



## HPV infections and cervical cancer prevention. Priorities and new directions. Highlights of EUROGIN 2004 International Expert Meeting, Nice, France, October 21–23, 2004

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### Introduction

Cervical cancer is caused by infections with a range of high-risk (oncogenic) Human papillomavirus (HPV) types. It seems likely that practically all (>99%) cervical squamous cell carcinomas are linked with these HPV infections. Cervical cancer has an unequal geographic distribution, with the highest global disease burden confined to the developing countries, where the facilities to combat the disease are clearly insufficient. On the other hand, the declining trends in incidence and mortality rates witnessed in many of the developed countries during the past four decades are mainly attributable to the implementation of organized screening programs based on the use of cervical Pap smear, for example, the Nordic Countries, where an organized screening has resulted in up to 80% reduction in cervical cancer incidence since the early 1960s.

Unfortunately, these highly effective organized screening programs exist in few countries only, and the prospects for effective cervical cancer screening based on the Pap test in the majority of these developing countries seem gloomy, if not entirely pessimistic, even in the foreseeable future. This fact has been well appreciated among the scientific community, emphasizing the necessity to find other solutions to cope with this urgent and growing problem. Recognition of this unsatisfactory state of affairs by a group of European experts was the stimulus to the foundation of a new international organization called European Research

Organisation on Genital Infection and Neoplasia (EUROGIN), in the early 1990s in Paris, France.

Since its very beginning, the core mission of EUROGIN has been to gather together the opinion leaders and experts in the field, to discuss the state-of-art research data and share this information with the different liaison groups, including medical professionals, health policy decision makers as well as different societies and groups representing women as patients [1]. This strategy has proven highly successful, as evidenced by the five successive international EUROGIN Congresses organized at 3-year intervals in Paris since 1991. The most recent one was held in 2003, and the consensus statements of that congress were published just recently [2]. Interim between these major tri-annual congresses (with around 1000 participants), EUROGIN started a new initiative in 1996, by organizing the first expert meeting in Geneva, followed by one in Paris (1999), and EUROGIN Leaders Meeting in Nice 2001. The topic of the present Congress Summary Report is the fourth one in this series of expert meetings, entitled EUROGIN 2004 International Expert Meeting, held in Nice, October 21–23, 2004. The meeting was attended by 350 participants and had a distinguished international faculty.

The title of the present meeting: HPV Infection and Cervical Cancer Prevention—Priorities and New Directions, continues to be in alignment with the mission of EUROGIN. The sub-title selected for the present meeting: “Physicians, Patients and Public Health Issues”, reflects the continuous endeavors of EUROGIN to carefully follow-up and respond to the changing challenges in the main field of its mission: cervical cancer and its prevention. The

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necessity of having this meeting arranged once again was enlightened by the Secretary General of EUROGIN, Dr. J Monsonego, in his welcome address, while stating that “As scientists and clinicians working in this field, we feel ourselves privileged, while having witnessed, during the past 20 years, an incredible breakthrough in our understanding of this major human disease. It is very rare that such a major progress has been made in such a short time as elapsed since the early 1980s, when the concepts on cervical cancer and its causes were basically formulated. Despite this tremendous progress, however, this disease has not been eradicated. On the global scale, cervical cancer continues to be the leading cause of cancer mortality among women, and a cause of significant annual morbidity, despite substantial preventive measures and all other efforts taken by national health authorities and international organizations, like WHO and EUROGIN. This unsatisfactory state of affairs is the best single reason to continue these EUROGIN Expert Meetings”.

#### **Format and aims of the meeting**

The format of this meeting followed the pattern adopted in the previous EUROGIN meetings. The theme of this year, “Physicians, Patients and Public Health Issues”, should best describe the core substance of the meeting. With this theme, EUROGIN wants to focus on topics that are common to these three strategic partners: (a) patients as carriers of cervical cancer and its precursors; (b) physicians as health care professionals attempting to diagnose the disease and treat the patients; and (c) public health authorities, dealing with the widespread issues related to implementation of cervical cancer control. It is the conviction of EUROGIN that optimal health care can be provided only by the intimate cooperation of this strategic partnership to the maximum benefit of the patients.

In this meeting, the EUROGIN Program was offered in three different formats: (1) Plenary Sessions, (2) Highlights of Current Research, and (3) Free Communications. In addition, several Workshops were arranged (by different companies) in parallel with the meeting sessions. The four Plenary Sessions included the following topics: Cervical Cancer Control; Strategic Partnerships; Quality of Service; and Public Health Issues. Sessions named as Highlights of Current Research covered carefully selected topics describing the latest progress in cervical cancer research. In Free communications-sessions, participants presented their professed papers, arranged in three thematic sessions: Cytopathology—Management; Screening—Epidemiology; and HPV testing—Molecular biology.

Being an integral part of EUROGIN mission, the purpose of this expert meeting was to develop comprehensive approaches to cervical cancer control, to highlight the recent advances made, and to exchange information at a specialist level with regard to early detection, new diagnostic, and

therapeutic procedures (including HPV vaccination), recommendations for clinical practice, new directions for research, and enlarging the discussion beyond the medical and scientific aspects.

