1. Summary

Cervical cancer is the third most common cancer among women worldwide, with approximately 370,000 cases/year and 190,000 deaths. Organised cytological screening protects against cervical cancer, and screening programmes today identify women with abnormal cytology for further examinations by colposcopy and cervical biopsy, and eventually surgical removal of a histologically verified cervical intraepithelial neoplasia (CIN), the precursor to cervical cancer. Follow-up after treatment has so far consisted of repeat cytology and possibly colposcopy.

Cervical screening ensures early cancer detection and diagnosis, and has been shown to be effective in reducing mortality due to the cancer of the uterine cervix in the Member States. Essential in the organisation of an effective population-based preventive programme, are high quality of laboratory screening, the continuous monitoring of abnormal smears screening results, including the long term follow-up of positive cases. The Network activities were performed in accordance with the planned activities, and the obtained results of the Network in the 4 chapters are summarised below:

- Quality Assurance and Quality Control (Part 1),
- Monitoring, Epidemiology and Evaluation of Cervical Screening (Part 2),
- New Technologies in Cervical Screening (Part 3), and
- Dissemination of Network Results (Part 4).

Quality Assurance and Quality Control (Part 1)

In Germany a number of 26,249 screening patterns with new features were acquired. The improvement of the quality control and quality assurance tools was the first objective of the planned work in the period December 2000 to December 2001. The development work for improving the defined tools was started in January 2001, the conceptual work on efficiency of the tools for Quality Assurance and Control was performed until March 2001, and the new tools were implemented into routine procedures for screening 26,249 smears.

The diagnostic properties of rapid screening were evaluated, and collaboration work was performed with Scientific Institute of Public Health – Louis Pasteur in Brussels in improving the quality control in cervical screening.

The study "Continuous grading systems for the diagnosis of intraepithelial lesions – a contribution for overcoming problems of translating among different terminologies" was continued in co-operation with the Technical University of Munich.

Work was performed with the aim of updating the European Guidelines for Quality Assurance in Cervical Cancer Screening. The results were discussed with European experts during the Network Workshop "Guidelines for Cervical Cancer Screening" in Ormylia, Greece from 25-29. September 2001. The multilingual access to the WEB FORUM was developed, and supports an open discussion between the network partners, and also integrates the feedback from a large number of specialists outside of the
Network. The first draft of the "Updated European Guidelines for Quality Assurance in Cervical Cancer Screening" was released as an internal document, and collection of the contributions of the network partners about Guidelines improvements was started in December 2001.

In Belgium the work was concentrated on studying the gain in diagnostic performance of thin layer liquid based cytology coupled with ancillary HPV DNA. A randomised trial called "Primary versus triage based HPV detection in combination with Thin layer cytology" was conducted in co-operation with the Free University of Brussels with the aim of improving the quality of screening. Work was performed in evaluating the diagnostic properties of rapid screening, and collaborating with the Cytological Institute in Munich in improving the quality control in cervical screening.

In Greece (Hellenic Society of Oncology, Athens) the project work was performed by using own funds, with no request of financial support from the European Commission. The 4th Round of the Screening Programme to the county of Messinia has been completed. Screening was performed on vaginal, ectocervical, and endocervical smears. The 5th round of the Cervical Cancer Screening program was prepared and started in the county of Ilia. Invitation letters were sent to the target population in this region, inviting them to participate to the program. The Cervical Assessment Steady Unit was founded in Athens by the Hellenic Society of Oncology and the Hellenic Anticancer Institute and continues with great success to carry out its activities, as a permanent cytological laboratory. High standards of laboratory practices are ensured by advanced quality assurance procedures. The staff/workload ration is satisfactory, one cytopathologist screens 15-20 cervical smears daily.

In Greece (Our Lady Who Loves Mankind, Chalkidike) work was continued to closely follow-up all women tested positive and regularly update their screening files with all available data on further assessment and treatment. Data on 6,408 patients and their smears was recorded, 1,293 tests were classified as abnormal, and a reliability study of smear reading on a random sample of Pap-smear test was performed. Co-operation work was performed with the Cytology Laboratory of the General Hospital of University of Athens, which is the Greek national centre of excellence in cytopathology and epidemiological research.

