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EUROGIN and the Division of Noncommunicable Diseases of WHO jointly convened a workshop to review new
technologies in cervical cancer screening and prevention. The workshop was convened by J. Monsonego (Institut Alfred Fournier, Paris, France), Executive Secretary of EUROGIN, and was held June 17–19, 1996, at the WHO headquarters in Geneva, Switzerland. M. Tsechkovski and V. Korotitchouk (WHO, Geneva, Switzerland) welcomed the participants and gave an overview of the priorities of WHO. H. zur Hausen (German Cancer Research Center, Heidelberg, Germany) was the chairman of the meeting, with A. Singer (Whittington Hospital, London, England) serving as Vice-Chairman and E. Franco as General Rapporteur.

Thirty-two speakers presented 62 papers distributed in nine sessions on the following topics: (I) epidemiology of cervical cancer and HPV infection; (II) natural history of cervical cancer and its implications on screening policy; (III) cervical cancer screening programs; (IV) advantages, limitations, and optimization of cytology; (V) automated screening devices; (VI) HPV testing; (VII) adjuvant tests to cytology; (VIII) development of HPV vaccines; and (IX) public health aspects. An in-depth report with the recommendations compiled by all session rapporteurs will be published later in 1996 as a WHO Technical Document. The papers presented at the meeting and the discussion highlights will be published separately in book form by EUROGIN early in 1997.

In session I, N. Muñoz (IARC, Lyon, France) showed that there is now ample evidence to implicate infection by certain HPV types as the main cause of cervical neoplasia. HPV infection by types 16 and 18 fits the IARC definition of human carcinogens. Some other HPV types are considered probable carcinogens. The association between HPV and cervical cancer satisfies all of Hill’s criteria for causality. It is now apparent that the vast majority of cervical cancers are attributable to HPV infection.

E. Franco (McGill University, Montreal, Canada) reviewed the methodological developments in molecular epidemiology studies of HPV and cervical neoplasia. Earlier studies using assays of insufficient specificity and sensitivity failed to show unequivocally that HPV was sexually transmitted and that HPV infection was the biological precursor of cervical neoplasia. The continuous improvement of amplified and nonamplified DNA hybridization protocols has enabled the demonstration of the sexual transmissibility of HPV infection, making a coherent case for HPV in the etiology of cervical cancer.

F. X. Bosch (Catalan Oncology Institute, Barcelona, Spain) showed that detection of penile HPV DNA among male partners was not a uniformly strong predictor of risk of cervical cancer in the IARC study in Spain and Colombia. Proper understanding of the role of men as vectors in cervical cancer may be limited by geographical differences in HPV endemity among males. Research on the natural history of genital HPV infection in males is likely to contribute to our understanding of the role of the virus in the genesis of cervical neoplasia.

M. Hakama (University of Tampere, Tampere, Finland) reviewed the historical trends of declining rates of invasive cervical cancer due to mass screening by cytology in Scandinavian countries. D. M. Parkin (IARC, Lyon, France) discussed the value of time series data before and after implementation of screening. The reduction in rates is generally correlated with the extent of coverage. Studies examining individual changes in cancer risk due to screening are not prone to the difficulties in interpretation of historical trends in whole populations. These studies show reductions in cancer risk among screened women as compared to unscreened women and complement historical trends in providing evidence for the effectiveness of cytology screening in Western populations.

In session II, H. zur Hausen reviewed the molecular pathogenesis of HPV infection, describing the correlation between the morphological spectrum of cervical lesions and specific genetic modifications due to persistent HPV infection interfering in cellular functions. Recent evidence from molecular biology studies show that HPV infection can be considered a sufficient cervical carcinogen. A. Ferenczy (Jewish General Hospital, Montreal, Canada) described the problems associated with diagnosing glandular lesions and preinvasive adenocarcinoma. These lesions are on the rise in women younger than 35 years and are primarily associated with HPV 18.