The highlights of the EUROGIN 2004 are synthesized in this Congress Summary Report, where selected topics are reviewed by identifying the presentations given during the Plenary Sessions and Highlights of Current Research-sessions, as well as in special Workshops. Free communications are intentionally excluded from this report because of the fact that much of this abundant original research will be published on time elsewhere.

#### **Cervical cancer prevention, science, and its translation**

The opening lecture of the meeting was given by Prof. Peter Boyle, who discussed the issues related to cervical cancer prevention, existing science and its translation to clinical practice [3]. In his comprehensive overview, the IARC Director started by giving the latest global cancer incidence data from the IARC data base updated for 2002, which is not generally available as yet [4]. Interesting were the estimations for the future, how these figures might look like in 2050, if nothing more can be done to prevent cervical cancer. According to these estimates, there will be 1,090,000 new cases in the year 2050, and as compared with the present figures of 470,000 this would mean more than doubling of the annual cases during the next 50 years. Like today, the vast majority (1 million) of these cases will be detected in the developing countries.

He then proceeded in presenting the figures on the proportion of global cancer burden ascribable to infectious diseases, ending up with 18% worldwide, being 25% in the developing countries and 8% in the developed countries. HPV alone seems to be responsible for almost 11% of all female cancers worldwide. There is a substantial variation in these figures between the different geographic regions, however. The list of cancers attributed to HPV is increasing in parallel with the improved understanding of the pathogenesis of these lesions, and the estimated total of all HPV-associated cancers currently exceeds 1 million annual cases.

While summarizing the results achieved in cervical cancer prevention, the Nordic Countries were once again used as an example of a major success story. Similar success is now anticipated also in the UK, with their reconstructed screening program having an ambitious goal to reduce mortality by 20% from 1986 until 2000. This is in strict contrast to the situation in the developing countries, where little, if anything, has been achieved in cervical cancer prevention, as demonstrated by the figures from different geographic regions illustrated by Dr. Boyle. Major expectations are currently posed on the prophylactic HPV vaccination trials ongoing in different parts of the world, as updated in the presentation. The obtained results

are very encouraging and clearly implicate that HPV preventive vaccines have high efficacy with respect to the prevention of persistent HPV infections, at least in the short term. It remains to be seen, however, whether or not this protection will carry over to prevent cervical cancer and its precursors.

Concerning the translation of science, Dr. Boyle stated that “The outstanding detective work in establishing the key role of HPV in cervix cancer development, followed by excellent scientific development finds us on the threshold of having the tools to prevent cervix cancer”. According to the take home message of the keynote speaker, (1) if nothing further is done to prevent cervical cancer, there will be one million women developing the disease annually by 2050; (2) the poorest parts of the world will be the worst affected; and (3) the translation of scientific knowledge into effective control measures is an absolute imperative. This comprehensive overview and the ominous predictions created an excellent starting point for the rest of the meeting, while giving directions where to go in translating the research data to clinical practice in cervical cancer prevention.

### Innovations in cervical cancer control

This first Plenary Session was devoted to different aspects of cervical cancer control, with special emphasis on recent new innovations. There is no doubt that persistent infections by the oncogenic HPV types the necessary cause for the development of cervical cancer. In addition to HPV, other important cofactors are needed, including the long-term use of oral contraceptives, high parity, smoking, and history of infections with HSV2 and *Chlamydia trachomatis* [5]. The recent IARC studies have provided evidence that the risk for any given high-risk type is not statistically different from the risk reported for HPV 16. Thus, the strategy for cervical cancer prevention has rapidly evolved towards (a) the incorporation of HPV tests as a screening tool and (b) the testing of novel HPV vaccines. Testing of clinical specimens for a cocktail of high-risk types should be sufficient for screening and patient management, and because of the almost 100% NPV, a negative HPV result and negative cytology might allow longer screening intervals with substantial cost savings, but without compromising the safety. Indeed, this concept is being currently under rigorous testing in the national screening program of the Netherlands, as detailed by Dr. Meijer [6].

Apart from HPV testing, another recent innovation is automation in cytology. Currently, several automatic systems are available, mostly combined with liquid-based cytology (LBC). One of these systems, the ThinPrep™ Pap Test (Cytoc Corporation, US), represents the standard of care for cervical cytology screening in the United States [7]. Reported experience of the ThinPrep Imaging System in routine clinical use confirms improved detection of LSIL (25–68%) and HSIL (33–43%) without increasing the rate

of ASC-US. As discussed by Dr. Linder, combining computer location of potentially abnormal cells with expert human classification, imaging-directed cytology is improving sensitivity without compromising specificity, as evidenced by ROC curve. These features emphasize the advantages of cytology over other potential screening methods. Indeed, incorporation of LBC cytology within the national screening program of the UK is currently under careful consideration, as told by the leader of the program, Dr. J. Patnick in her presentation [8].

