

## Editorial

# Global challenges of cervical cancer prevention

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The Eurogin 2000 4<sup>th</sup> International Multidisciplinary Conference was held at the Paris Convention Center from April 5 to 9, 2000. It provided an update on the most recent status of technological and therapeutic research and development in the area of cervical precancers and cancers and papillomavirus infections.

Cancer of the uterine cervix is one of the most widespread cancers in the world. In developed countries, a woman's risk of cervical cancer is currently estimated at 1% compared to 5% in developing countries that do not have screening programs, thus suggesting the preponderant role of screening in the prevention of this disease. In fact, it has been clearly demonstrated that appropriate management of precancerous lesions of the uterine cervix, based on a process involving cytologic screening, colposcopy after an abnormal smear, treatment and proper follow-up of precancerous lesions, makes it possible to avoid the disease. The most effective possible early diagnosis remains the challenge to be met by all practitioners involved in this field [1].

## Papillomavirus infection

The prevalence of genital papillomavirus infection in women over the age of 15 is estimated at 10-15% for the detection of HPV DNA, 1-1.5% for condylomata acuminata and 3% for intraepithelial lesions of the cervix [2]. Based on a worldwide female population of approximately 2,623,000, we estimate that CIN 1 affects 8.8 million women in developed countries and 30 million in developing countries; CIN 2 and 3 affect 5.9 million in developed countries and 20 million in developing countries; while 590,000 women are apparently affected by cervical cancer in developed countries and 2 million in developing countries [3].

This high prevalence of papillomavirus infection and the lesions it generates raise an immense public health problem. The incidence of cervical cancer is estimated at 400,000 new cases each year worldwide; 75% of these cases occur in developing countries. In Europe, there are approximately 58,000 new cases of cervical cancer each year and 16,000 in the United States. The mortality rates are 30,000 and 5,000, respectively [3].

After age thirty-five, 5 to 10% still have high risk papillomaviruses in the form of persistent infection [4, 5]. The prevalence of the infection is approximately 10% in developed countries and 15% in developing countries. We recognize that 325 million women worldwide are HPV carriers in a subclinical or clinical form.

## HPV, leading cause of cervical cancer

The prevalence of HPV infection in cervical lesions is currently well documented due to very effective gene hybridization and amplification techniques. The prevalence of the infection is estimated at 70 to 90% for CIN 1, 2 and 3 and practically 100% for carcinoma in situ and invasive cancer [6, 7]. The relative risk of a female papillomavirus carrier having an abnormal smear is estimated at 40. Recent data on the epidemiology of the infection have made it possible to clarify the natural history and show the role of persistent infection as a predictive factor of significant current or future cervical lesions, which are most often precancerous, as well as future cervical cancer.

According to Meijer *et al.*, the relative risk of low grade SIL progressing to histologically confirmed high grade SIL is 32.7 [8]. According to Koutsky *et al.*, the relative risk of a woman with a normal smear developing a histologically confirmed high grade lesion within two years compared to women with no papillomavirus in their normal smears is 11 [9]. According to Ho *et al.*, the relative risk associated with ongoing hi-

gh risk papillomavirus infection of developing a SIL is 37.2 [10]. Recently, Wallyn *et al.* showed that the relative risk of a woman developing invasive cervical cancer when a high risk papillomavirus was found on previously normal smears was 16.4 [11].

All of these recent studies show the role of persistent viral infection as a risk factor for subjacent or significant future precancerous and cancerous cervical lesions.

High risk papillomaviruses are recognized as independent etiologic factors in cervical cancer. Papillomavirus DNA is capable of inducing cancer by deregulating the mechanisms of tumor suppressor genes (p53 and pRb). Persistent papillomavirus infection emphasizes the risk of significant cervical lesions in women over the age of 30. Sexual activity and immune status influence exposure to the disease and its natural history. It has now been proven that papillomaviruses are carcinogenic agents in humans [12].

