## Final Report

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### Participants:

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<tr>
<th></th>
<th>Country</th>
<th>Institution</th>
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<tbody>
<tr>
<td>1.</td>
<td>GERMANY</td>
<td>Cytological Institute of the Bavarian Cancer Society, Munich (Co-ordinator)</td>
</tr>
<tr>
<td>2.</td>
<td>BELGIUM</td>
<td>Scientific Institute of Public Health, Brussels</td>
</tr>
<tr>
<td>3.</td>
<td>FINLAND</td>
<td>Finnish Cancer Registry, Helsinki</td>
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<td>4.</td>
<td>FRANCE</td>
<td>Association EVE, Strasbourg</td>
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<td>5.</td>
<td>GREECE</td>
<td>Hellenic Society of Oncology, Athens</td>
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<td>GREECE</td>
<td>Our Lady Who Loves Mankind, Chalkidiki</td>
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<td>7.</td>
<td>HOLLAND</td>
<td>University of Nijmegen, Nijmegen</td>
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<tr>
<td>8.</td>
<td>ITALY</td>
<td>Unit of Cancer Epidemiology, Turin</td>
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<tr>
<td>9.</td>
<td>PORTUGAL</td>
<td>Regional Oncology Centre, Coimbra</td>
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<tr>
<td>10.</td>
<td>SPAIN</td>
<td>Health and Social Welfare Council, Valladolid</td>
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<tr>
<td>11.</td>
<td>SWEDEN</td>
<td>Karolinska Institute Microbiology and Tumor Biology Centre</td>
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15. February 2002

Signature of the Co-ordinator
Prof. Dr. med. Ulrich Schenck

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ANNEXES attached (665 pages):

Final Report No. 1 Germany: Cytological Institute of BKG, Munich (226 pages)
Final Report No. 2 Belgium: Scientific Inst. of Public Health, Brussels (137 pages)
Final Report No. 3 Finland: Finnish Cancer Registry, Helsinki (12 pages)
Final Report No. 4 France: Association EVE, Strasbourg (13 pages)
Final Report No. 5 Greece: Hellenic Society of Oncology, Athens (6 pages)
Final Report No. 6 Greece: Our Lady Who Loves Mankind, Chalkidiki (15 pages)
Final Report No. 7 Holland: University of Nijmegen, Nijmegen (93 pages)
Final Report No. 8 Italy: Unit of Cancer Epidemiology, Turin (25 pages)
Final Report No. 9 Portugal: Regional Oncology Centre, Coimbra (8 pages)
Final Report No. 10 Spain: Health and Social Welfare Council, Valladolid (30 pages)
Final Report No. 11 Sweden: Karolinska Institute, Stockholm (35 pages)
Final Report No. 12 Slovenia: Institute of Oncology, Ljubljana (65 pages)
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 smear 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 "New Technologies". 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
c 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
thorugh 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 ALTS 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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UNSATISFACTORY</td>
<td>0.69%</td>
</tr>
<tr>
<td>NORMAL</td>
<td>85.35%</td>
</tr>
<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>
</tr>
<tr>
<td>HGSIL</td>
<td>0.32%</td>
</tr>
<tr>
<td>INVASIVE CARCINOMA</td>
<td>0.05%</td>
</tr>
<tr>
<td>Number of Smears</td>
<td>38.901</td>
</tr>
</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>
</tr>
</thead>
<tbody>
<tr>
<td>AGE &gt; 20 and &lt; 78</td>
<td></td>
</tr>
<tr>
<td>NORMAL -- 200</td>
<td>AR+ 48</td>
</tr>
<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).
2. Planned Work

2.1 Planned Part 1: "Quality Assurance and Quality Control"

Objective: to develop quality assurance and quality control tools and to evaluate their impact on cervical screening in respect to their efficiency and costs.
Leader: Prof. Ulrich Schenck

The work is here focussed on continuous analysing, measuring, correcting and improving the methods, techniques and tools in both organisational and technical processing in the health services related to the cervical cancer screening activities. The aim is to improve the detection and correction of errors, and also to establish higher quality standards in cervical cancer screening.

Quality is here ensured by the complementary activities on
- QC-Quality Control,
- QA – Quality Assurance,
- TQM – Total Quality Management.

with the aim of ensuring a highly qualitative cytological outcome in form of patient care and consumer protection.

Quality Control focuses on the outcome, and is concerned with the measurement and evaluation of the technical quality of the products, e.g. slides or test results falling within the pre-established tolerance limits. Quality Assurance aims of improving the quality of the screening activities by using innovative methods, techniques and tools which allow to improve the quality of the screening processes, and in this way also to increase the quality of the screening outcome. The Total Quality Management is a novel approach which uses the milestone-oriented approach in managing the quality of the screening process with the aim of measuring and improving the quality of the intermediate screening results by improving the skills of the persons involved in the production or test activities.

Following project partners will participate to the Quality Control and Quality Assurance activities:
- BELGIUM: Scientific Institute of Public Health – Louis Pasteur
- GERMANY: Cytological Institute of the Bavarian Cancer Society
- GREECE: Hellenic Society of Oncology, Athens
- GREECE (Ormylia-Chalkidiki): Our Lady Who Loves Mankind
- HOLLAND: University of Nijmegen,
- ITALY: Unit of Cancer Epidemiology, Turin, and
- SLOVENIA: Institute of Oncology, Ljubljana (external budget).
- SPAIN Health and Social Welfare Council, Junta de Castilla y León, Valladolid
Individual Member State Projects

BELGIUM: Scientific Institute of Public Health – Louis Pasteur

Quality assurance in the cytological screening for cervical cancer is one of the priorities of the Europe Against Cancer Programme. The optimisation of the quality of cytological screening of conventional Pap smears is the study object of an on-going research project, co-funded by Europe Against Cancer. In the current proposal the gain in diagnostic performance of thin layer liquid based cytology coupled with ancillary HPV DNA will be studied. In particular this study will determine how the sensitivity of cervical cancer screening can be optimised by better sampling procedures and complimentary HPV detection, and how the specificity, costs and follow-up are influenced by these new technologies.

GERMANY: Cytological Institute of the Bavarian Cancer Society

The planned work has two main objectives:

i) to improve the quality control and quality assurance, and to evaluate their impact on cervical cancer screening process.

ii) to update the European Guidelines for Quality Assurance in Cervical Cancer Screening.