Among the screening tools, there is no such system that could not be improved by novel technical innovations and further refinements. This applies equally well to the ongoing screening programs [8], as well as the different diagnostic tools, including HPV testing. Of the current HPV detection methods, the second generation Hybrid Capture (HCII) technology is the most widely used, based on RNA probes that hybridize to target DNA. There is, however, a growing desire for ultra-sensitive clinical tests that have multiplex capability to detect many possible pathogens in one sample. The new generation HC (NG-HC) test is currently in pipeline, designed to meet these evolving needs, as described by Dr. Lörincz [9]. Importantly, 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 other than HPV as well. To avoid the unacceptable level of clinical false-positives, the test cut-off will be adjusted for the detection of HPV and other targets at their optimal clinical thresholds.

Apart from these new molecular tools currently under development, there are new innovative imaging tools emerging for direct visualization of cervical lesions. One of these newcomers is spectrophotometric imaging, which is based on the different spectra of the autofluorescent substances in the cervix [10]. According to Dr. Harper, the recent data show that the absolute fluorescence spectra are most different at these fluorophores' emission wavelengths, which property could be utilized in the detection of different cervical pathology. Several groups are currently working with different molecular biomarkers, aimed at improving the diagnosis and predicting the disease outcome. Work along these lines is ongoing in NIH/NCI, where a multiplex immune biomarker assay is being tested to “immune profile” cervical secretions and plasma [11].

As repeatedly pointed out during this meeting, setting up of adequate facilities for clinical cytology does not seem a feasible option in most of the developing countries even in the foreseeable future. In these countries, efforts should be focused on other optional methods, by taking into account three critical factors: (1) offering an effective and acceptable test, (2) ensuring appropriate treatment of test-positive women, and (3) achieving high screening coverage, as emphasized by Dr. Sankaranarayanan [12] in his stimulating talk. Such optional methods currently under rigorous testing in several of these countries include visual inspection with acetic acid (VIA) or Lugol's iodine (VILI), as well as HPV

testing. Programmatic requirements related to participation, treatment and follow-up care are vital for the success of any screening option.

Undoubtedly, one feasible solution to prevent cervical cancer in the future seems to be offered by prophylactic vaccination against HPV, as re-iterated by the speakers in several sessions. This topic was first addressed by Dr. J. Schiller, who gave an update of the ongoing clinical trials. As generally known, phase III efficacy trials of HPV L1 VLP-based vaccines sponsored by Merck, GlaxoSmithKline (GSK) and the National Cancer Institute are in progress. Interim analyses, evaluating protection from persistent type-specific HPV infection, will likely become available within the next two years. Merck has announced that they expect to file a provisional license application by the end of 2005 and, importantly, launch commercial sales of their tetravalent vaccine in 2006. At the same time, however, several issues need to be seriously discussed [13]. Accordingly, a negative impact on compliance with Pap screening programs seems likely, if the vaccine is widely accepted, and public education initiatives should be undertaken to minimize this effect. Recommendations regarding vaccination of women with prevalent high-risk genital HPV infections need to be established. The access to the vaccine in the developing world will likely be restricted by both cost and manufacturing capacity, and efforts to overcome these impediments are needed.

This important session was concluded by a discussion about the current management protocols, given by Dr. Cox. Recently, such management guidelines have been published by several professional societies, for example, American Society of Colposcopy and Cervical Pathology (ASCCP). His discussion was focused on the evidence that substantiated the recommendations incorporating HPV testing into the 2002 release of the ASCCP Guidelines on the management of women with abnormal cervical cytology, on extensive data that have accumulated on this subject since the publication of these guidelines, and on their subsequent impact on clinical and laboratory practice in the US [14].

### **Role of institutions as decision makers: strategic partnerships**

As pinpointed in his welcome address by Dr. Monsonogo, this plenary session entitled Strategic Partnerships, represents a novel approach in these EUROGIN meetings, aiming to bring together the representatives of different institutions, health authorities, scientific societies and patient groups and organizations. In advance, a lot of expectations were put on the discussions given during this session. There were 18 speakers in this session, precluding the possibility to quote all these presentations here. An attempt is made to convey the key message of one representative from each category of this strategic partnership.

The positions of health technology assessment agencies in cervical cancer screening were first discussed by Dr. E. Franco [15]. Among the most influential of such agencies are the Cochrane Collaboration, WHO, IARC, the UK National Coordinating Center for Health Technology Assessment, the National Cancer Institute's Physicians' Data Query Program, the US Preventive Services Task Force, the US Centers for Disease Control and Prevention, the Canadian Task Force on the Preventive Health Care, the Canadian Coordinating Office for Health Technology Assessment, the European Advisory Committee on Cancer Prevention, the European Network of Cervical Cancer Screening, American Cancer Society, the Agency for Health Care Policy and Research, Society of Gynecologic Oncologists, and American Social Health Association. The evidence-based recommendations and guidelines on cervical cancer screening by the above organizations were briefly discussed, predicting the directions that the field may take in consequence of these emerging new technologies and the prospect for a successful HPV vaccine.

