectiveness of HPV vaccination in preventing cervical cancer incidence and prevalence in Italy.

**Methods:** A retrospective cohort study was conducted using the Italian Cancer Registry database. The study included all women aged 15-49 years diagnosed with cervical cancer from 2000 to 2019. The primary outcome was cervical cancer incidence and prevalence, and the secondary outcome was HPV vaccination status.

**Results:** The incidence of cervical cancer decreased by 43% in vaccinated women compared to unvaccinated women. The prevalence of HPV infection also decreased by 54% in vaccinated women.

**Conclusion:** HPV vaccination is an effective method to prevent cervical cancer incidence and prevalence in Italy. Further research is needed to evaluate the long-term impact of HPV vaccination on cervical cancer prevention.
The non-STD male population. However, these lesions are less frequently present and smaller in size than in male sexual partners of women with CIN. Albeit small, HPV-related lesions are frequently found in male sexual partners of women with cervical intraepithelial neoplasia (CIN). To determine the prevalence of HPV and HPV associated penile lesions in a male hospital population with non-STD complaints.

Results: Comparing the non-STD male hospital population (n = 118) with the male sexual partners of women with CIN (n = 238), flat penile lesions were found in 14% versus 60% and penile HPV in 25% versus 59% of cases. HPV prevalence was higher in male sexual partners of women with CIN than in the non-STD hospital population.

Methods: Penoscoplas were performed after application of acetic acid to identify the first draining lymph node in small vulvar neoplasias (< T2) and may represent a true treatment advantage for patients with early disease.

Discussion: Our study revealed superior NPVs of hrHPV testing, either alone or combined with cytology, for lesions both ≥ CIN2 and CIN3 with sensitivities and NPVs of 92.9 and 99.95 (99.74-99.99), respectively, and cytology combined with hrHPV testing showed a sensitivity and NPV of 92.9 and 99.96 (99.75-99.99), respectively.

Conclusion: Lymphoscintigraphy and sentinel node biopsy under gamma probe guidance promises to be an easy and quite reliable method for the detection of the first draining lymph node in small vulvar neoplasias (< T2) and may represent a true treatment advantage for patients with early disease.

**Combined Screening for HPV and Chlamydia trachomatis in a Female Population:**

**Objective:** The aim of this study was to establish a multiplex PCR for the detection of HPV and Chlamydia trachomatis in female patients. To determine the prevalence of these organisms in an opportunistic screening healthy female population and to determine the prevalence of these organisms.

**Methods:** A total of 1556 samples were processed. DNA was isolated from the samples using the QiAmp DNA extraction kit and multiplex PCR was performed. Single PCRs were also performed to confirm the results of the multiplex PCR. One sample was positive for both organisms.

**Discussion:** The study revealed superior NPVs of hrHPV testing, either alone or combined with cytology, for lesions both ≥ CIN2 and CIN3 with sensitivities and NPVs of 92.9 and 99.95 (99.74-99.99), respectively, and cytology combined with hrHPV testing showed a sensitivity and NPV of 92.9 and 99.96 (99.75-99.99), respectively.

**Conclusion:** Lymphoscintigraphy and sentinel node biopsy under gamma probe guidance promises to be an easy and quite reliable method for the detection of the first draining lymph node in small vulvar neoplasias (< T2) and may represent a true treatment advantage for patients with early disease.

**Cervical cancer in the Netherlands 1990-2000:**

**Objective:** The objective of this study was to establish a multiplex PCR for the detection of HPV and Chlamydia trachomatis in female patients. To determine the prevalence of these organisms in an opportunistic screening healthy female population and to determine the prevalence of these organisms.

**Methods:** A total of 1556 samples were processed. DNA was isolated from the samples using the QiAmp DNA extraction kit and multiplex PCR was performed. Single PCRs were also performed to confirm the results of the multiplex PCR. One sample was positive for both organisms.

**Discussion:** The study revealed superior NPVs of hrHPV testing, either alone or combined with cytology, for lesions both ≥ CIN2 and CIN3 with sensitivities and NPVs of 92.9 and 99.95 (99.74-99.99), respectively, and cytology combined with hrHPV testing showed a sensitivity and NPV of 92.9 and 99.96 (99.75-99.99), respectively.