In Holland work was continued in implementing optimally integrated screening (evidence based) of cervical cancer in general practice and to transfer experiences from one country to another. This can be achieved in a phased manner. In previous projects, as a member of the EC Network for Cervical Cancer Screening, the group has developed and tested a general practice-based call system in a population-based screening programme for cervical cancer. In addition, at a local level, the evaluation of two different communication systems between smear-taking general practices and the cytological laboratories took place (based on the European Guidelines for Quality Assurance in Cervical Cancer Screening, the national guidelines of the Dutch College for General Practitioners, and the guidelines for Pathology laboratories concerning cervical smears) to maximise follow-up of abnormal and unsatisfactory smears.
In Italy the work performed is concentrated in another area, in "Monitoring, Epidemiology and Evaluation". However, the addressed topic "Improving methods for data collection and analysis for cervical cancer screening evaluation" is an important feedback information for the area "Quality Assurance and Control". In particular, the collection of data about the "women screened for the first time" and "women participating to following rounds" is of great importance. Here separate evaluation tables are needed, because the expected detection rate of histologically confirmed intraepithelial lesions (and measures depending on disease prevalence as the Positive Predictive Value) changes if the "prevalence" screen, or following rounds are considered.

In Portugal a combined study was conducted, Pap smear by ThinPrep Method and HPV testing, over a period of one year on women whose first cytological test was done within the Cervical Cancer Screening Programme of the Central Zone of Portugal and whose smears result in the cytological diagnosis of ASCUS/AGUS. The objective was to find criteria for the selection of patients to be referred for colposcopy, in order to establish a suitable follow-up, avoiding over-diagnosis and unnecessary treatment, thus making the process more cost-efficient.

The study took place in 17 counties of the Central Zone that are remote from urban centres and whose health-care systems are not yet incorporated into the Cervical Screening Programme, meaning that screening is only done occasionally and on a small scale. The target population are women aged between 20 and 64, those under 20 who have already had sexual intercourse, and those over 64 that have not had previous cytological tests. Excluded from the study are women who have had hysterectomies and those with previous diagnoses of intra-epithelial lesions or cervical carcinoma.

Smears from 38,901 women were screened independently of the phase of the programme. The obtained cytological results show that the number of unsatisfactory smears seems lower but they don’t reflect the unsatisfactory smears obscured by inflammation. These cases are included in the inflammatory category that need to repeat the smear after treatment.

In Slovenia (external contract, Candidate State) two specialists in cytopathology from Slovenia have re-screened all 599 non-negative smears and additionally a random sample of the same number of negative smears were screened separately by 2 specialists. They analysed smears for: smear adequacy and epithelial changes. The degree of agreement between pairs of observers was quantified using pairwise "kappa" statistics. Kappa values greater than 0,75 were used for "excellent agreement", values between 0,75 and 0,40 for "good agreement", and values below 0,40 for "poor agreement". National guidelines on reporting cervical smears have been prepared, and will be published.

In Spain work was performed as planned. The computer-based data acquisition of information about cervical cancer occurrence in the target group of women aged 25-65 living in Spanish regions Castilla and León was continued. Data collection of 58,383 smears was performed and the smear analysed, and this data was stored together with diagnosis data. Appropriate evaluation parameters were used for the Quality Control of the tests, and the results were made available to the GPs of these regions.
Monitoring, Epidemiology and Evaluation of Cervical Screening (Part 2)

In Belgium following work was performed:

- Activities of the Working Party for Uniformisation of Cytology were continued, creating the "Working Group on Quality Assurance and Optimisation".
- The annual meeting of the Belgian Society took place, without support from the E.U.
- Development of a common policy in cervical cancer screening throughout the European Union by in general comparing existing strategies applied in the member states and updating European guidelines of all the main aspects of organised cervical cancer screening, and in particular coordinate activities dealing with the evaluation of new screening techniques.

In France evaluation of the diagnostic performance of the two monolayer methods was performed, as planned: the historical comparison for each of the laboratories of the distribution of smear tests according to the obtained cytological result during two 12-month periods before, and after the introduction of the new technique. The training period of the thin layer technique of 6 months was excluded. A control group of laboratories still using conventional Pap was also included.