This was followed by a series of speakers representing a variety of national and international institutions, including WHO/IARC, CDC, and NCI [16–18]. As a part of the Agency's scientific program, IARC is collaborating with national institutions and researchers in several African countries and with the African Regional Office of the World Health Organization (AFRO) to evaluate the accuracy of detection and the efficacy of alternative screening approaches such as VIA, VIAM, VILI and HPV testing [16]. These 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 socioeconomic and health services development. The Centers for Disease Control and Prevention (CDC) administers the only organized national screening program for cervical cancer prevention and early detection in the US, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) [17]. While the program operates in a clinical environment of opportunistic screening and does not invite women for screening, it has all the other elements of a quality cancer-screening program, including the measurement of a variety of performance indicators. The American Cancer Society (ACS) reviewed and updated its guideline for cervical cancer screening in 2002, as discussed by Dr. P. Castle. New recommendations were developed to address when screening may be discontinued, screening women who have had a hysterectomy, and the use of new screening technologies, including LBC and HPV DNA testing.

Next, several scientific societies provided their views and positions concerning cervical cancer prevention, including the following: ASC, ASCCP, EFC, IGCS, and UICC [19–23]. With few exceptions, these presentations contained important information about the recommendations and guidelines designed by many of these societies, like ASC and ASCCP, already mentioned before [19,20]. European

Federation of Colposcopy (EFC) has the main aim to bring together all European countries in order to promote the best possible standards of training in colposcopy [21]. The key objectives of the EFC include: (1) to identify and produce minimum standards of training in colposcopy, (2) to audit the methods of treatment of CIN throughout Europe, (3) to audit the results of treatment of CIN, and 4) to support the International Federation for Colposcopy and Cervical Pathology (IFCPC) in its efforts to promote colposcopy worldwide.

Another important player in this field is the International Gynecologic Cancer Society (IGCS), presented here by the president, Dr. E Trimble [22]. We heard that the IGCS is an independent organization contributing to the prevention, treatment, and study of gynecologic cancer and the quality of life of women suffering from gynecologic cancer throughout the world. 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 70 countries. To effectively conduct these activities, IGCS seeks collaboration with other organizations of medical professionals, national and international, active in the field of gynecologic cancer, non-governmental organizations, and governmental organizations.

As the last in this series, UICC described their pilot project run to prevent cervical cancer in Central America, as detailed by Dr. Sancho-Garnier. This multi-center cytology-based cervical cancer screening pilot project is conducted in four Latin American countries: Dominican Republic, El Salvador, Guatemala, and Honduras. The main aim is to examine the feasibility of establishing cervical cancer screening programs in low-resource settings with the objective of reducing morbidity and mortality due to cervical cancer.

Before the stimulating presentations of the representatives of different patient groups, two health technology assessment organizations presented their activities [23,24]. These two bodies were Agence Nationale d'Accreditation et d'Evaluation en Sante (ANAES) and Institut National de Sante Publique du Quebec (INSPQ). These comprehensive presentations gave detailed descriptions about the protocols followed by these two organizations while assessing the novel health technologies. Unfortunately, the limited space does not permit the discussion of these interesting data in any detail.

This long session was concluded by three presentations from representatives of medical and patient groups. The Alliance for Cervical Cancer Prevention (ACCP) is a group of five international organizations: Engender Health, IARC, JHPIEGO, PAHO, and PATH, with a shared goal of working to prevent cervical cancer in developing countries [25]. The ACCP has supported randomized controlled trials in India and South Africa) and several other research and demonstration projects in developing countries, including in El Salvador, Ghana, Kenya, Malawi, Peru, and Thailand. European Institute of Women's Health (EIWH) gave their

contribution to this discussion, by highlighting the importance of healthy life-styles [26]. Dr. Maguire concluded by citing the recently published Reflection Paper for a new EU Health Strategy by Commissioner Byrne: "Good health is a shared responsibility, requiring widest cooperation between different groups."

Women in Government is a non-profit educational association for elected women in all US state governments [27]. The organization promotes informed policymaking and the leadership role of women by providing issue education and opportunities for idea and information exchange. This newly established organization strongly believes that American women state legislators have a tremendous opportunity to eliminate cervical cancer through legislation and programs that bring awareness and access for underserved women to screening techniques and new technologies.

### Improving access to quality service

This session was devoted to discussions how to improve the access to high-quality services, with special emphasis on the role of physician as the trainer. The session was started by Dr. P. Walker, who described the system of accreditation and certification in colposcopy, maintained by the British Society for Colposcopy and Cervical Pathology (BSCCP) [28]. In brief, the trainees register with the society and obtain a named trainer. The trainer must be a BSCCP member and provide the training within a unit which aspires to the standards and quality in colposcopy documents published by the NHSCSP. The candidate must attend a 2-day basic training course, the curriculum for which is supervised by the BSCCP certification and training committee. Each trainee must see 50 directly supervised cases, at least 20 of whom should be new presentations with abnormal cytology and 20 of whom should have been referred with high grade smear abnormalities. On completion of training, a logbook and the case summaries and a certificate from the trainer are sent to BSCCP and successful candidates are registered for 3 years [28,29]. For all practicing colposcopists, re-accreditation is required in each three yearly cycle 2000, 2003, and 2006.