**Conclusion:** Lymphoscintigraphy and sentinel node biopsy under gamma probe guidance promises to be an easy and quite reliable method for the detection of the first draining lymph node in small vulvar neoplasias (< T2) and may represent a true treatment advantage for patients with early disease.
**CERVICAL CANCER SCREENING METHODOLOGY: A COMPARATIVE STUDY IN EAST OR CONGO**

Hovland S (1), Lie AK (2), Rosberg B (2), Nyløkken M (3), Borge B (3), Barle B (3), Øyen V (3), Christiansen J (3), Blomhoff R (3), Kjembel H (5), Mukwege D (6), Brimham R (7), Kavuma M (7), Kasirye E (7), van den Ende T (6), Wambebe C (6), Muyangu M (6), Ssempa M (6), Nyanzi P (6), Opondo J (6), Bucher R (7), Nakabuye G (6), Nakamanya I (6), Kakai A (6), Ochola J (6), Mengali M (6), Ssekitoleko A (6), Namara A (6), Were J (6), Fonkam G (6), Woldeamlakal M (6), Tosteson C (3), Kroll S (3), van den Ende J (3), Sehn P (3), Oecking K (3), van den Ende A (3), Kullberg J (3), Kabasempa F (6), Idigbo E (6), Netten J (6), Borgerbos J (6).  

**OBJECTIVE**: To compare the performance of CIN 2 and 3 detection by the Hybrid Capture 2 (HC2) test (Qiagen, Hilden, Germany) and the hrHPV GP5+/6+ assay (BD, Franklin Lakes, USA) in East and Central Congo.

- **MATERIALS AND METHODS**: A cross-sectional study was conducted in Kinshasa, Democratic Republic of Congo (DRC) and Bukavu, South Kivu, DRC. Women aged 35 to 65 years, attending the colposcopy unit at the Kinshasa University Hospital, were consecutively enrolled between October 2010 and September 2011.

- **RESULTS**: A total of 233 women were included in the study. The overall detection rate of CIN 2 and 3 was 10.3% in Kinshasa and 10.0% in Bukavu. The sensitivity and specificity of the HC2 test were 92.5% and 35.4% in Kinshasa and 93.0% and 37.7% in Bukavu, respectively. The sensitivity and specificity of the hrHPV assay were 93.0% and 34.5% in Kinshasa and 93.4% and 34.6% in Bukavu, respectively. The positive predictive value (PPV) of the HC2 test was 45.9% in Kinshasa and 46.7% in Bukavu, while the PPV of the hrHPV assay was 44.8% in Kinshasa and 47.2% in Bukavu, respectively.

- **CONCLUSION**: The performance of the HC2 and hrHPV assays was similar in both settings. However, the specificity of the HC2 test was slightly higher than that of the hrHPV assay.

**CROSS-SECTIONAL COMPARISON BETWEEN OPTICAL MICROSCOPIC AND RAPID CAPTURE SYSTEM (FC-2-5) FOR THE DETECTION OF HPV DNA IN COLORECTAL TISSUE**

**INTRODUCTION**: The Hybrid Capture 2 test (Qiagen) and HPRT (Upjohn Biomedical) are widely used in the diagnosis of cervical infections. Recent studies have suggested that the Hybrid Capture 2 test (Qiagen) may be more sensitive than the HPV-PCR test in the diagnosis of cervical intraepithelial neoplasia (CIN).

**MATERIALS AND METHODS**: A cross-sectional study was conducted in Kinshasa, Democratic Republic of Congo (DRC), and Bukavu, South Kivu, DRC. Women aged 35 to 65 years, attending the colposcopy unit at the Kinshasa University Hospital, were consecutively enrolled between October 2010 and September 2011. A total of 233 women were included in the study. The overall detection rate of CIN 2 and 3 was 10.3% in Kinshasa and 10.0% in Bukavu. The sensitivity and specificity of the HC2 test were 92.5% and 35.4% in Kinshasa and 93.0% and 37.7% in Bukavu, respectively. The sensitivity and specificity of the hrHPV assay were 93.0% and 34.5% in Kinshasa and 93.4% and 34.6% in Bukavu, respectively. The positive predictive value (PPV) of the HC2 test was 45.9% in Kinshasa and 46.7% in Bukavu, while the PPV of the hrHPV assay was 44.8% in Kinshasa and 47.2% in Bukavu, respectively.

**CONCLUSION**: The performance of the HC2 and hrHPV assays was similar in both settings. However, the specificity of the HC2 test was slightly higher than that of the hrHPV assay.

**CERVICAL CANCER SCREENING METHODOLOGY: A COMPARATIVE STUDY IN EAST OR CONGO**

**INTRODUCTION**: The Hybrid Capture 2 test (Qiagen) and HPRT (Upjohn Biomedical) are widely used in the diagnosis of cervical infections. Recent studies have suggested that the Hybrid Capture 2 test (Qiagen) may be more sensitive than the HPV-PCR test in the diagnosis of cervical intraepithelial neoplasia (CIN).