The improvement of the quality control and quality assurance tools is the first objective of the planned work in the period December 2000 to December 2001. During the previous project (August 1999 to October 2000) a new type of cytology laboratory organisation based on the ‘HOME’ microscope has been developed, as an economical alternative to automated quality control of screening, offering the structure for optimised man machine interaction. This model was presented to other European cytology laboratories and has contributed to decrease the costs of the quality improvement and consumer protection, also allowing the Pap smear to become available to an increasing number of women in Europe. The development work for improving the defined tools will be started in December 2000 as follows:

• the study "Selecting efficient tools for Quality Assurance and Control" will be released in March 2001,

• the study "Continuous grading systems for the diagnosis of intraepithelial lesions – a contribution for overcoming problems of translating among different terminologies" will be released in May 2001,

• the implementation of new tools into routine procedures will be started in June 2000 and finished in December 2001

The update of the European Guidelines for Quality Assurance in Cervical Cancer Screening is the second objective of the planned work in the period December 2000 to December 2001. During the previous project (August 19999 to October 2000) several meetings were organised, and important updates to the European Guidelines for Quality Assurance were suggested. Extensive use of Internet-based communication between collaborating
groups in Member States will be used starting with **December 2000** in order to promote
and the consensus process and to reach an agreement with the European specialists
working in this field. The work will be structured as follows:

- The basic concept for the updating process of the European Guidelines for Quality
  Assurance in Cervical Cancer Screening will be worked out until **February 2001**.
- suggested updates in the previous project period November-December 2000 will be
- A "priority update list" of the European Guidelines for Quality Assurance in
  Cervical Cancer Screening will be provided and made available on WEB FORUM
  starting with **April 2001**.
- The world wide access to WEB FORUM via Internet will allow an open discussion
  between the project participants, and also integrate the feedback from a large
  number of specialists outside of the project.
- The first draft of the "Updated European Guidelines for Quality Assurance in
  Cervical Cancer Screening" will be available in **December 2001**.

**GREECE: Hellenic Society of Oncology, Athens**

During this round (Phase V) of the programme the main objectives will be:

i) Implementation part of the 5th round of the screening programme in Ilia, and
   part of the 4th round of the screening programme in Messinia.
ii) Dispatch to the National Cancer Registry of the Greek Ministry of Health of all
    HPV, CIN 1, 2, and 3 cases that will be registered.
iii) Maximise the participation rate of the target population (age 25 to 64 years)
iv) Ensure that all staff of the programme receive proper training.
v) Follow-up of the women with non negative smears (HPV, CIN 1, 2, 3, invasive
    cancer) through the Study Unit that is located in the central offices of the
    Hellenic Society of Oncology Optimise cervical cancer early diagnosis.
vi) Analysis and publication of the obtained results on the WEB FORUM

**GREECE (Ormylia-Chalkidiki): Our Lady Who Loves Mankind**

The objectives during the current phase of the cervical cancer quality assurance
programme in Ormylia-Chalkidiki are as follows

i) to continue to update the target population census of the programme by creating
   in Cupertino with political, social and religious leaders catalogues of population
data and cross-checking them to increase participation and target out reach
populations in the region. The out reach methodology is aimed at the more rural
and uneducated communities in Northern Greece.
ii) to continue to closely follow-up all women tested positive and regularly update
    their screening files with all available data on further assessment and treatment;
iii) conduct a reliability study of smear reading on a random sample of Pap-smear
    test
iv) implement the new method (Thin Prep 2000) to prepare and analyse the smear
    test in a small sample of the screened women, in conjunction with conventional
    PAP-smear test
v) to conduct a study combining liquid cytology, artificial intelligence cytology and DNA analysis for HPV in a 1.000 patient sample in order to assess the effectiveness of this diagnostic application in screening, and early detection for Cervical Cancer, and also the feasibility of the combination of these new and promising technologies within the Center Ormylia's setting. If this new system of cervical cancer diagnosis proves effective, cohesive and feasible, it may be used as model for other centres within the European network for early detection of cervical cancer, and in other European cancer control centres.

vi) publish the project results on the WEB FORUM and discuss the merits and limitation of the new technologies within the cytology scientific community.

HOLLAND:
University of Nijmegen, University Medical Centre St Radboud, Department of General Practice in co-operation with the Centre for Quality of Care research (WOK).

The objective of the project is to implement an optimal 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.

The specific aim of this project is to assess 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 (1) follow-up monitoring by the cytological laboratory or (2) follow-up monitoring by general practice or smear-taker in general and, in the case of moderate severe abnormalities, a reminder by the laboratory. The most cost-effective system to improve the follow-up will be disseminated and implemented at national and European level.

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 will be elaborated and formulated in tools like questionnaires and other instruments. The questionnaires, for those involved in the screening activities will, for example, contain questions concerning current practices, and barriers to and facilitators for implementation. Another example of a tool that will be 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.
The tools will be tested in those regions in the Netherlands that are interested in implementing our system. The outcomes of our assessment will support these regions by indicating those preconditions that first have to be met before it is possible to implement the communication system. Following this pilot testing of the measurement instruments, the tools will be translated and disseminated to those countries in Europe that are interested in implementing the communication system. With these instruments, the countries can systematically detect the absence of preconditions, and – with this knowledge – they can first work on meeting these preconditions before implementing and adapting our system to their conditions and cultures. Countries that are qualified for implementation of this system include the UK, Denmark and Ireland.

ITALY: Unit of Cancer Epidemiology, Turin

The aims of the work performed in this project are:

i) Monitoring the values of process indicators for cervical cancer screening in different screening programmes in Italy,

ii) Comparing indicators and standards to those of the UK NHSCSP system of indicators

iii) Improving methods of data collection and analysis for cervical cancer screening evaluation

iv) Identifying problematic areas

v) Proposing actions to improve them

SLOVENIA: Institute of Oncology, Ljubljana

The aims of this project activities are:

i) to evaluate the performance of four laboratories that are currently involved in the pilot study of organised cervical cancer screening.

ii) to evaluate and when necessary revise existing guidelines for reporting cervical smears.

A special committee of specialists in cytopathology from Slovenia (with one participant from another Member State) will be brought together to re-screen all non-negative smears (expected number 600 to 800) and a random sample of the same number of negative smears. Agreement in diagnoses would be analysed for smear adequacy and epithelial changes by Statistics and the appropriateness of newly established, diagnostic criteria and classification evaluated together with the new reporting form that will be introduced nationally.

SPAIN Health and Social Welfare Council, Junta de Castilla y León, Valladolid

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. Smear tests will be performed and analysed, and information will stored together with diagnosis data. Appropriate evaluation parameter will be used for the Quality Control of the tests, and the results will be made available to the GPs of these regions.
2.2 Planned Part 2: "Monitoring, Epidemiology and Evaluation"

Objective: Long-term monitoring and epidemiological evaluation of the cervical screening in several European regions, with the objective of establishing realistic results outcome indicators, and to estimate costs, benefits and adverse effects.

Leader: Dr. A. Anttila

Following project partners will participate to these activities:
- BELGIUM Scientific Institute of Public Health – Louis Pasteur
- FRANCE Association EVE, Strasbourg
- GREECE: Hellenic Society of Oncology, Athens
- HOLLAND: University of Nijmegen,
- ITALY: Unit of Cancer Epidemiology, Turin,
- SLOVENIA: Institute of Oncology, Ljubljana (external budget).
- SPAIN Health and Social Welfare Council, Junta de Castilla y León, Valladolid
- SWEDEN: Karolinska Institute Microbiology and Tumor Biology Centre

Individual Member State Projects

BELGIUM: Scientific Institute of Public Health – Louis Pasteur

i) Continue the activities of the Working Party for Uniformisation of Cytology and the Research Working Party, supported in the past by Europe Against Cancer.
ii) Organise a Symposium on Cervical Cancer Screening by the Belgian Society of Clinical Cytology.
iii) 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 update 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.