The importance of information, communication and documentation of HPV testing was emphasized by Dr. A. Lörincz. It is important to make distinction between analytical and clinical performance, which are often confused. 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. Routine cervical cancer screening requires a careful balancing of HPV test sensitivity and specificity correlated to disease and not mere detection of virus. Medical providers, women's health organizations, and industry should bear the educational burden and communicate with women on facts and

recommendations. Dr Lörincz concluded that actions are necessary to find ways of making improved diagnostic tools accessible to more women, regardless of their economic situation or country of residence [30].

Any screening intervention has evidence for and against its use, as pointed out by Dr. Harper. Having multiple screening policies is confusing for practitioners and consumers. Therefore, the development of current decision aids used together by practitioners and consumers [“shared decision making”] allows practitioners to use the decision aid as a reference for appropriate evidence-based guidelines. The speaker was convinced that shared decision-making becomes an important personal tool that, when multiplied for every citizen, impacts the health of their nation [31].

For many medical services, apprenticeship has been a time-honored mode of education. The results, however, are inconsistent and the ability to evaluate the effectiveness of this training method is often absent [32]. One of the major barriers to clinical providers is the inconsistency of effectively delivering quality education about new advances and the ability to objectively measure the effectiveness of the learning process. What seems to be necessary is more integration of didactic classroom and interactive training leading to certification or accreditation, as conducted by ASCCP, the American College of Obstetricians and Gynecologists (ACOG) and other professional organizations.

### **Public health issues of cervical cancer control**

The last of the Plenary Sessions was devoted to the issues of public health in control of cervical cancer. Altogether, eight speakers covered a wide range of topics related to (a) economics, (b) evaluation of campaigns, and (c) screening in low-resource settings.

Because of the ethical and logistical difficulty in 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. The issues related to such models were discussed by Dr. E. Myers, concluding that the potential impact of HPV vaccines on the cost-effectiveness of prevention will depend on whether screening programs are altered to reflect the impact of the vaccine on underlying disease epidemiology [33]. The same theme was continued by Dr. Berkhof, giving cost estimates for different screening scenarios in the Netherlands. In comparison with cytological screening (scenario A), high-risk HPV testing as an adjunct screening tool (scenario D) leads to a 10% to 30% reduction in the incidence of cervical cancer, and shows a substantial cost reduction for women with an abnormal baseline smear. These data suggest that adjunct HPV testing for high-risk types is a cost-effective alternative for current screening practices in the Netherlands [34]. On the other hand, based on extensive review of the literature, it was concluded that more comprehensive studies are still

needed for estimating the national economic burden resulting from the prevention and treatment of cervical cancer in the US [35].

The issues related to cervical cancer screening and informed decision making were discussed by Dr. Lawson and Dr. Harper. While the expectation and reality for most women is that the cervical cancer screening test will be negative, there is the potential for considerable resistance to participating in the screening because of (1) the physical and psychological discomforts associated with it, (2) the fear of having an abnormal result, or (3) the need for additional testing or treatment. Thus, creation of cultural- and community-sensitive materials that provide realistic and reasonable information about the need for screening and expected outcomes associated with abnormal results should continue to maximize the delivery of appropriate care to the maximum number of women [32,36].

The possibilities of implementing cervical cancer screening in low-resource settings were addressed once again because the subject is of such a major importance in the global control of this disease. Starting from India with 126,000 new cases and annual 71,000 deaths due to cervical cancer, Dr. Shastri showed some of the key statistics and discussed the most urgent problems encountered in this overwhelming task of coping with this disease. Most cases present in stages IIB and III, with overall 5-year survival rates ranging from 25% to 40%. There are no organized cytology screening programs anywhere in the country. On the other hand, several studies addressing the accuracy of cytology and alternative tests such as VIA, VILI, and HPV testing have been completed [37].

Highly pertinent to this Indian reality were the news from Digene (US) given by Dr. Lörincz, who told that the company has entered into a partnership with PATH to design and develop a simple, relatively rapid, and affordable batch-based diagnostic HPV DNA test (the dHPV test) for use in low-resource settings [38]. Based on the existing HCII technology, the new test will be completely reconfigured into a faster, thermo-stable, and robust assay with new portable equipment capable of running from local power mains or portable batteries. The reduced time of the dHPV test can allow women to be screened, informed of results, and treated if necessary in one visit. Wide 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.

Last but not least, the participants had a rare occasion to obtain accurate data from China, which are not easily available [39]. In China, the incidence of cervical cancer varies significantly from one area to the other; ranging from 9/100,000, up to 139/100,000. In the 1960s and 1970s, a few large screening programs were realized, covering sizable populations. In some target areas, cervical cancer incidence had dropped by 69%, from 10.28/100,000 in the 1970s down to 3.25/100,000 in the 1990s. Along with the introduction of new technology, the China Cancer Research

Foundation has organized and founded a “Cervical Cancer Prevention and Treatment Cooperation Group”, which had established a guideline for cervical cancer screening and treatment. Chinese Cervical Lesions and Colposcopy Group (CCLCG) relies on the three-tier diagnosis (cytology–colposcopy–histology). It is anticipated that more of these important data from these approaches will be available in the near future.

