Final Report
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Participants:

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<td>GERMANY</td>
<td>Cytological Institute of the Bavarian Cancer Society, Munich (Co-ordinator)</td>
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<td>BELGIUM</td>
<td>Scientific Institute of Public Health, Brussels</td>
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15. January 2003

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

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[European Commission Logo]
EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
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Final Report
110 pages

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ANNEXES attached (767 pages):

Final Report No. 1 Germany: Cytological Institute of BKG, Munich (48 pages)
Final Report No. 2 Belgium: Scientific Inst. of Public Health, Brussels (492 pages)
Final Report No. 3 Finland: Finnish Cancer Registry, Helsinki (13 pages)
Final Report No. 4 France: Association EVE, Strasbourg (20 pages)
Final Report No. 5 Germany: South-west Saxony Tumorcentre Zwickau (46 pages)
Final Report No. 6 Greece: Hellenic Society of Oncology, Athens (14 pages)
Final Report No. 7 Greece: Our Lady Who Loves Mankind, Chalkidiki (16 pages)
Final Report No. 8 Holland: University of Nijmegen, Nijmegen (6 pages)
Final Report No. 9 Italy: Unit of Cancer Epidemiology, Turin (22 pages)
Final Report No. 10 Portugal: Regional Oncology Centre, Coimbra (5 pages)
Final Report No. 12 Sweden: Karolinska Institute, Stockholm (26 pages)
Final Report No. 13 UK: Birmingham Women's Hospital (27 pages)
1. Summary

Cervical cancer has now become the second most common cancer among women in the world, with up to 500,000 new cases/year and up to 300,000 premature deaths a year. It is the most common female cancer in large areas of the developing world where an estimated 80% of new cases arise. Because of the long preclinical period cervical cancer can be prevented by screening, diagnosis, and treatment of premalignant cervical lesions. 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 colposcopy.

Infection with oncogenic human papillomaviruses (HPVs) is the most important cause of cervical cancer worldwide. After infection there is a long latency period of at least 10 to 15 years during which cervical cancer develops in a small proportion of originally infected women. Prevention of HPV infections by vaccination may result in a 5–10% reduction of cancer mortality worldwide. Preventive HPV vaccines are entering clinical efficacy (phase III) trials:

- plain virus-like particles (VLPs),
- DNA free capsids comprising the major viral capsid (L1) protein, and
- chimeric VLPs (CVLP) containing various combinations of early viral proteins attached in different ways to the major L1 or the minor (L2) capsid proteins of the virus.

Randomised clinical trials will define the efficacy of the different vaccines against persistent HPV infection and other surrogate end points, such as cervical intraepithelial neoplasia grade II/III. Considerable gains at the individual and societal level would be obtained if cervical cancer could be prevented.

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 in “New Technologies”, including HPV clinical detection. 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 of section 2, and the obtained results are here summarised. The detailed descriptions of the work and obtained results in 11 Member States are provided in the attached 13 Final Reports:

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2. Planned Work

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

Objectives: To develop quality assurance and quality control tools and to evaluate their impact on cervical screening with respect to their efficiency and costs. To update the "European Guidelines for Quality Assurance in Cervical Cancer Screening"

Leader: Prof. Ulrich Schenck

The work in this cluster integrates 6 projects from 6 Member States and 3 projects from 2 Candidate States. The cluster activities aim at 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. That will increase the detection and correction of diagnostic errors, and also establish higher quality standards in cervical cancer screening.

Quality is here ensured by the complementary activities on Quality Control, Quality Assurance, and Total Quality Management with the aim of ensuring a highly qualitative cytological outcome in form of patient care and protection. Quality Assurance aims at 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 aims at measuring and improving the quality of the intermediate screening results by improving the skills of the persons involved in the production and testing. 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.