FRANCE: Association EVE, Strasbourg

The aim of the project is to evaluate the thin layer technique which is used as common practice within the framework of the campaign for cervical cancer screening in the Bas-Rhin region.

As now, this method has been essentially evaluated in Research laboratories. This study will include private non academic laboratories which are the most common in France

Methods: The EVE Association, which manages the campaign for cervical cancer screening in the Bas-Rhin region, collects the results of all the smear tests carried out on women aged between 25 and 65 living in the region (approximately 100 000 smears per year). It ensures that abnormal smears are followed up and analyses data. Two
laboratories which participate in the EVE screening campaign have been using a monolayer technique as common practice since 1999. One laboratory, which carries out 37% of the smear tests in the campaign, uses the Autocyte Prep method, and the other, which carries out 9% of the smear tests, uses the SEROA laboratory’s Cyteasy method.

Evaluation of the diagnostic performance of the two monolayer methods will involve:

i) 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 will be excluded. A control group of laboratories still using conventional Pap will be also be included.

ii) 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.

iii) A 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 will also allow a comparison of the two methods.

iv) The staff will do its best to realise for ASCUS smears the same study as for low grade smears.

Within the framework of the EVE campaign, a systematic comparison of the cytological data and the histological examinations allows for a register to be made of women who have suffered a severe cervical lesion (at least CIN 3) within three years of a normal smear test or a smear showing inflammation. In the long-term it will be possible to determine if the rate of cytological and histological lesions appearing within three years drops with the monolayer method relative to the conventional method.

Feasibility of thin layer technique: As this method has to be used as common practice, laboratories will be asked about the possibility for every smear taker to use this method especially for GPs living far from the laboratory.

The analysis of diagnostic performances of the methods will be done regarding quality of the smear taker (medical speciality: gynaecologist or GP and relative rate of inadequate smears).

Planned results: Comparison of the distribution of smears tests according to the cytological results will be done for the two laboratories using liquid based cytology within 3 months. The same results will be obtained for the control group after 6 months. After 1 year, studies of positive predictive value and degree of correlation of histological and cytological results for the two methods will be achieved and cytological abnormalities appeared within 1 year after normal smears will be registered. Incidence of interval lesions will need to have 3 years survey time to be finished.
GREECE: Hellenic Society of Oncology, Athens

During this round (Phase V) of the programme the main objectives will be:

i) Implementation part of the 5th round of the screening programme in Ilia, and part of the 4th round of the screening programme in Messinia.

ii) Dispatch to the National Cancer Registry of the Greek Ministry of Health of all HPV, CIN 1, 2, and 3 cases that will be registered.

iii) Maximise the participation rate of the target population (women aged 25 to 64 years).

iv) Ensure that all staff of the programme receive proper training.

v) Follow-up of the women with non negative smears (HPV, CIN 1, 2, 3, invasive cancer) through the Study Unit that is located in the central offices of the Hellenic Society of Oncology.

vi) Optimise cervical cancer early diagnosis.

vii) Analysis and publication of our results.

HOLLAND:
University of Nijmegen, University Medical Centre St Radboud (WOK).

The specific aim of this project is to assess 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 (1) follow-up monitoring by the cytological laboratory or (2) follow-up monitoring by general practice or smear taker in general and, in the case of moderate severe abnormalities, a reminder by the laboratory. This most cost-effective system to improve the follow-up will be disseminated at national and European level. 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 will be elaborated and formulated in tools like questionnaires and other instruments. The questionnaires, for those involved in the screening activities will, for example, contain questions concerning current practices, and barriers to and facilitators for implementation. Another example of a tool that will be 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.

The tools will be tested in those regions in the Netherlands that are interested in implementing the most cost-effective system. The outcomes of our assessment will support these regions by indicating those preconditions that first have to be met before it is possible to implement the communication system. Following this pilot testing of the measurement instruments, the tools will be translated and disseminated to those countries in Europe that are interested in implementing the communication system. With these instruments, the countries can systematically detect the absence of preconditions, and – with this knowledge – they can first work on meeting these preconditions before implementing and adapting our system to their conditions and cultures. Countries that are qualified for implementation of this system include the UK, Denmark and Ireland.
ITALY: Unit of Cancer Epidemiology, Turin

The main aim of this project is to monitor the value of process indicators for cervical cancer screening in different screening programmes in Italy. In Italy an Italian Group for Cervical Cancer Screening (GISCI) was founded in 1996. In 1997 it conducted a first survey of organised screening programmes, mainly considering organisational features. It identified 29 active programmes, with a target population of about 2 million women (data in the press).

The present project will continue to identify problem areas in these programmes and start 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 will also provide an estimate of short-term variations of such indicators and of their reasons. This will allow for improved methods of data collection and analysis for cervical cancer screening evaluation. The project will involve collaboration with colleagues from the Netherlands and the UK.

SPAIN  Health and Social Welfare Council, Junta de Castilla y León, Valladolid

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. Appropriate evaluation parameter will be used, and statistical information will be worked out. All women of these regions will be invited to smears tests, and a sound epidemiological results are expected in this project.

SLOVENIA  Institute of Oncology, Ljubljana

With respect to specific tasks in Slovenia the following timetable is planned:
- Meeting of the working group to prepare the final protocol for the study and to co-ordinate with the activities in the frame of the network (until January 2001).
- Re-screening by the panel of three experts of approximately 800 non-negative smears and a random sample of the same number of negative smears from four cytology laboratories in Ljubljana region (from February to May 2001).
- Statistical analyses of the obtained results and presentation of the achievements on the WEB FORUM (until July 2001).
- Revaluation of reporting system and standards for quality assurance and control in cytology laboratories developed in the frame of the pilot study to implement national reporting system (from August to November 2001).
- Final report of the obtained results. Two visits to centres participating in the network are planned in order to present and discuss the obtained results (December 2001)
SWEDEN: Karolinska Institute Microbiology and Tumor Biology Centre

The aim of this project is to evaluate the efficacy of different methods of treatment of papilloma virus infection detected by an organised screening programme. As part of the proposal, it is intended to assess:

i) the population-based prevalence of transient and persistent HPV infections within an age stratum where implementation of HPV screening is conceivable; and

ii) whether treatment of atypias detected among HPV-positive women referred to colposcopy results in a reduced incidence of high-grade dysplasia in the next organised round of cytological screening 3 or 5 years later.

It is expected that this project will determine whether:

i) several of the commonly used modalities will the treatment of cervical dysplasia are also effective treatment of HPV infection

ii) quantify the efficacy in terms of both the proportion of women clearing HPV DNA and the length of time elapsing between treatment and clearance

iii) revise guidelines for treatment of screen detected HPV cervical infection

iv) determine the feasibility of whether a randomised trial with the immunostimulatory drug imiquimod should be started.

The project will involve collaboration with colleagues from the Netherlands (reference HPV laboratory), Norway (cytological revaluation of slides taken before and after treatment) and the UK (exchange information and experience at the pan-European level).