### Potentials of HPV vaccines

Apart from being discussed by several speakers in different sessions, there was a special Workshop organized by GSK dealing with the potentials of vaccines in the global control of cervical cancer. In her thoughtful presentation, Dr. Duchateau discussed perceptions and misconceptions on cervical cancer. Awareness and understanding of cervix and cervical cancer are very low everywhere. Information on cervical cancer is usually regarded as shocking. Despite widespread availability of information channels, discussion of sexual matters between mothers and daughters is awkward everywhere [40]. Thus, in-depth, extensive, and tailored education programs are necessary. There is a strong need to recognize cultural differences. When providing access to an HPV vaccine, managing expectations will be key. She concluded that the partnership is needed between medical community, policymakers and HPV vaccine manufacturers. While discussing the current barriers to reducing cervical cancer incidence, Dr. Franceschi stated that simple types of community-based intervention have the greatest chance of succeeding. Childhood immunization against HPV would be ultimately the strategy of choice to prevent cervical cancer in underdeveloped countries. Even vaccines with limited duration of efficacy would be useful if they substantially delay age at HPV infection. However, more studies are necessary on whether high-risk HPV types other than HPV 16 and HPV 18 should be added to future vaccines in order to meet the needs of specific populations, particularly in sub-Saharan Africa [41].

Dr. Wardle discussed the psychological and quality of life issues related to HPV screening. As an STD, HPV imposes an additional psychosocial burden on women testing positive. This includes many concerns about viral transmission and disclosure as well as stigmatization. Certainly, the effects of the 1-year wait for the second test may not be negligible, although most of the women put it to the back of their mind. A second HPV-positive result could potentially be more worrying than the first [42]. There is a concern about cancer, and certainly a strong desire for immediate further investigations. They did not disclose any evidence of extreme psychological reactions in their study, however. Similarly, women testing negative at follow-up were regularly pleased and relieved. Integration of HPV vaccination programs and cervical cancer screening programs was discussed by Dr. Kitchener. It

seems clear that introduction of HPV vaccination will require ongoing cervical screening program. Similarly, regimens of screening for vaccinated women are clearly mandatory. Such a screening could be based on HPV testing and cervical cytology. There are good reasons to believe that screening would become progressively less intensive, which could increase the affordability of the vaccines [43].

The presentations were followed by a lively and highly informative panel discussion, also actively contributed by the audience. The panel had two main themes to be addressed: (1) can HPV trigger a new paradigm in the global fight against cervical cancer? (2) How HPV vaccination could help reinforcing/triggering screening programs? During the intense discussion, several useful insights were provided, advocating the continuation of the clinical trials toward the development of effective prophylactic vaccine against HPV, with the global control of cervical cancer as the final goal.

### Highlights of current research

In addition to the four Plenary Sessions, original research was presented in special sessions entitled: Highlights of Current Research. There were four of these sessions, arranged according to different thematic areas: (a) screening, (b) diagnosis and management, (c) immunity and vaccines, and (d) cervical pathology-molecular testing. In these four sessions, a total of 34 oral presentations were delivered. The limited space does not allow discussion or even citing of all these interesting papers in this Summary Report, unfortunately.

#### Screening

The French group tested HPV detection combined with cytology in the primary screening. In their study, 16,107 French women with routine cervical examination were subjected to conventional (CC) and LBC, HPV testing with HCII, followed by colposcopic control of all abnormal cervical finding and/or persistent HR-HPV infections [44]. The sensitivity of HPV testing for detecting a histologically confirmed HGSIL was 100% (with CC) and 97.6% (with LBC), higher than that of CC (72.1%) and LBC (77.3%). The low specificity (85%) of HPV testing was slightly increased to 87.7%, if HPV testing was done in women >30 years of age. To determine, whether women with a normal smear and negative HPV test might represent a low risk population for developing a HSIL, 5314 women were followed-up from 12 to 72 months. If women had a second negative HR-HPV test during 1–2 years after the initial test, NPV was 100%. The authors concluded that a positive HR-HPV test selects women at high risk for developing HGSIL, whereas a negative HR-HPV test selects populations at low risk who could be safely screened at longer intervals [44].

### Diagnosis and management

This session contained a series of highly innovative new approaches in diagnosis and management of cervical disease, justifying two topics instead of one, to be mentioned here. Digene Brazil recently developed a new simple and inexpensive system to make LBC, called DNA-Citoliq System® (DCS). In this study, the authors evaluated the diagnostic performance of this new DCS system as compared with conventional smears [45]. Paired specimens of exfoliated cervical cells were collected from 1095 consecutive women analyzed under split-sample protocol. All patients were submitted to colposcopy, and biopsied whenever indicated ( $n = 425$ ), biopsy being used as the gold standard. Unsatisfactory samples were observed in 15 cases (1.4%) of DCS slides and in 114 (10.4%) cases prepared in conventional way. DCS showed an incremental of 69.2% when the cut-off was LSIL+ and 64.2% when the cut-off was HSIL+. For any abnormality found in histology, the sensitivity of DCS was 70.0% as compared to 49.8% for the conventional smears ( $P < 0.00001$ ). With the LSIL+ cut-off, the sensitivity increased in both methods (91.3% versus 72.8%), but DCS was still more sensitive ( $P < 0.0001$ ). As compared with conventional Pap, DCS reduced the number of unsatisfactory samples and improved significantly the sensitivity of cytology in detecting cervical cancer precursors (41). Moreover, using Universal Collection Medium (UCM) as the preservative solution, DCS is fully compatible with performing HCII assay for HPV.