### **Benefit of the screening smear**

It has been clearly shown that the introduction of screening programs over the past 40 years, particularly in the Nordic countries, has brought about a very extensive reduction in the incidence and mortality of cervical cancer. Consequently, in those countries, there has been a decrease of 50 to 17.2%, depending on the age group [13].

In France, with 3,600 new annual cases, the incidence of cervical cancer is approximately 10 per 100,000 and there has been a regular decrease of approximately 1.5% per year for 20 years. The merits of screening are undeniable. Since the introduction of the smear as a screening test some 50 years ago, there has been a decrease in the incidence of cervical cancer of approximately 70%. A woman's risk of developing cervical cancer during her lifetime is estimated at 1% compared to 5% in countries with no screening program. The smear remains the only screening test that spares human lives and has a high cost benefit. The test is widely used throughout the world and is well known to women. On the whole, the technology has been mastered and the majority of professionals are experienced in that technique. However, its success depends on the quality of the program and the coordinated involvement of the various participants in the screening. Its effectiveness requires proficiency at all levels and sufficient resources.

Despite the fact that it is nearly always possible to prevent it and despite the introduction of screening programs and vast information campaigns in many industrialized countries, as well as the very large number of smears done every year, cervical cancer remains a worrisome reality. The incidence rates reflect the magnitude of the risk factors and the effectiveness of the screening programs. In 1995, there were 27,000 new cases in Europe and 16,000 in the USA, resulting in 13,000 and 5,000 deaths, respectively. In Europe, the mean incidence is approximately 10 per 100,000; this rate varies from 4 to 16 per 100,000 depending on the country [3].

In several developed countries, it has been established that implementing and monitoring a screening program is a complex, difficult and costly undertaking whose cost/benefit ratio depends on its quality and the effectiveness of its evaluation. These difficulties reflect the extensive disparities in the benefit expected from screening from one program to the next.

It has been proven that the smear's sensitivity does not exceed 70% [14] and, more recently, an unacceptable number of invasive cancer cases have been found in women who regularly receive smears [1]. Based as it is on the notion that cervical cancer is inevitable, this detection error, as limited as it may be, has unleashed the idea that smear screening might not be optimal in terms of detection. In reality, these failures are the combined consequence of insufficient coverage of the target population, the attenuated sensitivity of the cytologic test and the false negatives that result, and the inappropriate management and follow-up of patients who are treated for abnormal smears.

In addition to the difficulties associated with the smear's lack of sensitivity, another negative effect of cytologic screening concerns false positives. The introduction of the Bethesda classification system as the most appropriate terminology for reporting smear results and its very positive impact on describing the quality of the specimens and facilitating communication between practitioners and pathologists, has also brought about new challenges for the practitioner and for patient management [15]. The terms, such as ASCUS, which accounts for 3 to 6% of all smears, have led to confusion and a challenge for the practitioner due to the lack of reproducibility of that category in laboratories [16] and the sub-classifications of lesions biopsied by colposcopy. Consequently, histologically confirmed cases of CIN 1 are subject to a lack of reproducibility as well

as interobserver and intraobserver variability [17]. This subjectivity is a source of over-diagnosis, needless treatment and follow-up, and stress for the patient.

While colposcopy is considered the reference technique for managing abnormal smears due to its very high sensitivity in recognizing precancerous lesions (greater than 90%), its less than 50% specificity generates the same difficulties [18]. Interobserver and intraobserver variations are significant [19] and kappa statistics are low for colposcopy and biopsy. The confusion created by interobserver variability, subclassifications and lack of reproducibility of lesions with minor atypia is a source of inappropriate patient management practices. Colposcopy requires ongoing training and extensive experience, which is in contradiction to a procedure that is widely used by the majority of physicians.

### **I - Efficacy of smears prepared from a liquid suspension**

The conventional smear is often limited due to the poor quality of the specimen. We acknowledge that:

- 80% of the collected cells remain in the sampling material and are not analyzed;
- 50 to 70% of false negatives are due to suboptimal specimens;
- More than 40% of smears are compromised by blood, mucus or inflammation.