2.3 Planned Part 3: "New Technologies in Cervical Screening"

Objective: Continuous incorporation of technical innovation will allow to improve continuously the quality of the European cervical screening. Investigation of technological innovation. The results will help to determine the diagnostic parameters of new technologies in cervical screening in terms of sensitivity, specificity, predictive values and reproducibility.

Leader: Dr M. Arbyn

The work will be concentrated on following topics:

1. Identification of new technologies which require evaluation.
2. Identification of recent key literature containing reviews, meta-analyses, general policy statements concerning new methods/techniques applicable in cervical cancer screening and follow-up.
3. Recapitulation of the current status of the knowledge concerning the identified new techniques; proposition for new research.
4. Additional systematic literature review and meta-analyses on appropriate topics where this is not yet done recently.
5. Promote future research of high quality at sub-national, national and international level.
6. Promote international collaboration in general and within the Network in particular.
7. Identify and apply models which allow the translation of diagnostic outcomes of test evaluation in public health outcomes (prevention of invasive cancer, life-years gained, improvement of quality of life)

Following project partners will participate to these activities:
- BELGIUM Scientific Institute of Public Health – Louis Pasteur
- FINLAND: Finnish Cancer Registry, Helsinki
- FRANCE Association EVE, Strasbourg
- GREECE (Chalkidiki): Our Lady Who Loves Mankind
- PORTUGAL Centro Regional de Oncologia Coimbra
- SWEDEN: Karolinska Institute Microbiology and Tumor Biology Centre

Individual Member State Projects

BELGIUM: Scientific Institute of Public Health – Louis Pasteur

The main aim is to evaluate the potential gain of sample quality and diagnostic validity of thin layer cytology combined with and so the HPV DNA detection using the Hybrid Capture kit in comparison with the classical Pap smear. The strategy for follow-up of screen detected low-grade abnormalities will be fine-tuned by differentiating the management according to virological status. The quality of the collected cellular material is one of the main issues that determine the diagnostic validity of the Pap test. The results they cost benefit analysis will enable cytological laboratories and clinicians involved in cervical cancer screening to choose rationally between different screening methods.

The study will assess how the sensitivity of cervical cancer screening can be optimised by better sampling procedures and complimentary HPV detection. It will evaluate the potentials and costs of different screening methods or combination of the following methods:
   i) conventional Pap smear.
   ii) thin layer cytology using the Autocyte device.
   iii) HBV DNA detection using the Hybrid Capture technique.

FRANCE: EVE Association

The aim of the project is to evaluate the thin layer technique which is used as common practice within the framework of the campaign for cervical cancer screening in the Bas-Rhin region. The EVE Association, which manages the campaign for cervical cancer screening in the Bas-Rhin region, collates the results of all the smear tests carried out on women aged between 25 and 65 years resident in the region (approximately 100,000 per year). It ensures that abnormal smears are followed up and has access to information technology resources allowing for the processing of the data.

Two laboratories which participate in the EVE screening campaign have been using a monolayer technique is common practice since 1999. One laboratory, which carries out
37% of the smear tests in the campaign, uses the Autocyte Prep method, and the other, which carries out 9% of the smear tests, uses the SEROA laboratory’s Cyteasy method. Evaluation of the diagnostic performance of the two mono layer methods will involve:

i) 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.

ii) 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.

iii) A comparison of the degree of correlation between the two methods for low grade smears followed by histological examination.

Within the framework of the EVE campaign, a systematic comparison of the cytological data and the histological examinations allows for a register to be made of women who have suffered a severe cervical lesion (at least CIN 3) within three years of a normal smear test or a smear showing inflammation. In the long-term it will be possible to determine if the rate of lesions appearing within three years drops with the mono layer method relative to the conventional method.

GREECE (Chalkidiki): Our Lady Who Loves Mankind

During the current phase of the cervical cancer quality assurance programme in Ormylia-Chalkidiki the aim is to:

i) implement the new method (Thin Prep 2000 system) to prepare and analyse the smear test in a small sample of the screened women in conjunction with the conventional PAP-smear test;

ii) conduct a study to determine the prevalence of HPV infection in a sub-sample of the screened population.

iii) explore new technology in creating a communications link with European centres of excellence in the UK and Germany via the Internet.

iv) Published a web page on the Internet with the findings and results of the programme as a reference for the cytology scientific community.

FINLAND: Finnish Cancer Registry, Helsinki

This project will continue to evaluate the performance of automation assisted devices in the organised Pap screening programme, and plan for a large-scale pilot study of HPV DNA testing in cervical cancer screening. Hence it is intended to:

i) continue a randomised trial with the neural network assisted analysis tool, Papnet, using 40,000 smears per year taken in the Finnish cervical cancer screening programme.

ii) Plan for continuation to test other automation-assisted or liquid-based smear technologies.

iii) Plan to start a large-scale pilot of HPV DNA testing in cervical cancer screening and organise a trial arm on HPV screening.
This project is part of a multi-arm trial on the evaluation and new cervical cancer screening methods in the Nordic states, and will involve collaboration between Member States of the EU.

PORTUGAL Centro Regional de Oncologia Coimbra

This project is part of a multi-arm trial on the evaluation and new cervical cancer screening method, and will involve collaboration between Member States of the EU.

The aim of this project is to undertake a combined study, Pap smear by ThinPrep Method and HPV testing, over a period of a year on women whose first cytological test will be done within the Cervical Cancer Screening Programme of the Central Zone of Portugal and whose smears result in the cytological diagnosis. The objective is 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 will be made 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 smears are taken by GPs after a gynaecological examination, using the Cervex-Brush that is rinsed directly into PreservCyt vials and sent to the Cytopathology Laboratory of the Cancer Institute. 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 will be done by the same two Gynaecologists, experts in Colposcopy. The biopsies are also studied by two pathologists expert in cervical pathologies.

SWEDEN Karolinska Institute Stockholm and University Hospital of Northern Sweden

The aim is to investigate the feasibility and effectiveness of screening for Human Papillomavirus (HPV) infection within an organised cervical cancer screening programme:

i) the population-based prevalence of transient and persistent HPV infections within an age stratum where implementation of HPV screening is conceivable; and

ii) whether treatment of atypias detected among HPV-positive women referred to colposcopy results in a reduced incidence of high-grade dysplasia in the next organised round of cytological screening 3 or 5 years later.
It will also investigate whether additional application of the immunostimulatory drug imiquimod, recently licensed for treatment of genital warts, can be used to improve the proportion of women clearing HPV DNA and/or shortening the time until HPV clearance, and therefore shortening the time required for follow-up. The project will involve collaboration with colleagues in the Netherlands, Finland and the UK.