The study of the positive predictive value of the thin layer method relative to conventional Pap smear was conducted. Comparison of the distribution of smear tests according to the cytological results was done for the two laboratories (A and B):

- In laboratory A a number of 37,440 smears from the first period (i.e. 12 months before introducing the new technique) and a number of 38,222 smears from the second period (i.e. 12 months after introducing the new technique) were included in the study.
- In laboratory B a number of 8,759 smears from the first period (i.e. 12 months before introducing the new technique) and a number of 10,699 smears from the second period (i.e. 12 months after introducing the new technique) were included in the study.

The Control Group addressed a number of 39,442 smears from the first period, and 43,376 from the second period.

The preliminary study shows better diagnostic parameters for monolayers than for conventional pap smears. However, as the duration of the follow-up was longer for the later ones, we can not conclude at the moment which technique is better, and additional work is needed.

In Holland we have assessed the successful implementation of the most cost-effective communication system at national and European level. From the previous project it is known that the most cost-effective communication system between cytological laboratories and general practices for maximising follow-up of abnormal unsatisfactory smears is either

- follow-up monitoring by the cytological laboratory or
- follow-up monitoring by general practice or smeartaker in general and, in the case of moderate severe abnormalities, a reminder by the laboratory.

However, to guarantee a successful implementation of the communication system, it is important to systematically assess the presence or absence of preconditions for the successful implementation. To determine these preconditions, the experiences of our
previous project were elaborated and formulated in 4 tools (2 questionnaires and 2 checklists). The questionnaires, for those involved in the screening activities contain questions concerning current practices, and barriers to and facilitators for implementation. Another example of a tool that was developed, concerns a checklist that contains the elements of the pathology laboratory configurations for processing and storing Pap smear classifications and criteria for follow-up.

Following the pilot testing of the measurement instruments, the 4 tools are suitable for countries in Europe with preventive programmes for cervical cancer screening, and in which smears are taken by the general practitioner in general practice, for example in UK, Denmark and Ireland.

In Italy work was performed in order to monitor the value of process indicators for cervical cancer screening in 73 different organised screening programmes in Italy. The target population includes 8,372,646 women aged 25 to 64 years (about 52% of women). We have continued to identify problem areas in Italian screening programmes and have started actions to improve them. Quality indicators need to be quite stable in time and relevant variations should be observed only if real changes of the situation arise. The project has analysed data on process indicators, obtained from 52 organised programmes active in 2000. In the year 2000 a number of 1,325,663 women were invited, and 502,884 were screened. The obtained results include:

- Distribution of cytological diagnosis
- Percentage of women referred for colposcopy by each Italian centre
- Positive Predictive Value (PPV) of a AGUS or more severe cytology in predicting a CIN II or more severe histology. In 7 of 42 programmes PPV was significantly lower than expected, suggesting that criteria for cytology classification were too broad.
- The detection rate of histologically confirmed CIN II or more severe lesions was analysed by a Poisson regression model.

First data on treatment of screen-detected lesions were obtained. Among both CIN I and CIN II-III lesions, treatment was unknown for 12% cases. Among CIN II-III cases most (50,5%) were treated by LEEP or similar methods, 22,5% by surgery or laser conisation. Hysterectomy was performed in 0,6% of CIN I and 6,2 % of CIN II-III.

The performed work allowed the indentification of areas and situations that require improvement, and information dissemination of the obtained results was performed at local level, with the aim of improving methods of data collection and analysis for cervical cancer screening evaluation.

In Spain work was continued in the computer-based data acquisition, data monitoring and evaluation of information about patients with cervical cancer for the target group of women aged 25-65 living in Castilla and León regions. All women of these regions were invited to smears tests, and a set of sound epidemiological results were provided. Data collection of 58,383 smears was performed together with smear analysis, and the information was stored together with diagnosis data. Appropriate evaluation parameter were used, and statistical information was worked out.
In Sweden the experimental work on the HPV treatment methods was continued. The evaluation of the treatment methods is also relevant to Part 3 "NewTechnologies".

A cohort of 109 women with cervical intraepithelial neoplasia, referred for treatment have been followed with repeated HPV tests at 0, 3, 6, 9 and 12 months post treatment, some women even 24 months post treatment. The cohort was enrolled already before the start of the contract and during the term of the contract the work with database control and manuscript preparation was performed. The results show that HPV is quickly cleared after surgical treatment for CIN, usually after 3 months. HPV is cleared more quickly among women treated with conization than among women treated with cryotherapy.