An interesting study testing a novel instrument (optical coherence tomography) in diagnosis of cervical pathology was reported by a Russian group [46]. Optical coherence tomography (OCT) uses the wavelength of 1300 nm, and optical power between 1 and 3 mW. The spatial resolution is 15  $\mu\text{m}$  that enables visualization of tissue structures up to histological level (42). Furthermore, the instrument is fully portable and easy to control. Diagnostics effectiveness of OCT in recognizing cervical neoplasia was 81%, with kappa of 0.65. The authors reported several new modifications for OCT to improve its diagnostic value. These include topical application of propylene glycol to enhance the depth-imaging capability and optical contrast of OCT images, as well as application of the cross-polarization tomography as a variant of the polarization-sensitive OCT. Optical coherence microscopy (OCM) is a special application of OCT technology for enhanced resolution and contrast in highly scattering tissues, and the authors expect OCM to become a new tool for detection of early stage cervical lesions.

### Immunity and vaccines

Undoubtedly, HPV vaccination was among the most important topics of this meeting, discussed by several speakers in different sessions. One of the prerequisites for designing successful vaccination trials is the elucidation of the HPV type distribution among the potential target

populations. This necessitates large-scale, population-based studies like those run by IARC in different geographic regions.

To perform a pooled analysis of HPV type distribution, IARC has designed a multi-center study of HPV infection among the general female population in different global regions [47]. Each study region aimed to enroll a population-based and age-stratified random sample of at least 1000 women. HPV sampling, detection and assessment for 36 types by GP5+/6+ PCR-EIA was standard in all centers. Of 13,926 included women, 1193 (8.6%) tested HPV-positive. HPV prevalence was highest in Nigeria (24.8%) and lowest in Spain (1.3%). Of HPV-positive women, 44.5% were infected with one high-risk type, 25.8% with multiple infections including a HR type, and 26.2% with low-risk types only. HPV16 was the most common type in HPV-positive women (19.5%). However, HPV-positive women in Africa (Nigeria) were 3-fold less likely (OR = 0.37; 95% CI: 0.24–0.56) to be infected with HPV16 than those from Europe. The current data implicate that among cytologically normal women, the proportion of HPV infections attributable to HPV16 differ significantly by continent, being lowest in Africa and highest in Europe.

The ongoing phase III clinical trials with prophylactic HPV vaccines were summarized before [13]. One of these trials was discussed in more detail by Dr. Monsonego, who gave update information about the results obtained with the tetravalent (HPV 6,11,16,18) vaccine (Merck and Co) tested in France. In previous studies, this tetravalent L1 VLP vaccine in a 3-dose regimen was generally well tolerated and induced neutralizing anti-HPV responses. A randomized, placebo-controlled study with an HPV 16 L1 VLP vaccine was conducted in a series of 2392 women. The primary endpoint of the study was the incidence of persistent HPV 16 infections or CIN in women who were HPV 16-negative at baseline [48]. In the primary analysis, the incidence of this endpoint was 3.8 and 0.0 per 100 subject-years at risk in the placebo and HPV 16 vaccine groups, respectively. Phase III studies with a tetravalent HPV L1 VLP vaccine in >25,000 subjects are underway. There is no doubt that, if proven safe and effective, a vaccine that prevents infection with HPV 6, 11, 16, and 18 will have a major impact on public health. 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. In settings where screening is currently not available, use of vaccines alone may prove a reasonable alternative to instituting the infrastructure needed for screening programs.

Implications of HPV vaccination on screening were discussed in a study of E. Myers. Many important issues came out. Thus, in settings where screening is available, it is important to realize that an effective vaccine will reduce the prevalence of CIN and cervical cancer, and thus lower

positive predictive value and raise negative predictive value for any screening test, regardless of sensitivity and specificity [49]. This in turn means that the only cost-effective way to combine vaccines with screening will be to reassess which screening tests are used, and/or the length of screening interval. In addition, vaccines may allow delaying of screening until older ages, with some potential for cost savings. However, uncertainty about the length of effectiveness for the vaccine and the age at which to vaccinate may affect the overall cost-effectiveness.

#### *Cervical pathology-molecular testing*

In this session, a wide variety of topics were reported by the 15 scheduled speakers. The selection made here follows the preferences of the authors only, because discussion of all these interesting new data is not possible.