In this thematic cluster are 6 projects from 6 Member States:
- BELGIUM: Scientific Institute of Public Health – Louis Pasteur
- FRANCE: Association EVE, Strasbourg
- GERMANY: Cytological Institute of the Bavarian Cancer Society
- GREECE: (Ormylia-Chalkidike): Our Lady Who Loves Mankind
- HOLLAND: University of Nijmegen, and
- UK: Birmingham Women's Hospital

GERMANY: Cytological Institute of the Bavarian Cancer Society

The planned work has three main objectives:

i) to improve the Quality Assurance and Control Tools, and to evaluate their impact on cervical cancer screening process.

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

iii) to investigate the "Continuous grading of intraepithelial lesions" and study on DNA content of cases
During this project (December 2001 - December 2002) the Quality Assurance and Control Tools will be improved as follows:

i) the developed tools will be experimentally used for the screening work (until March 2002)

ii) their impact on the cervical cancer screening process will be evaluated (until June 2002)

iii) the tools will be improved (until September 2002), and the obtained quality improvement will be quantified (until October 2002),

iv) the new working procedures will be documented and disseminated via WEB FORUM to the project partners (from November to December 2002)

The update of the "European Guidelines for Quality Assurance in Cervical Cancer Screening" is the second working area in this project, and is structured as follows:

i) The first draft of the "Updated European Guidelines for Quality Assurance in Cervical Cancer Screening" (release in November 2001) will be revised (starting in December 2001).

ii) The up-dates will be analysed and a new version of the Guidelines will be released (March 2002) on the WEB FORUM and opinion of the international experts working in this field will be collected and presented to the Editorial Committee (until September 2002)

iii) This new version of the Guidelines will be presented at the European Congress of Cytology within the working group "Committee for Quality Assurance Training and Education of the European Federation of Cytology Societies" in Antwerp, 15.-19. September 2002 with the aim of obtaining the official approval of the specialists world wide.

The study of "Continuous grading of intraepithelial lesions" is the third working area in this project, and is structured as follows

i) Study (300 cases) concerning the reproducibility of continuous grading (release in March 2002)

ii) Study (600 cases) on the follow up of cases with mild or moderate dysplasia (release in June 2002)

iii) Study related to the question: Do low risk HPV statistically protect against the risk of high risk HPV ? (release in September 2002)

iv) Study on DNA content of cases of intraepithelial lesions of mild and moderate dysplasia related to cytological / histological follow up (regression, persistence, progression). This study will be released in November 2002.

BELGIUM: Scientific Institute of Public Health – Louis Pasteur

The main research objectives of the project are:

- Preparation of a case control study
- Application of HPV-DNA detection methods in (a) a primary screening setting, (b) triage of atypical or low grade cytological lesions, (c) follow-up of treated patients.
• Continuation of ongoing research concerning the comparison of liquid-based cytology versus conventional cytology.
• Trial of alternative therapeutic strategies for CIN-lesions: local surgery on cervix – topical application of immuno-modulators.

Following research work and other important project activities will be performed as described below:

i) Research work:
   • Preparation of a case control study consisting of 200 women with cervical cancer matched with 200 to 400 controls where differences of exposure to risk factors and screening history will be measured. Inclusion of archival HPV detection with PCR.
   • Application of HPV-DNA detection methods in (a) a primary screening setting, (b) triage of atypical or low grade cytological lesions, (c) follow-up of treated patients.
   • Continuation of ongoing research concerning the comparison of liquid-based cytology versus conventional cytology.
   • Trial of alternative therapeutic strategies for CIN-lesions: local surgery on cervix – topical application of immuno-modulators.

ii) Support to the Flemish technical Working Parties, Flemish Administration of Health Care, Steering Group for Cervical Cancer Screening, provincial coordination units responsible for invitation of women and health promotion in the framework of cervical cancer screening.

iii) Statistical analyses and reporting of data from the Flemish Cervical Screening Register. Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection.

iv) Support to cytological laboratories in uniform registration of cytological and histological data on cervical lesions. Computer support for data-entry, extraction and transmission.

v) Advanced statistical analyses of incidence and mortality trend concerning cervical and other uterine cancer: study of temporal and spatial variation in relation with influencing factors (screening, age-period-cohort effects, treatment, survival).


vii) Support to the organisation of cervical cancer screening in the Flemish Region and if possible in the other regions. Development of a Belgian policy to negotiate with the different Belgian authorities at the Federal and Community level.

viii) Organisation of the Symposium on Cervical Cancer Screening by the Belgian Society of Clinical Cytology.
FRANCE: Association EVE, Strasbourg

The aim of the project is to continue the work started in December 2000 in the previous Cervical Cancer Screening Network. We will 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. This study will also 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-months 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.