R. M. Richart (Columbia University, New York, NY) reviewed the common aspects of virally induced cancers and presented evidence for the similarity in natural histories of HPV infection and CIN. All studies conducted thus far show that women with persistently abnormal smears have a high probability of developing high-grade lesions and eventually invasive cancer. The notion that some lesions may arise as high grade without a detectable low-grade phase has gained acceptance following the results from some recent cohort studies. K. Syrjänen (University of Kuopio, Kuopio, Finland) presented evidence from the Finnish cohort for predicting likelihood of lesion progression as a function of morphological severity and HPV type. In immunocompromised hosts, such as HIV-in-

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2 The abbreviations used are: EUROGIN, European Research Organization on Genital Infection and Neoplasia; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; CLIA, Clinical Laboratory Improvement Act of 1988; VLP, virus-like particles.
fected women, there is a substantially increased risk of cervical HPV infection that eventually progresses rapidly to high-grade lesions [reviewed by T. C. Wright (Columbia University, New York, NY)].

In session III, as an introduction to the discussion of screening programs, F. X. Bosch showed the correlation between prevalence of risk factors and cervical cancer incidence worldwide, making the case for the role of screening, productive factors, and socioeconomic status. M. Hakama showed that, when properly organized and maintained, cytology screening is effective in reducing risk of invasive cervical cancer. The differences in national health care systems across Europe have not permitted a uniform reproduction of the Scandinavian experience. European guidelines on quality assurance have been published to indicate minimal and optimal standards to be achieved in ongoing model screening projects in the European Union [reviewed by C. De Wolf (European Programme Against Cancer, Luxemburg, Luxemburg)]. J. Patnick (NHS National Screening Programme, Sheffield, England) showed how population screening in the United Kingdom has begun to have an impact after extensive assessment of outcome indicators and of the reasons for failure of previous policies and procedures. J. Monsonego discussed the reasons for failure of opportunistic screening in general and the potential impact of policy recommendations in France. Presenters agreed that insufficient coverage, long interval between smears, low-quality cytology, inadequate management guidelines, and lack of enforcement are widely recognized as the most important problems hampering the success of national screening programs in Western countries.

These problems are considerably augmented when one examines the situation in developing countries [reviewed by I. Stjernswärd (WHO, Geneva, Switzerland) and P. Naud (University of Rio Grande do Sul, Porto Alegre, Brazil)]. In Costa Rica, for instance, high coverage has been the norm for at least 20 years but no impact has been observed in cervical cancer rates. A population-based study indicated absence of cytology quality control as the reason for the failure of mass screening [reviewed by R. Herrero (IARC, Lyon, France)]. Because of the limited financial resources and the high proportion of advanced cancers in developing countries, WHO has proposed a policy of “downstaging,” i.e., mass screening by cervical visual inspection during clinical examination as a means to detect early stage invasive cancers before they become untreatable. WHO has also advocated the strategy of opportunistic detection of cervical lesions to screen or not to screen revolves around the effect of cervical cytology slides to be screened by a cytotechnologist per day, a number that should be considered excessive. Also, the CLIA practice of rescreening 10% of negative smears can only provide marginal assurance that false negative results will not be substantial. False negative diagnoses have important medical, financial, and legal implications; the latter is a particularly acute problem in North America, where false negative cytologies are among the most frequent reasons for medical malpractice litigation. E. McGoogan (University of Edinburgh, Edinburgh, Scotland) showed that cervical cancers can arise after negative smears with rates varying from 24 to 40%, depending on the time since the last negative Pap smear (3–5 years). Few and small-sized abnormal cells are probably the most common cause of the reader’s failure to detect invasive carcinoma and high-grade precursors in these cases.

The advantages and disadvantages of screening for cervical cancer in an organized system (reviewed by M. Hakama) and on a voluntary (also called “opportunistic”) basis (reviewed by J. Monsonego) were presented during session IV. The decision to screen or not to screen revolves around the effect of screening on the length of life, the quality of life, and the cost. The first issue is well known, whereas there is a paucity of data concerning the latter two variables. In France, where voluntary screening has been the norm, there is concern that a proposed change in recommendations for screening intervals from annual to 3 years (following two successive negative smears 1 year apart) may lead to screening failure because of inadequate quality assurance in taking cervical smears and processing them.