Consequently, inadequate smears justify repeating the test. Liquid medium smears may be one of the answers to these problems. By improving slide preparation, thin layer smears improve the quality of the specimens [20].

Recent studies show a greater than 50% increase in the detection of intraepithelial lesions in the screened population compared to the conventional smear and a significant decrease in inadequate smears on the order of 50% [21-23].

In a recent French multicenter study [24] comparing the Thin Prep method to conventional smears using a dual sampling method, in 5,428 screened women it was shown that, in 39% of the cases, the Thin Prep smear significantly increased the detection of low grade and higher intraepithelial lesions. Fifty percent of low grade lesions and 18% of high grade lesions are more frequently screened by the Thin Prep smear compared to the conventional smear. Rescreening of the slides by an expert and the panel of investigators showed that the relative sensitivity of the conventional smear in detecting dysplastic lesions was 59% compared to 69% for the Thin Prep smear. This corresponds to an 18% increase relative in sensitivity. Other published studies show that, by using the sampling process of direct immersion in a liquid suspension, the Thin Prep smear generates a significant increase in sensitivity and equivalent specificity in the detection of intraepithelial lesions. By increasing the quality of the specimens, the technology has an impact on false negatives, reduces repeat smears and, at the same time, seems to have a positive cost/benefit ratio. The technique also has the advantage of preserving cells in liquid, so they may be subsequently used for the detection of papillomaviruses or other tests, such as for chlamydia and gonorrhea.

### **II - Automated screening and quality control**

Automated devices such as the Auto Pap QC 300 are intended for quality assurance use in laboratories. They select slides with a high probability of being a false negative for manual rescreening. It has been shown that the system improves the detection of false negatives compared to non-targeted selection by 10% in so-called normal smears (manual quality control).

Compared to manual screening, it has been reported that the machine has a greater capacity for detecting abnormal slides with ASCUS, low grade SIL and high grade SIL, by selecting 75% of the slides with a high probability of atypia. These are then manually reviewed simultaneously with quality control. In fact, the machine eliminates 25% of normal slides with a high probability of not being false negatives. The cost benefit of routine use of the machine is currently being evaluated [25-27].

### **III - Identifying women at risk for cervical cancer and streamlining patient management with the HPV test**

Cervical cancer is recognized as the leading virus-induced cancer in women. The following points have been demonstrated with respect to HPV infection and its connection to cervical cancer:

- Cervical precancers and cancers are nearly always associated with high risk HPV [6, 7].
- High risk HPVs are independent etiologic agents of cervical cancer [28].
- The positive predictive value of viral DNA detection significantly increases after age 35 [4].
- Viral load and persistent infection with oncogenic types are predictive indicators of subjacent CIN [29].

For all of these reasons, the HPV test has been suggested for optimizing conventional screening. The techniques used on a broad scale are PCR and, recently, the latest version of Hybrid Capture (HCII), which is more sensitive than the initial version.

### 1) Secondary screening

The HPV test has been reported as useful in patient management. ASCUS and low grade SIL smears, which represent 4 to 5% of all smears, are a heterogeneous group of cell changes which are not very simple to manage. Papillomavirus DNA detection is justified by its high negative predictive value.

**The repeat pap** is a simple and inexpensive approach, but its sensitivity is not absolute, since 25 to 30% of “silent” high grade CIN go undetected on smears [30]. This approach does not resolve the problem of false positives.

**Colposcopy/biopsy**, even though it is the method of choice for detecting subjacent high grade lesions [31-33], it is a technique whose effectiveness depends on the skill and experience of the physician. Consequently, intraobserver and interobserver variations remain high [19]. Even though this is a low-cost approach in some country, the subsequent CIN I here a lack of reproducibility [17-34]. This subjectivity often leads to over-diagnosis, occasional needless treatment, and stress for the patient. The result is that the traditional approach is cost ineffective in one out of every two cases.