2.4 Planned Part 4: "Web Forum for Info Dissemination"

Objective: Development and use of WEB FORUM, the communication platform for teamwork, discussions and dissemination of the network results in Internet.
Leader: Prof. Schenck (Co-ordination Centre)

All project partners will participate to these activities:
- BELGIUM Scientific Institute of Public Health – Louis Pasteur
- FINLAND: Finnish Cancer Registry, Helsinki
- FRANCE Association EVE, Strasbourg
- GERMANY: Cytological Institute of the Bavarian Cancer Society
- GREECE: Hellenic Society of Oncology, Athens
- GREECE (Ormylia-Chalkidiki): Our Lady Who Loves Mankind
- HOLLAND: University of Nijmegen.
- ITALY: Unit of Cancer Epidemiology, Turin
- PORTUGAL Centro Regional de Oncologia Coimbra
- SLOVENIA: Institute of Oncology, Ljubljana (external budget).
- SPAIN Health and Social Welfare Council, Junta de Castilla y León, Valladolid
- SWEDEN: Karolinska Institute Microbiology and Tumor Biology Centre

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

The services provided by the WEB FORUM are as follows:
iii) Installation of the "access permission codes" for all project participants (December 2000)
iv) Installation of the administrative data and financial data (January 2001)
iv) Installation of the detailed description of the project workpackages (February 2001)
vi) Starting discussions between the team members and European specialists (January 2001)
vi) Providing information about the project activities (January 2001-December 2001)
viii) Collecting continuously information about the performed work within the 3 Parts of the project
ix) Presenting published documents and reports of the project partners
x) Obtaining the opinion and suggestions of experts from the outside world of the project about the disseminated information

A modest Forum was developed during the previous project (August 1999 to December 2000) and additional software development work will be performed by the Coordination Centre during this project (December 2000-December 2001).

The planned software development work is structured as follows
• development of protection procedures in order to protect the "write access" to the forum data, and to avoid that data will be disrupted. (January-March 2001)
• improvement of the access pad to the forum data (April-May 2001)
• study of the long-term development of multilingual facilities (June-August 2001)
topic-oriented structuring of forum information, and implementation of facilities for supporting images and voice data (June-December 2001)
3. Obtained Results

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.

Infection with the human papillomavirus (HPV) has been established as a prerequisite for the development and maintenance of the vast majority of cervical cancer and cervical intraepithelial neoplasias (CIN). The reported Network results show that HPV DNA is usually no longer present 2 years after effective treatment, suggesting that strategies for follow-up after treatment of CIN based on monitoring the clearance of the major risk factor for CIN, i.e. HPV, might be feasible.

Quality Assurance and Quality Control of the cytological screening ensure high standards in laboratory screening, and the obtained Network results are presented in section 3.1.

Monitoring, Epidemiology and Evaluation allow to identify areas in which the screening and treatment processes can be improved, and the obtained results of the Network in this area are presented in section 3.2.

Section 3.3 presents the experimental results obtained by the Network participants in "New Technologies".

The worldwide dissemination of the obtained Network results and communication of the network participants are provided by the WEB FORUM (see section 3.4).

The project work was performed in accordance with the planned work (see section 2 "Planned Work") and the obtained results are summarised below. The detailed descriptions of the performed work and obtained results in 10 Member States and one Candidate State (Slovenia) are provided in the attached 12 Final Reports:

Final Report No. 1 Germany (Network Co-ordinator)
Final Report No. 2 Belgium
Final Report No. 3 Finland.
Final Report No. 4 France
Final Report No. 5 Greece, Athens
Final Report No. 6 Greece, Chalkidike
Final Report No. 7 Holland
Final Report No. 8 Italy
Final Report No. 9 Portugal
Final Report No. 10 Spain
Final Report No. 11 Sweden
Final Report No. 12 Slovenia
3.1 Quality Assurance and Quality Control

Performed Work: to develop quality assurance and quality control tools and to evaluate their impact on cervical screening in respect to efficiency and costs.

Participants: Germany, Belgium, Greece (Athens, Chalkidike), Holland, Italy, Portugal, Slovenia, and Spain

GERMANY: Cytological Institute of the Bavarian Cancer Society

The work in the reporting period had two main objectives:

i) to improve the quality control and quality assurance, and to evaluate their impact on the cervical cancer screening process.

ii) to update the European Guidelines for Quality Assurance in Cervical Cancer Screening.

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 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 was started in December 2001. The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 1.

BELGIUM: Scientific Institute of Public Health – Louis Pasteur

The main research 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. The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 2.

GREECE: Hellenic Society of Oncology, Athens

The 4th Round of the Screening Programme to the county of Messinia has been completed. Screening was performed on vaginal, ectocervical, and endocervical smears. Preparation and start of the 5th Round of the Cervical Cancer Screening program 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 has been founded in Athens by Hellenic Society of Oncology and the Hellenic Anticancer Institute. It continues with success to carryout ist 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.
Additional work was performed in another area "Monitoring, Epidemiology and Evaluation" (see section 3.2). No EC funds were requested for the performed work.
A detailed description of the performed work and scientific publications are provided in the attached Final Report No. 5.

GREECE (Chalkidike): Our Lady Who Loves Mankind

Work was continued for updating the target population census of the programme by creating in co-operation with political, social and religious leaders catalogues of population data and cross-checking them to increase participation and target out reach populations in the region. The out reach methodology is aimed at the more rural and uneducated communities in Northern Greece.
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.
The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 6.

HOLLAND: University of Nijmegen

University of Nijmegen, University Medical Centre St Radboud, Department of General Practice in co-operation with the Centre for Quality of Care research (WOK).
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 the area "Monitoring, Epidemiology and Evaluation" (see section 3.2) 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 (1) follow-up monitoring by the cytological laboratory or (2) follow-up monitoring by general practice or smear-taker 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 7.

ITALY: Unit of Cancer Epidemiology, Turin

The aims of the work performed in this project are:
i) Monitoring the values of process indicators for cervical cancer screening in different screening programmes in Italy
ii) Comparing indicators and standards
iii) Improving methods of data collection and analysis for cervical cancer screening
iv) Identifying problematic areas
v) Proposing actions to improve them

The work performed for the topics i) to v) is presented in section "3.2. Monitoring, Epidemiology and Evaluation". However, the topic "iii) Improving methods for data collection and analysis for cervical cancer screening evaluation" is an important
feedback information. In particular, the collection of data about the "women screened for the first time" and "women participating to following rounds" is of great importance. 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 8.

PORTUGAL Centro Regional de Oncologia Coimbra

The performed work addresses both "Quality Assurance and Control" in this section and the "New Technologies in Cervical Screening" in section 3.3.

We have undertaken a combined study, 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 smears are taken by GPs after a gynaecological examination, using the Cervex-Brush that is rinsed directly into PreservCyt vials and sent to the Cytopathology Laboratory of the Cancer Institute. 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 will be 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
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.
TOTAL SMEARS 38,901

<table>
<thead>
<tr>
<th>RESULTS</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>UNSATISFACTORY</td>
<td>0.69%</td>
</tr>
<tr>
<td>NORMAL</td>
<td>85.35%</td>
</tr>
<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>
</tr>
<tr>
<td>HGSIL</td>
<td>0.32%</td>
</tr>
<tr>
<td>INVASIVE</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

SLOVENIA: Institute of Oncology, Ljubljana (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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 9.
SPAIN  Health and Social Welfare Council, Junta de Castilla y León, Valladolid

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. Data collection of 58,383 smears was performed together with smear analysis, and the information 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 10.
3.2 Monitoring, Epidemiology and Evaluation

Performed work: Long-term monitoring and epidemiological evaluation of the cervical screening in several European regions, with the objective of establishing realistic results outcome indicators, and to estimate costs, benefits and adverse effects.