In session V, E. McGoogan reviewed the pros and cons of automation as used in cervical cytology. Automation has mainly focused on the following areas of laboratory work: clerical, specimen preparation, microscopic assessment, quality assurance, and training. The general requirements for an automated screening device include: sensitivity and specificity at least equal to conventional methods, relatively low cost as compared to the conventional approach, and relatively shorter time to obtain a diagnosis. There are several automated systems being marketed, ranging from robotic devices that process the cervical cell suspensions to computer-assisted thin-layer slides to computer-assisted slide scanners that map the smear to detect abnormal cells, thereby separating any slides that contain suspect images for subsequent reading by a cytotechnologist. Comparative trials mostly funded by the private sector are ongoing in many laboratories in North America and in Europe to answer questions related to screening efficacy and cost effectiveness of automated devices.

J. Linder (University of Nebraska, Omaha, NE) reviewed the trial results with the ThinPrep 2000 system (Cytyc Co.,
Boxborough, MA), a liquid-based alternative to the conventional method of Pap smear preparation, showing that automated thin-layer slides can improve detection of atypical cells, precursor lesions, and cancer by producing uniformly cleaner slides free of debris and cell clumps that interfere with microscopic reading. One attractive feature of this system is the ability to save the supernatant of remaining cells in a standardized fashion for subsequent HPV testing.

L. G. Koss gave an overview of historical developments in the technology of computer-assisted slide readers and presented the experience of his laboratory with the Papnet system (Neuromedical Systems, Inc., Suffern, NY), a device that applies neural network technology to "learn" to recognize relevant cellular abnormalities. During each slide scan, fields with the most representative abnormalities are selected for display on the computer screen for further inspection by the cytopathologist. M. E. Boon (Leiden Laboratory of Cytology and Pathology, Leiden, the Netherlands) complemented this overview with a personal account of the participation of engineers and pathologists involved with the development and validation of Papnet. In the United States, two devices have received Food and Drug Administration approval for review of negative smears in a quality control capacity, not as primary screening devices: the Papnet and AutoPap (Neopath, Inc. Redmond, WA) systems. The latter device uses high-speed imaging to compute a score that represents the likelihood of the presence of abnormalities in the smear. A slide batch can then be selected for rescreening by choosing a sampling fraction based on a suitable cutoff value for the score. Use of the AutoPap system in the United States is primarily intended to substitute for the 10% random rescreening of negative smears as mandated by CLIA. Papnet scanning is primarily used as a supplement to screening negative smears. M. E. Sherman presented data in support of the effectiveness of the two automated systems in identifying cervical smears containing abnormal cells that had been missed by conventional screening. R. M. Richart presented cost scenarios based on a variety of assumptions comparing the latter two systems in both quality control and screening capacities.

In session VI, speakers focused on the role of HPV assays as an adjunctive or primary screening test for cervical lesions. A. Lorincz (Digene Diagnostics, Inc., Silver Spring, MD) presented an overview of HPV testing methods in the context of clinical and screening practices, emphasizing the superiority of PCR and the Hybrid Capture (a liquid hybridization assay using immunocapture of DNA-RNA hybrids) techniques. New developments in this area have brought gains in sensitivity and specificity, quantitation of viral burden in cervical cells, and easy group-typing of high oncogenic risk viruses. Preliminary results from the Costa Rica study show promising results for HPV testing as a screening tool.

A few speakers documented the value of HPV testing as an adjunct to cytology in triaging women with abnormal smears. A. Ferenczy presented the experience of his laboratory in performing HPV testing coupled with liquid-based cytology in diagnosing low-grade and high-grade CIN in the secondary (alternate) triage of women with a first abnormal smear. Performing the HPV test on the remainder of the cell suspension used for preparing the thin-layer slide gives a potential advantage in eliminating an extra visit by a patient whose cytology contains minor grade atypia. The addition of HPV testing brought appreciable gains in specificity for detecting lesions. A. Singer discussed the value of HPV testing by Hybrid Capture technology in the diagnostic triage of low-grade lesions indicating that issues of cost, technology transfer, and skepticism as to the relevance of HPV in cervical carcinogenesis have delayed the introduction of HPV testing in clinical practice. M. Sherman presented data illustrating the use of HPV testing for oncogenic types to aid in the quality assurance of cytological diagnoses. The rationale for this strategy is the strong correlation between presence of oncogenic HPV types and lesion spectrum.