**The HPV test:** After ASCUS smears, the HPV test can sometimes clear up the confusion generated by the variability in diagnosing and histologically classifying the lesions. Due to its negative predictive value, the absence of HPV DNA in this type of atypia makes it possible to exclude actual cervical disease 8 to 9 times out of 10 [30, 31, 33], thereby providing quality assurance for the analyzed specimens. At the same time, the detection of high risk HPV DNA, particularly after age 35, indicates an actual subjacent lesion 7 times out of 10 (30). In the other cases, we consider that healthy HPV carriers are at risk for future lesions. By decreasing the number of colposcopies and biopsies and needless treatments, it has been demonstrated that this approach is cost-beneficial [30]. HPV typing done on the initial liquid specimen from the ASCUS smear gives this approach maximum sensitivity with no loss of specificity. At the same time, it avoids another appointment for this examination [35].

Recently, Kauffman *et al.* evaluated the HPV test in women after abnormal smears [36]. They concluded that the HPV test is not useful due to its low sensitivity in detecting CIN. This study was done with the initial version of the Hybrid Capture system. The failure to detect HPV in a high proportion of female CIN carriers suggests differences in populations, specimen collection problems, the lack of sensitivity of the first generation of the Hybrid Capture test or cytohistologic classification problems. A low detection rate of HPV in CIN may indicate difficulties establishing a suitable classification for these lesions whose variability increases with age. It has recently been proven that using the HPV test in colposcopic practice significantly increases the specificity of this method in patients with ASCUS or LG-SIL smears [37]. Practicing colposcopy on patients with ASCUS/LG-SIL and high-risk HPV positive results alone gives a two-fold increase in the frequency of detection of histologically confirmed HG-CIN, whereas the absence of HPV in these women excludes significant underlying lesions in 98% of cases. The HPV test increases the specificity and the positive predictive value of colposcopy [37].

Two recent studies demonstrate the benefit of the HPV test in managing ASCUS and low grade smears when that test is done on a liquid specimen (Thin Prep) using the latest generation HPV Hybrid Capture (HCII) test [38, 39]. Wright's study [39] indicates that the “reflex HPV test” done on the initial liquid specimen detects the majority of high grade CIN and is highly specific in detecting different grades of CIN, particularly in women over the age of 35 and women with ASCUS smears. The study by Manos *et al.* [30] of 7,500 women with ASCUS or low grade smears indicates maximum sensitivity in detecting 176 cases of SIL in women under the age of 30 with ASCUS smears. This represents a 56% increase in detection compared to the conventional smear, which detects only 64% of subjacent low grade SIL. The HPV test detects 100% of high grade CIN in women under the age of 30 with ASCUS or AGUS smears, while the repeat smear detects only 57% of high grade lesions.



## 2 - Primary screening

The HPV test alone or in combination with a smear is currently being evaluated for primary screening. Scenarios for determining the smear interval based on the risk according to type of papillomavirus are currently being studied in terms of smear frequency among women over the age of 35. The combined test (smear + HPV) is surmised to be more efficient in terms of screening, by increasing the detection of precancerous lesions, reducing routine colposcopies and increasing the smear interval in HPV negative women [8, 40-42]. In women over the age of 35, the high positive predictive value makes it possible to select women at risk and to focus screening efforts, in terms of management and cost, on that population with the greatest exposure. However, the high detection sensitivity and maximum protection afforded by the combined cytologic and HPV tests still need to be evaluated in terms of specificity and cost/benefit in screening programs [43].

In a recently published Costa Rica study of 8,554 women, using the Hybrid Capture test for primary screening, it was shown that this method makes it possible to detect high grade lesions 88.4% of the time compared to 77.7% with smears [44]. In addition, Hybrid Capture maintains acceptable specificity 89% of the time versus 94.2% with smears [38]. In developing countries self-administration has been suggested as an option for performing the test. Recent studies show that the sensitivity of the test using a vaginal tampon is as effective as cervical sampling by a physician [45] (*J. Sellors and J. Bellinson, paper, Eurogin 2000 Abstract Book*).