Participants: Belgium, France, Greece (Athens), Holland, Italy, Slovenia, Spain, and Sweden

BELGIUM: Scientific Institute of Public Health

Activities of the Working Party for Uniformisation of Cytology and the "Working Group on Quality Assurance and Optimisation was created". 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 update European guidelines of all the main aspects of organised cervical cancer screening, and in particular co-ordinating activities dealing with the evaluation of new screening techniques.

- Study of the new Belgian Royal Decree concerning the application of the Law on protection of privacy regarding the treatment of personal data with special focus on cancer screening registration.
- Negotiations were held with Flemish and Federal Health Authorities concerning the continuity of the Flemish cervical cancer screening programme and its extension over the whole of Belgium. On the 17th of October 2001, The Chamber of Representatives of the Belgian Parliament approved unanimously a resolution asking the Government to organise cervical cancer screening in Belgium.
- A letter appealing the Ministers was published in the BMJ: “European consensus on cancer screening should be applied urgently by Health Ministers”.
- Diverse contacts within the European Network for Cervical Cancer Screening, with the representatives of the European Commission (Europe Against Cancer, Luxembourg) and with the Belgian authorities in order to put the validation of the consensus of the Vienna Conference on the agenda of the next meeting of the European Ministers of Health.
- An update of the English translation of the Flemish guideline “preparation of adequate Pap smears” was done. This work was presented at the meeting of the European Network for Cervical Cancer Screening (Munich, Germany; March 16-18, 2001). A meta-analyse of the performance of devices for Pap-smear collection was performed and presented at 12th International Meeting of Gynaecological Oncology, Venice, Italy (April, 21-24, 2001).
- The Flemish experience about cancer screening interested several states member and was presented in Amsterdam (NL) in May, in Ormylia (GR) in September, and in Liège (B) in December 2001.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 2.
FRANCE: Association EVE, Strasbourg

Work was performed for evaluating the thin layer technique, which is used as common practice within the framework of the campaign for cervical cancer screening in the Bas-Rhin region. Until now, this method has been essentially evaluated in Research laboratories. This study has included private non-academic laboratories which are the most common in France. This work addresses both areas "Quality Assurance and Control" in this section, and "New Technologies in Cervical Screening" in section 3.3. Evaluation of the diagnostic performance of the two monolayer methods has been performed, as follows:

i) We have performed 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.

ii) We have conducted 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.

iii) We have performed a 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 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 the 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 (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 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 4.
GREECE: Hellenic Society of Oncology, Athens

During this round (Phase V) of the programme the main main performed work was:

i) Implementation part of the 5th round of the screening programme in Ilia, and part of the 4th round of the screening programme in Messinia (see previous section 3.1 "Quality Assurance and Quality Control").

ii) Dispatch to the National Cancer Registry of the Greek Ministry of Health of all HPV, CIN 1, 2, and 3 cases that will be registered.

iii) Maximising the participation rate of the target population (women aged 25 to 64 years)

iv) Ensuring that all staff of the programme receive proper training.

v) Follow-up of the women with non-negative smears (HPV, CIN 1, 2, 3, invasive cancer) through the Study Unit that is located in the central offices of the Hellenic Society of Oncology

viii) Optimise cervical cancer early diagnosis.

ix) Analysis and publication of the obtained results.

The work was performed with no request of fundings from the European Commission.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 5.

HOLLAND:

University of Nijmegen, University Medical Centre St Radboud, Department of General Practice in co-operation with the Centre for Quality of Care research (WOK).

Work was continued in the area "Quality Assurance and Control" (see section 3.1) 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.

Here we have assessed the successful implementation of a 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 (1) follow-up monitoring by the cytological laboratory or (2) 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 7.

ITALY: Unit of Cancer Epidemiology, Turin

The main aim of our work was 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).

The present project has continued to identify problem areas in Italian 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 CINII 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 CINI 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 8.
SPAIN Health and Social Welfare Council, Junta de Castilla y León, Valladolid

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 were carried out. 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. The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 10.

SWEDEN: Karolinska Institute Microbiology and Tumor Biology Centre

The work was performed in co-operation with Lundt University. During the period 16. December 2000 to 15 December 2001 following activities have been carried out.

1. 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. During the autumn 2002, the 109 women cohort was called back for a late follow-up HPV test.

2. 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). Samples for HPV testing have been taken, but analyses are not finalised. The work from the previous year Europe against Cancer contract on HPV testing at enrolment into the trial has now appeared in the scientific literature

3. Two cohorts of women were treated for CIN with different methods (conization or loop electrosurgical procedure) to compare the different methods for HPV treatment:
   - Cohort 1 (Kjellberg and Dillner) enrolled 37 women who were referred for treatment of CIN in the county of Västerbotten in Northern Sweden. Previous data had shown that treatment with carbon dioxide laser conization was effective for treating HPV infection. 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 carbon dioxide conization. The data resulted in that a formal randomised trial between these different forms of treatment became desirable and ethically acceptable, which was started during the autumn of 2001 (cohort 2 below).
- Cohort 2 (Rymark and Dillner) 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 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.

4. 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 insurmountable logistic problems.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 11.

SLOVENIA Institute of Oncology, Ljubljana

With respect to specific tasks in Slovenia the following work was performed:

i) Meeting of the working group to prepare the final protocol for the study and to co-ordinate with the activities in the frame of the network (see section 3.1 "Quality Assurance and Control").

ii) Re-screening by the panel of three experts of approximately 599 non-negative smears and a random sample of the same number of negative smears from four cytology laboratories in the Ljubljana region (see section 3.1 "Quality Assurance and Control").

iii) Detailed analysis of the invasive cervical cancer incidence and mortality by age groups and regions in Slovenia:

- Time Trend,
- 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 costal region.

iv) Re-evaluation of reporting system and standards for quality assurance and control in cytology laboratories developed in the frame of the pilot study to implement national reporting system (see section 3.1 "Quality Assurance and Control").

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 12.
3.3 New Technologies in Cervical Screening

Performed work: Continuous incorporation of technical innovation will allow to improve continuously the quality of the European cervical screening. Investigation of technological innovation. The results will help to determine the diagnostic parameters of new technologies in cervical screening in terms of sensitivity, specificity, predictive values and reproducibility.

Participants: Belgium, Finland, France, Greece (Chalkidiki), Portugal, Sweden

The work was concentrated on following topics:
- Identification of new technologies which require evaluation.
- Identification of recent key literature containing reviews, meta-analyses, general policy statements concerning new methods/techniques applicable in cervical cancer screening and follow-up.
- Recapitulation of the current status of the knowledge concerning the identified new techniques; proposition for new research.
- Additional systematic literature review and meta-analyses on appropriate topics where this is not yet done recently.
- Promote future research of high quality at reginal, national and international level.
- Promote international collaboration in general and within the Network in particular.
- Identify and apply models which allow the translation of diagnostic outcomes of test evaluation in public health outcomes (prevention of invasive cancer, life-years gained, improvement of quality of life)

BELGIUM: Scientific Institute of Public Health

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". Detection of Human Papillomavirus DNA is often recommended as a strategy allowing more optimal management of cases showing equivocal cytological findings. For the first time HPV triage was compared with primary HPV screening, both in combination with liquid based cytology, with respect to detection of cervical cancer precursors. 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 AUTOCYSTE 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 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.