The potential role of HPV testing as a primary screening tool was discussed by C. J. Meijer (Free University Hospital, Amsterdam, the Netherlands), J. Cuzick (Imperial Cancer Research Fund, London, England), and A. Lorincz in the context of large-scale screening in the Netherlands, the United Kingdom, and Costa Rica, respectively. The Dutch screening project is assessing the value of HPV testing by PCR as a mass screening tool combined with cytology using an age-stratified approach. The preliminary results have been encouraging in terms of cost and effectiveness in detecting high-grade lesions. The United Kingdom team has calculated a number of cost-benefit scenarios evaluating HPV testing alone versus cytology-based screening. Under various assumptions of HPV prevalence, diagnostic performance, and screening intervals, both tests were comparable with respect to the number of referrals for colposcopy. However, the HPV testing program projected relative savings because of increased spacing of screening intervals among HPV-negative, cytologically normal women. In discussing the United Kingdom situation, J. Cuzick presented data to support the notion that HPV testing coupled with quantitation of viral DNA in cervical cells improves the predictive value with respect to persistence of viral infection and presence of high-grade lesions.

E. Franco gave an overview of statistical issues affecting epidemiological studies of the natural history of HPV infection and cervical cancer and clinical trials of screening test combinations. The greatest emphasis was placed on the role of measurement errors of HPV status and CIN in the interpretation of epidemiological relations and on the fallacy of claiming gains in sensitivity when combining screening tests serially, as is the case when HPV testing is combined with cytology screening. Any such evaluations must be corrected for the inherent gain in sensitivity expected from chance alone when adding a second test. A study of HPV-cytology combination was presented to show that the real gain in diagnostic yield is in the specificity of the dual test approach, despite a misleading increase in joint sensitivity that did not differ from that expected by chance, assuming an equal HPV prevalence scenario.

In session VII, presenters gave an overview of additional adjunctive tests in cervical cancer screening. R. Barrasso (Bichat University Hospital, Paris, France) reviewed the role of colposcopy as the only method that can efficiently determine the nature and extent of a cervical epithelial abnormality in women with an abnormal smear. The traditional approach of referring for colposcopy any instances of high-grade lesions and persistent low-grade lesions has been in effect in most Western countries and should not be modified as screening programs are geared to accommodate new technologies. A. Singer discussed the value of cervicography, a technique in which a photograph of the cervix is obtained after application of 5% acetic acid and is evaluated by a specialist at a remote site for the presence of lesions. It offers potential as a screening test as indicated in a variety of small-scale studies and in one population-based trial in Costa Rica. The major drawback of cervicography is the low specificity leading to overreferral for colposcopy, a situation that may overburden health care resources in developing countries. A. Singer also discussed the value of the polar probe, a device that uses electrical and optical
stimulation of the cervical tissue to distinguish between malignant and nonmalignant areas. Normal, precancerous, and cancerous cervical tissue reflect the light and the voltage in characteristic patterns, which are detected by the tip of the probe and analyzed by a computer. Limited studies with the polar probe have shown promising results, but they need to be confirmed by formal comparative trials before it can be recommended as a screening tool in cervical cancer.

E. Franco discussed the value of molecular variant analysis as a tool to identify cases of persistent HPV infection in longitudinal studies. This method also has the potential to identify particular molecular “signatures” of oncogenic HPVs that may be correlated with lesion development or progression. Molecular variant analysis is being used in the Ludwig-McGill cohort study of HPV infection and cervical neoplasia in Brazil with the objective of distinguishing cases of transient infection by different molecular variants of the same HPV type from cases of persistent detection of the same variant of a given type. Most cases of presumably persistent infection by HPVs 16 and 18 have had the same variant isolated from the cervix in multiple visits. Persistent HPV infection is also associated with a greater probability of CIN than transient infections.

A key issue discussed in the meeting was whether or not the novel approaches to cervical cancer screening are feasible in developing countries. R. Herrero presented the preliminary results from the large population-based Costa Rican study, which is evaluating multiple screening techniques, such as automated cytology, cervicography, and HPV testing. There is an indication that the combination brings substantial gains in sensitivity, but it remains to be seen whether these are not offset by the losses in specificity, leading to overreferral for colposcopy.