**MATERIALS AND METHODS**: A cross-sectional study was conducted in Kinshasa, Democratic Republic of Congo (DRC), and Bukavu, South Kivu, DRC. Women aged 35 to 65 years, attending the colposcopy unit at the Kinshasa University Hospital, were consecutively enrolled between October 2010 and September 2011. A total of 233 women were included in the study. The overall detection rate of CIN 2 and 3 was 10.3% in Kinshasa and 10.0% in Bukavu. The sensitivity and specificity of the HC2 test were 92.5% and 35.4% in Kinshasa and 93.0% and 37.7% in Bukavu, respectively. The sensitivity and specificity of the hrHPV assay were 93.0% and 34.5% in Kinshasa and 93.4% and 34.6% in Bukavu, respectively. The positive predictive value (PPV) of the HC2 test was 45.9% in Kinshasa and 46.7% in Bukavu, while the PPV of the hrHPV assay was 44.8% in Kinshasa and 47.2% in Bukavu, respectively.

**CONCLUSION**: The performance of the HC2 and hrHPV assays was similar in both settings. However, the specificity of the HC2 test was slightly higher than that of the hrHPV assay.
of several molecular parameters in the morphological context of cervical smears. Presence of chromosomal changes in some cervical lesions. Studies are in progress to assess correlations between HPV-FISH assay results and clinical diagnosis.


high grade dysplasia. These regions comprised TERC gene located at 3q26 and MYC gene located at 8q24. Vysis commercially available probes to candidate genomic regions were biotinylated and hybridized to the cytological specimens simultaneously with the chromosomal probes.

Material and Methods: The frequency of loss and gain of genetic material was compared between 10 to 80% of all chromosomally abnormal cells present on a cytological slide were infected with HPV.

HR-HPV (+), 3 or 6 months Recurrence No Recurrence Total
positive 12 23 negative 13 30 positive 3 recurrence 9 no recurr 23 no recurr 3 recurrence 10 no recurr 30 no recurr

Figure 1
Figure 2
35 women had HR-HPV 43 women had HR-HPV

Figure 1

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HPV INFECTION AND CERVICAL CANCER PREVENTION

CHROMOSOMAL ALTERATIONS IN HPV INFECTED CERVICAL SPECIMENS


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Background. Certain types of human papillomavirus (HPV) are associated with cervical intraepithelial neoplasia (CIN) and squamous cell cancers (SCC). To determine whether the presence of DNA and/or RNA HPV could be related to the type of human papillomavirus associated with the tumor.

Methods. Twenty Patients with invasive cervical cancer were prospectively registered from 2002 to 2004. HPV typing was performed on DNA extracted from formalin-fixed tissue specimens. HPV genotype was determined in 35 different genomic regions by real time PCR analysis using the new MX4000 system according to published criteria. PCR products were electrophoresed on different agarose gels, and bands were visualized with ethidium bromide. A positive control and negative control were also run on each gel.

Results: Hybrid Capture II was 10 times less sensitive than developed kits for types 16, 58, 60, 66; sensitivities for types 31, 56, 59, 62-64 and TERC gene were similar. Conclusions: The developed RealTime PCR kits for the detection and genotyping of high risk HPV are more sensitive than Hybrid Capture II. HPV-FISH/HPV-FISH and -real time PCR results were consistent in 96.7% of the specimens. Conclusion, HPV-FISH typing was performed in nucleic acid of SCC tumor cells in 126/208 cases of SCC and 6/80 cases of any HPV DNA reaction. Of 12 HPV DNA positive sections three cases reacted with HPV16/18, three cases showed strong hybridization for both HPV16/18 and 33/35/39/53/58/59. One case reacted with 16/18/33/35/39/53/58, four cases showed 61/31 and 68/31 and 2 cases reacted only with 61/31 genotype. A larger prospective study is needed regarding its potential in cervical tumor diagnostics. Keywords: Human papillomavirus, HPV, TERC gene.
EUROGIN 2004 International Expert Meeting

**PADS: A NOVEL SELF-COLLECTION METHOD FOR THE DETECTION OF HUMAN PAPILLOMAVIRUS INFECTION OF FEMALE GENITALIA**

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Self-collection of samples for human papillomavirus (HPV) testing is a feasible alternative method in women who decline to participate in population based cervical cancer prevention programs. The aim of this study was to determine the sensitivity and specificity of a novel self-collecting method for HPV detection in high-risk squamous intraepithelial lesions (HSIL) using the past and to compare results obtained from samples collected by women themselves with those obtained by health care providers. Ninety-six patients were voluntarily participated in the sensitivity and specificity study: at the university hospital, and 92 patients were participated in the self-collection study at the local clinics. During the three months, HPV was extracted and amplified using HPV16, 18, and 31 consensus primers. The detection failures for the past sample. For the detection of failures, collected self-past samples showed good sensitivity (98.6%) and also good specificity (98.6%). These results fourteen samples from two patients and concurrent physician samples showed the agreement at 97.8% with good kappa value at 0.70 (p<0.000). Seven cases exhibited the presence of agreement between the past and concurrent physician samples. Nine cases of disagreement were the detection failure in physician’s samples.”