In the ongoing population-based HPV screening trial, 180 women with screen-detected persistent HPV infection have been referred to colposcopy and treated during the term of the contract. Digital images of the cervical lesions were recorded using computerized colposcopes.

Two cohorts of women treated for CIN with different methods (conization or loop electrosurgical procedure) to compare the different methods for HPV treatment:

- **Cohort 1** enrolled 37 women who were referred for treatment of CIN. Previous data had shown that treatment with carbon dioxide laser conization was effective for treating HPV infection. As a pilot study, the HPV clearance rate after treatment with LEEP was determined. The results showed a 96% clearance rate after 3 months, which was better than previously reported for carbon dioxide conization.

- **Cohort 2** had during the time of the contract enrolled 84 women who were referred for treatment with CIN. The women were randomised to treatment with either loop electrosurgical excision procedure or to conisation. During the time of the contract HPV testing and analyses of the data was completed for the pre-treatment samples of the first 64 women. Although all women enrolled into the study had had CIN as a reason for referral, on the date of treatment 19 of 68 women had a normal smear. Spontaneous regression and/or removal of the lesion by the diagnostic biopsy are possible reasons for this finding. As expected, 86% of women who still had a dysplastic smear were HPV-positive. As expected, HPV-positivity correlated strongly with presence of a dysplastic smear (OR: 19.5 (CI: 4.8-86.9)). The enrolment and the testing performed so far has been satisfactory.

A series of meetings have been held with both national and international representatives of the 3M Pharma company that manufactures the immunostimulatory drug Imiquimod. The decision from the company has been to not pursue a trial with Imiquimod for treatment of HPV infection, because of logistic problems.

In Slovenia the work was concentrated on detailed analysis of the invasive cervical cancer incidence and mortality by age groups and regions in Slovenia:

- Age specific incidence rate of CIN III with the peak in the age 30-34 in the period 1994-1998,
- Age specific incidence rate of invasive cervical cancer started to increase in younger women aged 30-39,
- Age specific incidence rates by birth cohorts, distribution of cervical cancer by stage at diagnosis with an increase in the age group 35-49 years,
- Relative 5-year survival rate of cervical cancer patients,
- Mortality trend (5.1 per 100,000)

Geographically distribution of cancer has a peak in the coastal region.
New Technologies in Cervical Cancer Screening
(Part 3)

In Belgium work was performed as planned, and in co-operation with the Free University of Brussels on the randomised trial on "Primary versus triage based HPV detection in combination with thin layer cytology". A number of 3.000 women, consulted in 2000 at the gynaecological department of the Hospital of the Free University of Brussels were randomised into two experimental arms A and B. From all women a liquid based cervical smear was taken using the AUTOCYTE preparation system. Samples from all women in group A were used for ancillary high risk Human Papillomavirus DNA detection using the HYBRID CAPTURE II method (primary screening setting). HPV testing in material from women in group B was limited to those showing atypical or low grade cytological lesions (triage setting). All women, being HPV positive or showing squamous high grade (HSIL+) or glandular abnormalities (AGUS+) or worse, were called in for further diagnostic exploration. Detection of histologically confirmed CIN-2/GIN-2 or worse was the main study outcome. The cross-sectional sensitivity and specificity of cytology and virology were assessed within each experimental arm. Cases that are co-negative for HPV and cytology were assumed being true negatives without histological verification.

⇒ Obtained Results  Both study groups did not differ significantly regarding age, clinical observations and accomplishment of follow-up. Cytological detection rates were comparable as well (p=0.92). The observed prevalence of moderate dysplasia or worse (CIN2+) was 1.28% in the primary screening situation and 1.01% in the triage setting. The detection rate ratio was 1.27 (95 % CI: 0.65-2.49).

Of the 19 CIN2+ lesions found in group A: 10 were detected by HC II alone, 1 by cytology alone and 8 by both methods. The sensitivity was 94.7% (CI: 74.0-99.8%) for the HPV test and 47.4% (CI: 24.4-71.1%) for thin layer cytology. The specificity was 97.1% for HPV testing and 99.9% for cytology. Differences in sensitivity and specificity were significant.

In the triage arm 15 CIN2+ lesions were found: 10 cases were found because of high grade or glandular cytological abnormalities; five extra cases were detected by subsequent HPV triage of the ASCUS or LSIL lesions.