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.

The Association will also run a long term survey of ASCUS, AGUS and immature metaplasia in an organized regional screening program.

**Background:** in 1997, ASCUS and AGUS were not very well known by physicians. Some of them will have been very aggressive, others will have considered these lesions as trivial.

**Inclusion:** All smears showing ASCUS, AGUS and immature metaplasia (all coded EVE 3 in our classification) registered in 4 laboratories in 1997: N = 2489. These laboratories carry out 65% of the smear tests of the EVE cervical cancer screening campaign and are representative of the situation of a defined region: the BAS-RHIN.

**Methods:** Long term survey consists in analysis of subsequent smear tests and possible histological examinations. 10% of the smears will be randomly selected in order to be reviewed together with control smears by external cytopathologists. In case of discrepancies a common reviewing will be done between the initial cytopathologist and the reviewer. together with control smears

**Expected results:** Proportion of misclassified smears obtained from the review of smears.

**Long term outcome:**
- Prevalence of smears which will evolve to high grade cytologic lesions or confirmed CIN3 or carcinoma within 1, 3 and 5 years.
- Proportion of smears with totally normal follow-up

Multivariate analysis including: age of women, cytological follow-up pattern and results, precise type of initial cytological abnormalities...

**Results schedule:** Beginning of the study 16.12.2001
- Review of smears and determination of proportion of misclassified smears as well as long term outcome at 1 and 3 years should be achieved within 6 months.
- Multivariate analysis for outcome at 3 years will be achieved at the end of the project (15.12.2002)
- Outcome at 5 years will require 6 months more because the end point is 31 December 2002.
GREECE (Ormylia-Chalkidike): Our Lady Who Loves Mankind

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

(i) Continue to update the target population census of the program 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. Study out reach methodology aimed at the more rural and uneducated communities in Northern Greece expanding our coverage of the community to the South and East.

(ii) Closely follow up all women tested positive and regularly update their screening files with all available data on further assessments and treatment.

(iii) Conduct a reliability study of smear reading on random samples of PAP smear tests increased to 10% utilising both conventional and AIC cytology.

(iv) We plan to conduct a preliminary study utilising IR. spectrometry as a cervical cancer diagnostic tool. This will involve a random sample of 15 pap smears that have already been diagnosed utilising conventional cytology practices and AIC quality control being analysed by the IR. spectrometer of our lab. This will occur in co-ordination with other leading centres in the USA who have pioneered this methodology and have demonstrated to some degree its accuracy and usefulness.

(v) Explore new technology in creating a communications link with European Centres of Excellence in the UK, Germany and other European Centres via the Internet.

(vi) Publish on the network WEB FORUM (in English) and on our own web site (in Greek) the findings and results of the program as a reference for the scientific community.

PLANNED WORK

The main tasks that will be performed during this phase of the quality assurance cervical cancer screening program at the Centre of Our Lady in Ormylia are as follows:

(i) Conduct a preliminary study utilising IR. spectrometry as a cervical cancer diagnostic tool. This will involve a random sample of 15 pap smears that have already been diagnosed utilising conventional cytology practices and AIC quality control being analysed by the IR. spectrometer of our lab (6, 9 months).

(ii) Conduct a study to determine the prevalence of HPV infection in a sub sample of the screened population (6, 8, 10 months).

(iii) Update the program’s data base of the target population by collecting population data in co-operation with civil, social, medical and religious authorities and leaders and then cross checking them. This will be done in order to better target persons who have not been screened, especially in the more rural and remote villages. Emphasis will be placed on the education levels of the people in order to create better outreach methodology, (0-3, 6, 10 months).