A paper by A. Ferenczy discussed the current guidelines for management of cervical cancer precursors. High-grade epithelial lesions and large-volume (area) low-grade lesions should be excised by loop electrosurgical excision procedures, although small ectocervical high-grade lesions can be treated by local ablation using CO₂ laser or cryotherapy. Small-volume (area) low-grade lesions that have been documented colposcopically or histologically may be managed conservatively by close cytological surveillance alone or, preferably, by combining HPV testing for oncogenic types.

In session VIII, N. Muñoz reviewed the progress to date with respect to the development of HPV vaccines. The recognition that persistent cervical infection by certain HPV types is the central cause in cervical cancer has spawned interest in immunization against HPV as the most promising strategy for preventing this neoplastic disease. Immunization may have greatest value in developing countries, where 80% of the global burden of half a million cases of cervical cancer occur each year and where screening programs have been largely ineffective. Two main types of vaccines are currently being developed: (a) prophylactic vaccines to prevent HPV infection and consequently the various HPV-associated diseases; and (b) therapeutic vaccines to induce regression of precancerous lesions or remission of advanced cervical cancer.

F. Breitburd (Institut Pasteur, Paris, France) reviewed the evidence for the efficacy of HPV vaccines in animal models. DNA-free VLPs synthesized by self-assembly of fusion proteins of the major capsid antigen L1 induce a strong humoral response with neutralizing antibodies. VLPs are thus the best candidate immunogen for vaccine trials. Protection seems to be type specific, and it will require the production of VLPs for a variety of other oncogenic types besides HPV 16. Many companies are now engaged in production of candidate VLP vaccines adequate for use in human trials.

L. Qiao (Loyola University, Chicago, IL) and L. Borysiewicz (University of Wales, Cardiff, United Kingdom) presented the evidence for a protective immune response against HPVs. The rationale for the development of therapeutic vaccines lies in the fact that the E6 and E7 viral oncoproteins are present in the majority of cervical cancer cells. Because neither protein is in the cell surface, the most effective mechanism for tumor cell destruction is likely to be CTL responses, which recognize intracellularly processed peptides presented with MHC antigens. Experimental studies suggest that E6 and E7 oncoproteins can act as tumor-rejection antigens. Small phase I therapeutic trials have been conducted in Australia and in the United Kingdom in women with advanced cervical cancer with no significant side effects due to vaccination. Another promising approach is the use of genetically modified cervical cancer cells to induce CTL responses specific to the HPV antigens present in carcinomas.

The final session of the meeting was devoted to public health aspects, with A. Meheus (University of Antwerp, Antwerp, Belgium) discussing the role of education and prevention on sexual behavior and R. Sankaranarayanan addressing the practicality of prevention measures in developing countries. Primary prevention of cervical cancer can be obtained through prevention and control of genital HPV infection. Health promotion strategies geared at a change in sexual behavior targeting all sexually transmitted infections of public health significance can be effective in preventing genital HPV infection. Although there is consensus that symptomatic HPV infection (genital warts) should be managed via treatment, counseling, and partner notification, active case-finding of asymptomatic HPV infection is currently not recommended as a control measure. Further research is needed to determine the effectiveness of such a strategy.

Organized cytology screening programs have been successful in industrialized countries but are not practical in many developing countries. In the Third World, these programs lack coverage, accessibility, effectiveness, and acceptability, conditions that are not likely to change in the near future due to competing public health priorities. Early detection of cervical cancer based on low-intensity cytology (e.g., one Pap smear every 10 years after age 35) and visual inspection to downstage the disease need to be evaluated in randomized controlled trials to determine cost-effectiveness. A general improvement in socioeconomic status and educational level of the population tends to have a positive impact on the risk of cervical cancer by altering some of the known risk factors, such as age at marriage, parity, and health care seeking behavior. Perhaps the best hope in developing countries is primary prevention by immunization against genital HPV infection. There is already a widespread commitment by the scientific and clinical community, as well as by funding agencies, to bring HPV vaccines to the fore in the battle against cervical cancer. One can only expect that the road ahead will show a different and exciting brand of research on cervical cancer prevention.
E Franco, K Syrjänen, C de Wolf, et al.

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