⇒ Conclusions  The relative sensitivity of thin layer cytology could be enhanced with a factor of 1.5 by subsequent HPV testing of ASCUS/LSIL. Still 27% more CIN2+ were found by testing all subjects for HPV. This additional yield was not significant in this limited trial but required consumption of 22 times more HPV tests. This trial needs extension in size and over time in order to verify the robustness of the findings and to estimate longitudinal outcomes that are more relevant for public health.

In Finland work was concentrated on the evaluation of new technologies in the cervical cancer screening programme. During the reporting period, we have had an on-going large-scale randomised trial using automation-assisted screening technology, Papnet, as well as a pilot study on HPV-screening. During the five-year inclusion period of the trial on new technologies, performance analyses will be done using the histologically confirmed findings as the outcome. These materials are also included in a later stage of the study into a long-term follow-up of cervical cancer incidence after screening visits,
using the files of the Finnish cancer registry. The long-term follow-up will investigate whether any improvements in the effectiveness of screening with the new technology were at stake.

**Study on automation-assisted cytology:** Considering the screening programme during the activity period, the randomisation process had included 164,272 invitations for the two arms, 55,043 invitations in the Papnet arm and 164,272 invitations for the traditional manual screening arm. The cumulated number of women randomised to the Papnet arm for 1999-2001 is more than 150,000. About 50,000 women were randomised to the Papnet arm during the course of 2001. In the automation-assisted pap-smear screening trial using Papnet, 38,3000 smears were scanned. The results of these screenings will be available in late 2002. A summary of the first and second year results suggest that automation-assisted screening may be at least as sensitive and specific as the conventional screening practice in Finland - in a country with highly effective and well documented screening programme. The overall rate of detecting a pre-cancerous lesions is materially the same in both of the arms (4.2 per one thousand in the Papnet vs. 4.4 in the conventional screening arm).

**Study on HPV-screening** The pilot study with 2,032 hospital smears has been finalised by analysing the data with various cytological methods (automation-assisted, liquid-based; these are done in addition to the routine manual cytological screening) and by collecting the histologically confirmed findings from cytologically positive women. Biostatistical analyses are on-going. The preliminary results show that among the 2,032 women tested, the frequency of HPV positivity, including only the high-risk HPV types was 23%. This corresponds roughly the prevalence of cytologically positives with a cut-off ascus+. It is apparent that the HPV-DNA method used (hr HC II) detected all the CIN2+ lesions which were diagnosed subsequently to positive cytological results, and that the specificity of HPV test is comparable to cytological ascus+ findings.

In the HPV pilot study the sensitivity estimates of Papnet screening with agus+ or ascus+ cut-offs were almost as high as that of the HPV-DNA test with the cut-off 1 rlu/co. The sensitivity estimate of the liquid-based cytology was somewhat lower, however (data not shown). The specificity estimates both for Papnet and liquid-based cytology were almost the same as for the routine manual screening.

Planning on a large-scale human papillomavirus (HPV) based screening trial within the Finnish programme has proceeded along with the pilot results. We arranged a Nordic meeting to finalise the planning aspects. This means that we need to recruit some 40,000 women per year for five years duration of the randomisation period to obtain 80% statistical power to detect a hypothetical 50% decrease in the cancer risk after the screening visits (comparison to manual pap smear screening).

In **France** work was performed during the reporting period as follows:

- a historical comparison for each of the laboratories of the distribution of smear tests according to the cytological result during two 12-month periods before and after the introduction of the new technique. The training period of the thin layer technique of 6 months was excluded. A control group of laboratories still using conventional Pap was also included.
- a study of the positive predictive value of the thin layer method relative to conventional Pap smear for high-grade smears where the systematic taking of a histological sample is compulsory.

- the comparison of the degree of cytological-histological correlation for the two methods for low grade smears followed by histological examination. For those followed by cytology only, results of subsequent smears have also allowed a comparison of the two methods.

*Feasibility of thin layer technique:* The analysis of diagnostic performances of the methods was done regarding quality of the smear taker (medical speciality gynaecologist or GP and relative rate of inadequate smears).