(iv) Closely follow up of the women tested positive and regularly update their screening files with all the available data on further assessment and treatment (0-3, 6, 9, 12 months).

(v) Conduct a reliability study of the slide test reading by selecting a stratified random sample, (10%) of smear tests previously read by the cytology
laboratory. All standard available information, age, date of last menstruation and history of any previous treatments, will be available, but code numbers or any other identifiers will be removed. The slides will be read blindly by the Alexandra’s Hospital cytology lab and by the Centre of Our Lady’s lab, in conjunction with other routine slides and they will be classified using standard classification headings. A random selection of smears will also be analysed by the Centre AIC system. A special record form will be prepared and all data will be analysed by means of the kappa statistic which provides us with an estimate of agreement between the different readings other than the expected to occur by chance, (3, 6, 9 months).

(vi) Continue the operation of routine Pap smear clinics, (3 times a week), with the presence of a gynaecologist, in addition to our large scale cancer prevention weeks campaigns, (0-3, 6, 9, 12 months).

(vii) Continue our screening public education initiatives and outreach efforts to recruit women through regularly broadcast video spots on the need for cervical cancer screening, as well as live televised talk shows and radio broadcasts. The Centre will continue to organise regular educational campaigns, lectures and group discussions using multimedia resources, for the villages with lower participation rates, lower social economic conditions, and lower educational levels, (0-3, 6, 9, 12 months, twice per month).

(viii) Investigate new communications technology to create augmented consultation communication links with European Centres of Excellence in Cervical Cancer Screening through the Internet (6, 9 months).

(ix) provide opportunity for Centre of Ourmylia cytology staff to visit cytology labs and participate in continuing education opportunities in the UK, Germany, Haifa/Israel and the USA.

Create continuing education opportunities in co-operation with other members of the network at the Centre of Our Lady and at European Centres for the cervical screening staff both via the web but also through participation of education seminars in Europe and at the Centre with European and other Western educators (8, 11 months).

UNITED KINGDOM: Birmingham Women's Hospital

The aims of this project activities are:

i) To identify and record the quality of colposcopy training programmes in the 14 member states of the European Federation for Colposcopy (EFC), together with the National Colposcopy Societies of Poland, Hungary, Slovakia, Czech Republic, and Israel.

ii) To agree minimum standards of the training (Quality Assurance Standards) necessary for colposcopists to be competent to see, assess and, if necessary, treat women with pre-cancerous conditions of the cervix, vagina and anus.

iii) To agree ongoing standards of treatment (Quality Assurance Standards) thereby maximising the quality of treatment offered to women with pre-cancerous conditions of the lower genital tract. This will include audit of treatment.

The Workshop in Greece in October 2001 will present the findings to all partners in the project, member Societies and representatives from all countries yet to establish a
National Colposcopy Society. The aim will be to achieve a consensus agreement on how each Member State (and foreseeable Member States) will then introduce agreed standards of training for all colposcopists in their country.

Integrate the initial status report and minimum quality standards of training as a constituent and ongoing part of the European Cervical Screening Network co-ordinated by Dr U Schenck commencing 16th December 2001.

Commencing the 16th December 2001 the next stage of the project will be:

i) To introduce agreed standards of training in colposcopy for each Member State

ii) To identify ways in which the quality of treatment can be measured, the aim being to ensure that all European women obtain the best possible quality of treatment for their pre-malignant disease.

To that end there will be two working groups:

1. Introduction of Standards in Colposcopy
   This group will implement the conclusions reached and agreed in Greece in October 2001. This group will consist of 5 or 6 members, each being a representative of a different Member State. It is anticipated that this group will meet twice over the next year i.e. in Paris.