## IV - Instantaneous real time screening

Screening for cervical cancer using an electronic device called the Polarprobe consists of applying a probe that analyzes its electrical and optical properties of the uterine cervix. This makes it possible to distinguish among normal cervix, precancer and cancer. This screening method is still being evaluated. It is intended for use by general practitioners as an initial approach to screening. The potential advantages are instant diagnosis, good acceptance and low cost to patients. The equipment is easily transportable and may, in future, be used in developing countries. The studies are still being evaluated, but the preliminary results confirm the benefits. No information is currently available regarding the sensitivity and specificity of this technique [46].

## V - Treatment of cervical intraepithelial neoplasia with immunomodulators

Imiquimod (*Aldara*<sup>TM</sup>) cream has been successfully used to treat external condylomata acuminata (*M. Owens, Eurogin 2000 Abstract Book*). This is a treatment applied by the patient that modifies the immune response by producing interferon alpha and other cytotoxins. The same effect was reported when the cream was applied by the vaginal route (*R. Miller, abstract, Eurogin 2000 Abstract Book*). Studies are currently in progress to determine whether the product can be used in treating low grade and high grade intraepithelial lesions when the cream is applied by the vaginal route. The studies are also evaluating the optimal dose, route of administration and local and systemic effects.

In a Phase 1 study on women volunteers to evaluate the effect of intravaginal administration of *Aldara*<sup>TM</sup> on the cervix, it was shown that self-application of 100 mg of the product with a vaginal applicator is feasible and devoid of side-effects (*K. Trofatter, abstract, Eurogin 2000 Abstract Book*). In another Phase 1 and 2 study conducted in Germany for treating CIN 1 and 2 (*Ikenberg, abstract, Eurogin 2000 Abstract Book*), it was shown that 250 mg of 5% Imiquimod applied locally three times a week for three months using a cervical cap resulted in 33.3% complete responses and 33.3% partial responses. The same results were found in a preliminary study of the treatment of VIN 2 and 3.

## VI - Anti-HPV vaccines

HPV-16 is the virus most frequently found in cervical cancers as the principal etiologic factor. The close relationship between viral infection and cervical cancer suggests that HPV is a necessary candidate for the development of prophylactic and therapeutic vaccines. Preliminary human studies of prophylactic vaccines for HPV-16 VLP (Virus-like Particles), composed of viral structural protein L1 involved in the development of virions, demonstrate that these VLP are well tolerated and immunogenic (*D. Lowy, Eurogin 2000 Abstract Book*).

Therapeutic vaccines could be used in the treatment of precancerous and cancerous cervical lesions. It has been reported that high risk papillomavirus genes may be introduced into cells through a viral vector like the virus of the vaccine. Tolerance studies on HPV-16, HPV-18, E6 and E7 vaccines are giving promising results, as was reported during the conference.

## Conclusion

The traditional approach to screening and management of precancerous lesions of the uterine cervix is effective as a winning strategy to prevent cervical cancer, particularly when there is extensive coverage of the screened population and when a quality assurance procedure is an integral part of the program.

However, the history of screening over these past 20 years highlights the difficulties of achieving these goals. Successful cervical cancer screening requires expertise in cytology and colposcopy, but also in terms of program quality and evaluation as well as appropriate management of lesions detected on smears. Until a prophylactic papillomavirus vaccine is available (results are promising, but an assessment of effects is still in the distant future), the introduction of new technologies can help make the development of these screening programs more operational and streamline the strategies for managing women with abnormal smears. They can be part of a logical sequence for optimizing screening methods. It is legitimate to think – today even more so than yesterday – that recent technological developments have a potential for bringing about a new era in this field and to believe that cervical cancer is a disease that stands a great chance of being eradicated.

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