*Obtained results:* Comparison of the distribution of smears tests according to the cytological results was done for the two laboratories (A and B). The work of the Control Group has also been performed as planned

- In laboratory A a number of 37,440 smears from the first period (i.e. 12 months before introducing the new technique) and a number of 38,222 smears from the second period (i.e. 12 months after introducing the new technique) were included in the study.
- In laboratory B a number of 8,759 smears from the first period and a number of 10,699 smears from the second period were included in the study.
- The Control Group has addressed a number of 39,442 smears from the first period, and 43,376 from the second period.

The preliminary study shows better diagnostic parameters for monolayers than for conventional pap smears. However, as the duration of the follow-up was longer for the later ones, we can not conclude at the moment which technique is better, and additional work is needed.

In Greece (Chalkidiki) experimental investigation of new screening technologies was performed in the reporting period in accordance with the planned activities. Estimations of the false-negative rate of Pap smears at the Center of Panagia Philanthropini cancer center vary according to the laboratory used, and a previous estimate of the false-negative rate ranged from zero to 29.7 percent. A 1999 technology assessment on the evaluation of cervical cytology screening was prepared for the Agency for Health Care Policy and Research (now known as the Agency for Healthcare Research and Quality). The study involved an exhaustive review of the accuracy of cervical cytology and new technologies. Unfortunately, the reviewers could not meet their objectives because of the lack of high-quality research. Sufficient precautions were taken to avoid bias in only three of 84 studies on cervical cytology. The sensitivity of the Pap smear in these three studies was relatively low (56, 53 and 29 percent), the test performed best in the detection of high-grade dysplasia, which is more likely to progress to cancer if left untreated.

*Improving Screening of pap-smears:* Measures to reduce errors were identified thorough the Center’s research and also in consultation with USA and European experts. A number of specific measures have been implemented to the degree that is feasible within the limited finances of the institution in order to correct the problem of false-negative Pap smears. These have included recommendations on the optimal technique in performing a Pap smear and improved methods to harvest cells from the
entire transformation zone (e.g., using a cytobrush with a plastic Ayre spatula). Cytopathology laboratories have been asked to establish procedures to optimize quality assurance. For example, lab chiefs were asked that the guidelines be implemented for workload limitations requiring a cytotechnologist to screen no more than 100 slides per day. Furthermore, 10 percent of all Pap smears read as “normal” must be manually re-screened.

→ **HPV Testing** was initiated to the degree that was economically feasible within the stringent budget and very limited resources of the Center. Research and literature searches performed this year yielded support for the strong relationship existing between infection with HPV and occurrence of cervical cancer and its precursors. Approximately 80 different types of HPV exist. These can be divided into high-risk HPV types (e.g., HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58) and low-risk types (e.g., HPV 6, 11, 42, 43 and 44). A number of studies have shown that women infected with HPV 16 or 18 have a higher rate of progression of cervical squamous intraepithelial lesions (SILs) to cancer. It has been hoped that the ability to identify patients with oncogenic HPV types will lead to improved detection in women more likely to have SILs. The potential value of HPV testing for cervical cancer and its precursors is based on this association.

→ **Hybrid Capture II** was used on a limited scale as the latest refinement of HPV tests and has been described as having enhanced sensitivity. Viewed as progressive since it can detect 13 high-risk types of HPV. The sample was collected with a cervical swab of the transformation zone and placed into transport medium. The test was also performed from residual material collected in liquid-based medium for monolayer preparation. In the laboratory, cellular DNA was denatured and mixed with a ribonucleic acid probe that binds only to HPV DNA. Antibodies coating the sides of the tube then captured the DNA “hybrid”. Next, a chemical is added, causing a chemo luminescent reaction. The amount of light that was measured was used to determine the presence of HPV and the viral load.

→ **Study on Thin Prep:** Initial studies and searches conducted on Thin Prep, suggested most of the increased sensitivity can be accounted for by an increase in the diagnosis of LSIL. There is controversy about whether patients significantly benefit from the detection of more low-grade lesions, which frequently regress without treatment. Papnet was used as a quality control measure with 5% of randomly selected smears being read. The high cost within the Greek private health system of this procedure has encouraged the Center to look beyond Greece for other European Centers that could perhaps provide this service for a decreased fee.