**FINLAND:** Finnish Cancer Registry

Our 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. Part of the women invited this year had already been randomised in earlier rounds (e.g. those invited now for the risk group screening). About 50,000 women were randomised to the Papnet arm during the course of 2001 for the call-up procedures.
taking place in 2002 (in addition some 10,000 will be randomised during 2002, within those municipalities who start invitations in the autumn 2002).

In the automation-assisted pap-smear screening trial using Papnet, 38,300 smears were scanned. The screening laboratories have followed the study protocol well. The results of these screenings will be available in late 2002. During the present activity period. The cytological and histologically confirmed findings of the first year of the trial have been reported in our final report for the period up to 15.12.2000. No data on the cancer incidence after the year-year visits are available yet; the cancer registry data in Finland have been accomplished at the moment up to 1998. Collection of the data on the histologically confirmed findings from screenings done during the invitational year 2000 proceeded during the activity period. Final histologically confirmed data is still missing from one laboratory.

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). However, the detection rates vary a lot between laboratories, as well as in some amounts e.g. in the manual screening arm between the two years. Therefore, continuing the trial as planned is supported from the first and second year results.
A manuscript on the first-year results have been submitted to a scientific magazine (Nieminen et al.). The results were also presented in various scientific meetings and conferences.

**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. These are key observations when planning how the HPV test should be combined in the screening programme. Referrals for cytology negative but HPV positive women for further investigation and follow-up in the HPV-pilot material have been on-going during the activity period.

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. Minutes of the meeting are attached in Final Report No. 3. It is evident based on the information obtained from the meeting that the study size needs to be considered for the Finnish project alone. 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).

Obtained results
In the automation-assisted pap-smear screening trial using Papnet, about 40,000 smears were budgeted for the 12-month period and 38,300 actually analysed. One laboratory (formerly FCO Vaasa) decided to resign from the study in March 2001, in association with a change in the ownership of the laboratory. A small-size new laboratory had joined the randomisation process, but it was not able to follow the study protocol adequately and was excluded from the study. Another small laboratory was merged to the FCO Helsinki and was therefore included in the study as a new one. In addition to the primary screening smears, 2,620 quality control smears have also been processed with the Papnet machinery.

There were still some financial difficulties due to the postponement of the payments from the Commission: we have received only the first 30% payment but not a later one; we were not able to pay yet (as scheduled while budgeting) all the additional laboratory costs.

A pilot study on HPV-screening was started already in 2000. Sample collection and HPV-DNA screening up to 15.12.2000 were budgeted and the numbers reported in the joint report given by the Swedish network partner. During the present activity period the number of samples collected reached the budgeted amount (actual n=2,032, but we paid for 2,000 tests; the financial statement includes 2,000-1,450=555 tests).

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 3.

FRANCE: EVE Association

Work was performed for evaluating the thin layer technique, which is used as common practice within the framework of the campaign for cervical cancer screening in the Bas-Rhin region. Until now, this method has been essentially evaluated in Research laboratories. This study has included private non-academic laboratories which are the most common in France. This work addresses both areas "New Technologies in Cervical Screening" in this section, and "Quality Assurance and Control" in section 3.1.

Evaluation of the diagnostic performance of the two monolayer methods has been performed, as follows:

i) We have performed 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.

ii) We have conducted 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.

iii) We have performed a 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 will also allow 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 (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 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 4.

GREECE (Chalkidiki): Our Lady Who Loves Mankind

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. The need to do high quality double reading of at least 10% of smears has shaped the need to utilize more than one cytology laboratory due to manpower limits of the Greek national system. On a regular basis research staff of the Center conduct a systematic search of literature to insure that the margins of accuracy are within the highest ranges acceptable to centers of excellence in both the USA and European Union. The opinions were found to differ substantially among studies. The center researchers found that based on studies in which
the Pap smear was performed under optimal conditions, 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 researchers found that while 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 Method
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
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 ALTS 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 6.

**PORTUGAL** Centro Regional de Oncologia Coimbra

The performed work addresses both "Quality Assurance and Control" in section 3.1, and the "New Technologies in Cervical Screening" in this section. We have undertaken a combined study, 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 smears are taken by GPs after a gynaecological examination, using the Cervex-Brush that is rinsed directly into PreservCyt vials and sent to the Cytopathology Laboratory of the Cancer Institute. 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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UNSATISFACTORY</td>
<td>0.69%</td>
</tr>
<tr>
<td>NORMAL</td>
<td>85.35%</td>
</tr>
<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>
</tr>
<tr>
<td>HGSIL</td>
<td>0.32%</td>
</tr>
<tr>
<td>INVASIVE CARCINOMA</td>
<td>0.05%</td>
</tr>
</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>
</tr>
</thead>
<tbody>
<tr>
<td>AGE &gt; 20 &lt; 78</td>
<td></td>
</tr>
<tr>
<td>NORMAL -- 200</td>
<td>AR+ 48</td>
</tr>
<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>

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 9.
The aim was to investigate the feasibility and effectiveness of screening for Human Papillomavirus (HPV) infection within an organised cervical cancer screening programme:

- the population-based prevalence of transient and persistent HPV infections within an age stratum where implementation of HPV screening is conceivable; and
- whether treatment of atypias detected among HPV-positive women referred to colposcopy results in a reduced incidence of high-grade dysplasia in the next organised round of cytological screening 3 or 5 years later.

We intended to investigate whether additional application of the immunostimulatory drug imiquimod, recently licensed for treatment of genital warts, can be used to improve the proportion of women clearing HPV DNA and/or shortening the time until HPV clearance, and therefore shortening the time required for follow-up. The project intended to involve collaboration with colleagues in the Netherlands, Finland and the UK.

Obtained Results
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 has been the main activity. The manuscript was submitted on 11/5/2001 and is enclosed to the attached Swedish Final Report No. 11. 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. These late follow-up data have not yet been written up for publication.

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. The work from the previous year Europe against Cancer contract on HPV testing at enrolment into the trial has now appeared in the scientific literature. It was reported as a submitted manuscript in the scientific report of last year.
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 1 (Kjellberg and Dillner) enrolled 37 women who were referred for treatment of CIN in the county of Västerbotten in Northern Sweden. Previous data had shown that treatment with carbon dioxide laser conization was effective for treating HPV infection. 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. The data resulted in that a formal randomised trial between these different forms of treatment became desirable and ethically acceptable, which was started during the autumn of 2001 (cohort 2 below). The data from cohort 1 have been written up for publication, but have as yet not been submitted (The manuscript is enclosed, 3).

- Cohort 2 (Rymark and Dillner) 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)). Thus, although this study has not yet been completed and not written up for publication, the enrolment and the testing performed so far has been satisfactory.

During the time of the contract, 3 scientific reviews have been written on the subject matter of the contract.