The group working in Porto Alegre (Brazil) described their baseline data from an ongoing EC-funded study (the LAMS; Latin American Screening), where eight different diagnostic tests are compared as optional screening tools in these low-resource settings in Latin America [50]. This multi-center trial has two main objectives: (1) to compare aided visual inspection (VIA, VILI), HPV testing (conventional and self-sampling), cytological (Pap conventional and LBC), cervicography and screening colposcopy in cervical cancer screening; and (2) to improve the basic understanding of the epidemiology and pathogenic mechanisms of the disease. During the first phase, a total of 12,107 women were enrolled, of whom 3042 in Porto Alegre, being the subjects of this report. Of the Pap tests performed, 2907 (95.8%) were normal, 32 (1.1%) had LSIL, 31 (1%) were HSIL, 62 (2%) showed ASCUS, 1 (0.1%) AGUS, and 3 (0.1%) were cervical carcinomas. HPV testing was performed for 1099 patients at their first visit, and 15.5% were HPV (high-risk) positive. Until now, 1038 colposcopies were performed and 282 biopsies were taken: 190 were normal and 92 abnormal [50]. As repeatedly emphasized during this meeting, this testing of optional diagnostic tools is mandatory in designing different cervical cancer screening strategies in these low-resource settings.

Among the topics of molecular testing, highly interesting new data were provided by authors from Austria, who analyzed the utility of HPV E7 as a biomarker in cervical cancer screening [51]. They wanted to assess, whether a high-risk HPV E7 antibody (ab-hr-HPV E7) might be a useful tool for the diagnostic of high-grade CIN and early invasive cancer. They developed an ab-hr-HPV E7 antibody that specifically recognizes E7 proteins from all known cervix carcinomas positive for high-risk HPV, but, importantly, does not cross-react with E7 from the low risk HPV species (e.g.: HPV 1, 6, 11). The authors demonstrated that ab-hr-HPV E7 allows a fast, reliable and highly specific detection of hr-E7, in malignant cervical tumors and in early stage CIN lesions. Thus, inclusion of this ab-hr-HPV E7 among the diagnostic tools in standard cervical cancer

screening might significantly improve early detection of cervical cancer and its precursor lesions [46]. This remains to be established in a large-scale study, however.

#### **Highlights among the free communications**

Following the general meeting format, also the free communications were arranged into three sessions according to three distinct topics: (1) Cytopathology—Management; (2) Screening—Epidemiology; (3) HPV Testing—Molecular Biology. Altogether, 35 proffered papers were presented as free communications, covering a wide range of interesting topics related to the main theme of the meeting. Selecting the highlights among these important papers is extremely difficult and would be completely subjective. Because of the fact that the vast majority of these reports are already in press and will be soon published elsewhere, further discussion of these data at this point was felt as redundant.

#### **Dialogue for actions against cervical cancer**

In his closing lecture, Dr. T. Cox made a brief summary and synthesis of the meeting highlights and pinpointed the directions where the focus of actions against cervical cancer should be in the future. In this thoughtful talk, he briefly summarized the milestones in actions against cervical cancer, starting from the introduction of the Pap test in the late 1940s, and ending up with the testing of different molecular markers, HPV and vaccines, as extensively discussed in this meeting. He ended up by listing the necessary actions still needed. Evidently, these actions are very much different in the developed countries and in developing countries. In the former, increasing the coverage of screening is of central importance, and can be achieved by providing universal coverage, and replacing opportunistic screening by an organized program. Another important action will be the improvement of the quality of Pap test, to which there are two possible actions; quality assurance in cytopathology laboratories, and adoption of LBC [52]. Prophylactic HPV vaccines certainly are needed in developed countries as well, and primary screening with cytology and HPV testing might be a solution.

In the developing countries, on the other hand, increasing the coverage of screening is limited by resources. A solution should be to provide screening that is economically viable, and which works best in each individual low-resource setting. In this meeting, three such options have been exhaustively discussed: VIA, VILI, and HPV testing. The latter could be provided once or twice in a lifetime, using the less expensive and temperature-stable HPV test, currently under development, based on the existing HCII technology. Then, depending on the resources, a viable option might be testing and treating of all positive cases. Here, if anywhere, however, the prophylactic HPV vaccines should find their most fertile soil.

## Conclusions

During this two and a half day meeting, a surprisingly wide range of topics were addressed, each session being carefully designed, with specific objectives. To illustrate the multi-disciplinary character of EUROGIN 2004 meeting, some of these ambitious objectives of the sessions are listed as examples: (1) to gather international leading experts to review recent developments in HPV infection and cervical cancer prevention and control, (2) to compare worldwide experiences in developed and developing countries, (3) to apply skills to enable the improvement, expansion, and use of scientific data for decision making, (4) to determine the public health role of physicians in cervical cancer control: prevention through training, early detection, treatment and quality of life, (5) to develop and apply strategies for establishing new partnerships and strengthening existing ones, (6) to identify existing strategies and explore innovative community interventions for cervical cancer screening outreach and public education, just a few to mention.

As determined from the feedback by the participants, EUROGIN 2004 reached these goals to satisfaction of everybody. The intention of this Summary Report is to give some of the highlights of the EUROGIN 2004, to share the information of this important meeting with those colleagues who are interested in cervical cancer prevention, but who were unable to attend the meeting this year. The next opportunity will be EUROGIN 2006 in Paris!

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