→ **Study for women with ASCUS:** Research conducted by Center staff regarding the ALT5 trial for women with ASCUS is still under investigation. A recent study reported the usefulness of HPV testing in women with ASCUS. In the literature HPV testing was reported as being done by reflex testing from Thin Prep fixative. Women who had ASCUS were selected from a large cohort who had routine Pap testing. All of the women had liquid-based cytology, HPV testing and subsequent repeat Pap tests and colposcopy including histological evaluation. Of 973 women who were eligible, 65 (6.7 percent) had histological high-grade squamous intraepithelial lesions or cancer. In these women, the HPV test had a sensitivity of 89.2 percent and a specificity of 64.1 percent. Other studies have shown sensitivities of approximately 90 percent or more for the second-generation HPV test. However, concern has been raised about its false-positive rate, which has ranged from 5 to 20 percent. The Center staff monitors developments
and reports on a regular basis. Researchers reviewed the results of nine studies that used Hybrid Capture II. The authors found no advantage of HPV testing over repeat Pap smear follow-up, although the analysis did not directly compare repeat cytology and HPV testing. This analysis also includes an analysis of HPV Profile testing, which has been shown to have low sensitivity and is not used.

In Portugal a combined study was performed, Pap smear by ThinPrep Method and HPV testing, over a period of one year on women whose first cytological test was done within the Cervical Cancer Screening Programme of the Central Zone of Portugal and whose smears result in the cytological diagnosis of ASCUS/AGUS. The objective was to find criteria for the selection of patients to be referred for colposcopy, in order to establish a suitable follow-up, avoiding over-diagnosis and unnecessary treatment, thus making the process more cost-efficient.

The study took place in 17 counties of the Central Zone that are remote from urban centres and whose health-care systems are not yet incorporated into the Cervical Screening Programme, meaning that screening is only done occasionally and on a small scale. The target population are women aged between 20 and 64, those under 20 who have already had sexual intercourse, and those over 64 that have not had previous cytological tests. Excluded from the study are women who have had hysterectomies and those with previous diagnoses of intra-epithelial lesions or cervical carcinoma.

The slides are prepared with the ThinPrep 2000 device, and screened and classified according to the Bethesda System. All the smears classified as ASCUS or AGUS are reviewed by two cytopathologists, submitted to a HPV test with Hybrid Capture II (HCH) and referred for colposcopy.

The colposcopies were done by the same two Gynaecologists, experts in Colposcopy. The biopsies are also studied by two pathologists expert in cervical pathologies. During the reporting period we have screened 38,901 women independently of the phase of the programme.

→ Cytological results

<table>
<thead>
<tr>
<th>RESULTS</th>
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<tbody>
<tr>
<td>UNSATISFACTORY</td>
<td>0.69%</td>
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<tr>
<td>NORMAL</td>
<td>85.35%</td>
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<tr>
<td>INFLAMMATORY</td>
<td>9.9%</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>3.1%</td>
</tr>
<tr>
<td>LGSIL</td>
<td>1.7%</td>
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<tr>
<td>HGSIL</td>
<td>0.32%</td>
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<tr>
<td>INVASIVE</td>
<td>0.05%</td>
</tr>
<tr>
<td>CARCINOMA</td>
<td></td>
</tr>
<tr>
<td><strong>Number of Smears</strong></td>
<td><strong>38,901</strong></td>
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</tbody>
</table>

The number of unsatisfactory smears seems lower but they don’t reflect the unsatisfactory smears obscured by inflammation. These cases are included in the inflammatory category that need to repeat the smear after treatment.

→ HYBRID CAPTURE II results
In this time we performed for 832 women the HPV TEST by HYBRID CAPTURE II. We realised the test not only in cases classified as ASCUS, but also in some NORMAL, LGSIL and recidive of squamous carcinoma and adenocarcinoma, and we found the following results:

<table>
<thead>
<tr>
<th>TOTAL CASES</th>
<th>832</th>
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<tbody>
<tr>
<td>AGE &gt; 20 and &lt; 78</td>
<td></td>
</tr>
<tr>
<td>NORMAL -- 200</td>
<td>AR+ 48</td>
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<tr>
<td>ASCUS -- 380</td>
<td>AR+ 130</td>
</tr>
<tr>
<td>LGSIL -- 245</td>
<td>AR+ 152</td>
</tr>
<tr>
<td>CARCINOMA/RECIDIVE -- 7</td>
<td>AR+ 7</td>
</tr>
</tbody>
</table>

In Sweden the experimental work on the HPV treatment methods was continued. The evaluation of the treatment methods is also relevant to Part 2.