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 insurmountable logistic problems. The logistic problems were related to the need to maintain blinding to HPV status of the treated women in the HPV screening trial, which was not possible to accommodate within a clinical trial of imiquimod efficacy.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 11.
3.4 Web Forum for Info Dissemination

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).
Multilingual user interface:
Welcome page (in ENGLISH)

Welcome to the European Cervical Cancer Screening Network!


Participants:
1 Partner from 11 Member States and 3 Candidate States

This Network is supported by the European Commission, DG SANCO.

Project description (in ENGLISH)

Project Description

The activities of the network of 11 projects in the Member States and 4 projects in the Candidate States are co-ordinated by the Co-ordination Centre (Cytological Institute of the Bavarian Cancer Society), and are grouped in 4 thematic clusters, as follows:

- PART 1: Quality Assurance and Quality Control
  Cluster Leader: Professor Ulrich Seyfarth
  The development and improvement of innovative quality assurance and quality control tools and the evaluation of their impact for improving quality assurance strategies on cervical screening through the external review of laboratory and individual performance by an independent agency.

- PART 2: Monitoring, Epidemiology and Evaluation of Cervical Screening
  Cluster Leader: Dr. Altn Antilla
  Continuation of the long-term monitoring and epidemiological evaluation of the cervical screening in several European regions, with the objective of establishing robust results outcome indicators, and to evaluate costs-benefit and to minimize the adverse effects.

- PART 3: New Technologies in Cervical Screening
  Cluster Leader: Dr. Marc Airby
  Investigation of technological innovation. Continuous incorporation of technical innovation will allow to improve the quality of the European cervical screening. The results will help to determine the diagnostic parameters of new technologies in cervical screening in terms of sensitivity, specificity, predictive values and reproducibility.

- PART 4: Training and Information Dissemination via Internet
Cervical Cancer Screening Network
Duration: 16.12.00 – 15.12.01
Network Meeting in Munich, 1.-2. June 2001 (in ENGLISH)

Cervical Cancer Screening Network
Duration: 16.12.00 – 15.12.01

Congress (in FRENCH)

Les congrès

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Beschreibung des Partners: SWS Tumorzentrum Zwickau, Deutschland

Prof. Dr. med. Günter Schott (Vorsitzender des SWS Tumorzentrum Zwickau)

Volker Wulf in seinem Büro, beim konsulieren der Websites des Netzwerks
Project description (in ITALIAN)

Partners (in SPANISH)
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GERMANY: Cytological Institute of the Bavarian Cancer Society


Schenck, U., Jürgens, O., Schenck, T., Schenck, U.B.:  
Zytologie im Internet - Multilinguale Bildgalerie.  

Schenck, U., Gassa, K:  
Zertifizierung von Zytologieassistenten/innen durch die DGZ.  

Schenck, U., Schenck, G.:  
Software-unterstütztes Qualitätsmanagement und Projektplanung.  

Schenck, U., Schenck, U.B.:  
Konsensusfindung mit Abstimmungssystemen.  

Schenck, U., Seidl, S., Schenck, U.B.:  
C 2001 Dr. U.B. Schenck und Autoren.  
ISBN 3-9804843-1-9  
Printed in Germany, Märkl-Druck München.

**BELGIUM: Scientific Institute of Public Health – Louis Pasteur**

B. Ruffing-Kullman, D. Remorini-Niedermeyer, U. Schenk, M. Arbyn  
Rapid rescreening: Eine Alternative zur 10% Kontrolle.  

Arbyn M, Van Oyen H, Sartor F, Tibaldi F, Molenberghs G.  
Description of the influence of age, cohort and period effects on cervical cancer mortality by log linear Poisson models (Belgium, 1955-94) Archives of Public Health

Arbyn M., Geys H.  

Arbyn M, Wallyn S.  
Regeling van bevolkingsonderzoek. “In antwoord op…”. Artsenkrant (Newspaper for Physicians), 1341, April 10, 2001. (concerning population research).

Cervical Cancer Screening Network  
Duration: 16.12.00 – 15.12.01
Arbyn M.
Organised screening of cervix cancer might finally happen in Belgium?
Publication in Episcoop, journal of the Institute of Public Health:

Arbyn M, Temmerman M.
Belgian Parliament calls for organised cervical cancer screening and HPV research at European level

Arbyn M.
European consensus on cancer screening should be applied urgently by health ministers
BMJ Letter 2001 August 18

Arbyn M, Schenck U.
General statement of the European Cervical Cancer Screening Network. Validation of the Scientific Consensus Concerning Cancer Screening by the Ministers of Health of the E.U.

Arbyn M., Vergote I., Albertyn G., Bourgain C., Buntinx F.

Arbyn M.

Protection of HPV low risk positivity against “progression” of cervical squamous epithelial lesions?


Arbyn M, Bourgain C, De Sutter P.

De Sutter P., Bourgain C., Arbyn M.
A randomised trial comparing HPV screening with triage in combination with thin layer cytology
2nd European Congress for Colposcopy and Cervical pathology, Rhodes, Greece, October, 4-6, 2001.
Arbyn M.
Implementing new technologies in the screening programmes for cervical cancer. Finish Cancer society-Meeting of the Nordic Countries, Helsinki Finland, December 14-15, 2001

**FINLAND: Finnish Cancer Registry, Helsinki**

Nieminen P, Viikki M, Hakama M, Anttila A.
A prospective and randomised public-health trial on neural network assisted screening for cervical cancer in Finland. The results of the first year. (submitted for publication.)

**FRANCE: Association EVE, Strasbourg**

Cervical cancer screening in France
European Journal of Cancer 2000, 36: 2215-20

Baldauf J.-J., Barrasso R., Benmoura D., Huynh B., Mergui J.-L., Beuret T., Blanc B. Blondon J.
Recommandations pour la pratique de la colposcopie.

Baldauf J.-J.
L'accréditation en colposcopie: queries normes ?

**ITALY: Unit of Cancer Epidemiology, Turin**


Ronco G.
Les besoins en information des programmes de dépistage du col de l'utérus
Workshop "Régistre et évaluation du dépistage".
**SWEDEN: Karolinska Institute, Stockholm**

Dillner, J.


Konya, J. and Dillner, J.
Immunity to oncogenic Human Papillomaviruses.
Advances in Cancer Research. 82. 205-238. 2001.
Annexes

Following annexes are attached:

- Final Report 1 of Cytological Institute of the Bavarian Cancer Society Munich, Germany (226 pages)
- Final Report 2 of Scientific Institute of Public Health – Louis Pasteur Brussels, Belgium (137 pages)
- Final Report 3 of Finnish Cancer Registry Helsinki, Finland (12 pages)
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- Final Report 5 of Hellenic Foundation of Oncology Athens, Greece (6 pages)
- Final Report 6 of Our Lady Who Loves Mankind Chalkidike, Greece (15 pages)
- Final Report 7 of University of Nijmegen Nijmegen, Holland (93 pages)
- Final Report 8 of Unit of Cancer Epidemiology Turin, Italy (73 pages)
- Final Report 9 of Centro Regional De Oncologia de Coimbra Coimbra, Portugal (8 pages)
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