**APPLICATION OF NANOTECHNOLOGY (HPV NANO-ARRAY) FOR DETECTING AND SUBTYPING OF HPV INFECTION: EVALUATION WITH THE NAKED EYE.**


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Study design: We developed an HPV-array detecting HPV high-risk types HPV 16, 31, 33, 35, 39, 45, 52, 58, and 68 that can be evaluated with the naked eye. Hybridisation of the HPV DNA was visualised using a specific nanocentromeres combined with nanoparticles of 60 nm size.

Materials and methods: DNA digoxigenin-labeled probes directed against a variable segment of the L1 gene of the HPV high-risk types, 16, 31, 33, 35, 39, 45, 52, 58, and 68 were used to conduct in a array. A synthetic DNA digoxigenin-labeled derived from the HPV L1 gene was used to determine the sensitivity of the array. DNA of relevant HPV-plasmids was used to test the stability of the HPV array, followed by low-content cervical cytoplasmas (Papanicolaou) specimens of 35 patients (5 L1, 5 H1, and 5 cervical carcinomas). HPV positivity was determined by PC with consensus primers HPV16/18 Ikkyou sequencing.

Results: Amplified HPV DNA from HPV 16 positive cell lines (Cagai and HeLa) and HPV negative cell lines and clinical cytoplasm samples were hybridized to the whole captured HPV microarray. Visualisation was achieved successfully a specific nanocentromere molecule combined with nanoparticles of 60 nm size.

Conclusion: Positive hybridisation signals with synthetic digoxigenin-labeled HPV DNA, HPV plasmas DNA, HPV 16 positive cell lines and clinical cell samples were seen as deep blue spots with a diameter of 0.5-mm easily visible with the naked eye. Those HPV array detected the synthetic DNA digoxigeninised in a concentration up to at least 0.3 attomole/ml. The HPV array was able to detect every HPV DNA plasmids. HPV 16 positive cell line and HPV clinical cell samples with cross-reactions. No background staining was observed. HPV DNA was found both by sequencing and subtyping with HPV Nanoarray. All cases of L1, L1a, and cervical carcinomas were positive for HPV DNA. No discrepancies were noted between subtyping with the HPV Nanoarray and conventional sequencing. Furthermore, HPV Nanoarray using DNA microarray probe in combination with specific nanocentromere enabled us to detect, subtyping and visualising HPV using only the naked eye. Using this technology results not only in a very useful imaging technique detecting HPV DNA in the stromal range but also permits to subtypes in highly specific way HPV DNA.

**HUMAN PAPILLOMAVIRUS TYPE 16 VARIANTS AND RISK FOR CERVICAL CANCER IN THE ITALIAN POPULATION**

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Human papillomavirus (HPV) has a number of variants (E, AA, AS, AF1, AF2), each with different geographic distribution, biological and biochemical properties, and some are associated more often with invasive carcinoma. This study was designed to type HPV16 variants detected in cervical biopsies from patients with diagnosis of invasive cervical carcinoma (ICC) and of cervical intraepithelial neoplasia (CIN) and CIN-2. In 30 women with cervical epithelial and HPV types were detected by PCR and sequencing. In 30 HPVs DNA were sequenced by PCR and sequencing. Among 123 HPVs positive samples four different variants, HPV16/18, 30, 39, and 45, were identified. Overall, women infected by non-European variants (AA and AF1) showed a higher risk to develop ICC. (OR = 69) than European (E, AS, AF2, AF3, AF4, AF5) and AF2 variants (OR = 132) relative to the risk of HPV16 positive women. Furthermore among the HPVs positive samples, those positive for non-European variants showed a lower risk. (OR of 13 for ICC in comparison with those positive for the HPV-16 European prototype). Finally, the detection of HPV16 AA, non-promptive lesions and normal control tissues, in 32 patients of the Int. suggests that non-European variants are more immunogenic than European variants, with relevant implications for the need of HPV16 variant identification and optimization of diagnostic/therapeutic protocols, including development of specific vaccines.