A cohort of 109 women with cervical intraepithelial neoplasia, referred for treatment have been followed with repeated HPV tests at 0, 3, 6, 9 and 12 months post treatment, some women even 24 months post treatment. The results show that HPV is quickly cleared after surgical treatment for CIN, usually after 3 months. HPV is cleared more quickly among women treated with conization than among women treated with cryotherapy. During the autumn 2002, the 109 women in this cohort were called back for one additional, late follow-up HPV test.

In the ongoing population-based HPV screening trial, 180 women with screen-detected persistent HPV infection have been referred to colposcopy and treated during the term of the contract. Digital images of the cervical lesions were recorded using computerized colposcopes. The data from the colposcopy visits are being put together to a scientific manuscript (Elfgren et al), but it is not yet ready to be enclosed. Samples for HPV testing have been taken, but analyses are not finalised as yet.

Two cohorts of women treated for CIN with different methods (conization or loop electrosurgical procedure) to compare the different methods for HPV treatment was started.

- Cohort enrolled 37 women who were referred for treatment of CIN. As a pilot study to see whether using the more simple loop electrosurgical excision procedure (LEEP) was also effective, the HPV clearance rate after treatment with LEEP was determined. The results showed a 96% clearance rate already after 3 months, which was even better than previously reported for the carbondioxide conization.

- Cohort 2 had during the time of the contract enrolled 84 women who were referred for treatment with CIN. The women were randomised to treatment with either loop electrosurgical excision procedure or to conisation. Another 116 women will be enrolled into the cohort before the study is closed. During the time of the contract HPV testing and analyses of the data was completed for the pre-treatment samples of the first 64 women. Although all women enrolled into the study had had CIN as a reason for referral, on the date of treatment 19/68 women had a normal smear. Spontaneous regression and/or removal of the lesion by the diagnostic biopsy are possible reasons for this finding. As expected, 86% of women who still had a dysplastic smear were HPV-positive. As expected, HPV-positivity correlated strongly with presence of a dysplastic smear (OR: 19.5 (CI: 4.8-86.9).
Dissemination of the Network Results via WEB FORUM
(Part 4)

Performed work: Development and use of WEB FORUM, the communication platform for teamwork, discussions and dissemination of the network results in Internet.

Participants: Belgium, Finland, France, Germany, Greece (Athens, Chalkidiki), Holland, Italy, Portugal, Slovenia, Spain, Sweden

Individual Member State Projects
All individual projects have access to WEB FORUM. Discussions within the project team improve the team work. Dissemination of the obtained project results is performed world wide, and facilitates the feedback from a large number of specialists in cervical screening.

Previous work
The project WEB was developed and installed in the previous period (August 1999 to December 2000) at the Co-ordination Centre in Germany, and a WEB FORUM prototype was installed (http://www.cancer-network.de)
The integration of the web sites of the European Breast Cancer Network and of the European project VIDEOCOM (Video-communication workplace) was performed with the aim of promoting the co-operation with these European projects, and for providing a direct access world-wide of the medical staff via Internet to the project results.
The Network results were made available to the specialists in international conferences and medical journals and books by 78 publications (41 publications from Germany, 21 from Belgium, 4 from Finland, 9 from Italy, and 3 from Sweden).

Development work in reporting period
The software development work performed by the Co-ordination Centre during the reporting period (16. December 2000 to 15. December 2001) is as follows:

- development of protection procedures in order to protect the "write access",
- improvement of the access pad to the forum data,
- development of multilingual facilities,
- topic-oriented structuring of forum information,
- implementation of facilities for supporting images and voice data.

Services of WEB FORUM facilities:

- Multilingual access in 6 languages
- Installation of the "access permission codes" for network administration
- Installation of the administrative data and financial data
  (the financial data was in the audit of the project SI2.168540(2000CVF2-002)
- Starting discussions between the team members and European specialists
- Providing information about the project activities, congresses, etc.
- Collecting continuously information about the performed work of the partners
- Dissemination of project results and obtaining feedback via Internet.

The Network results were made available to the specialists in international conferences and medical journals and books by 44 publications (20 publications from Germany, 15 from Belgium, 1 from Finland, 3 from France, 2 from Italy, and 3 from Sweden).
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