2. Assessment of Standards of Treatment (of women with pre-malignant disease of the lower genital tract)
   This group will seek to introduce way by which the outcome of treatment can be measured and audited with a view to identifying areas in which treatment can be improved. This group will consist of 5 or 6 members, each being a representative of a different Member State. It is anticipated that this group will meet twice over the next year i.e. in Paris.
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

In this thematic cluster are 7 projects from 7 Member States:
- BELGIUM: Scientific Institute of Public Health – Louis Pasteur
- FINLAND: Finnish Cancer Registry, Helsinki
- GERMANY: SWS Tumorcentre Zwickau
- GREECE: Hellenic Foundation of Oncology, Athens
- HOLLAND: University of Nijmegen
- ITALY: Unit of Cancer Epidemiology, Turin
- SPAIN: Health and Social Welfare Council, Junta de Castilla y León, Valladolid
- SWEDEN: Lund University at Malmö

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

The aims of this project are:
- Advanced statistical analyses of incidence and mortality trend
- Statistical analyses and reporting of data from the Flemish Cervical Screening Register.
- Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection.

**PLANNED WORK**

i) Statistical analyses and reporting of data from the Flemish Cervical Screening Register.

ii) Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection.

iii) Support to cytological laboratories in uniform registration of cytological and histological data on cervical lesions. Computer support for data-entry, extraction and transmission.

iv) Advanced statistical analyses of incidence and mortality trend concerning cervical and other uterine cancer: study of temporal and spatial variation in relation with influencing factors (screening, age-period-cohort effects, treatment, survival).

v) Organisation of the Symposium on Cervical Cancer Screening by the Belgian Society of Clinical Cytology.
FINLAND: Finnish Cancer Registry, Helsinki

The aim of this project is the evaluation of the effects of screening on cervical cancer incidence and mortality rates in Europe. There are major differences in the European Union member states in their screening policies (EJC 2000). There's no reliable overall evaluation available on how the effectiveness of screening has developed in these countries, however. The goal of the proposal is to study in which magnitude the different screening policies in Europe affect cervical cancer incidence and mortality rates:

i) Summarise historical knowledge and up-date the present-day status of the screening policies in Europe (in collaboration with the screening network); summarise also some aggregate data on the biological background risk, such as sexual behaviour, smoking, and hysterectomy whenever possible;

ii) Assess the use of the cervical cancer incidence and mortality data banks in the trend analysis, e.g., if there are differences in various countries in the registration on cervix uteri (ICD-7 171), consider also, e.g., uterus unspecified; the rates drawn from the WHO and ENCR data bases;

iii) Study the associations between historical data on screening in the EU countries and cervical cancer rates, analytical before-after analysis where the main determinants of screening are:
   • screening modalities (organised and/or spontaneous)
   • target age range, coverage, compliance, and screening interval
   • with some data on screening findings and diagnostic & clinical processes;

iv) Consider also potential differences in the background risk factors on the trends and screening effects.

What will be gained? We shall demonstrate the recent developments and the overall impact of screening in the European Union as an entity, as well as for various nationwide modalities that are in action in Europe. We also expect to learn which are the main areas of concern of the activity, by studying potential sources of heterogeneity between different programmes and settings in contributing screening effectiveness.

GERMANY: SWS Tumorcentre Zwickau

The aims of this project activities are:

• Advanced statistical analyses of incidence and mortality trend
• Statistical analyses and reporting of data from the Saxony Cancer Register concerning cervical and other uterine cancers
• Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection.

PLANNED WORK

i) Statistical analyses and reporting of data from the Saxony Cancer Register concerning cervical and other uterine cancers.

ii) Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection.
iii) Support to cytological laboratories in uniform registration of cytological and histological data on cervical lesions. Computer support for data-entry, extraction and transmission.

iv) Advanced statistical analyses of incidence and mortality trend concerning cervical and other uterine cancer: study of temporal and spatial variation in relation with influencing factors (screening, age-period-cohort effects, treatment, survival).

v) Organisation of the International Symposium on Oncology in Zwickau.

GREECE: Hellenic Foundation of Oncology, Athens

During this project the main objectives will be:

i) Implementation part of the 6th round of the screening programme in Ilia, and part of the 5th round of the screening programme in Messinia.

ii) Follow-up of the women with non negative smears (HPV, CIN I, II, III, invasive cancer) through the Control Unit that is located in the central offices of the Hellenic Foundation of Oncology.

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) Optimise cervical cancer early diagnosis.

vi) Dissemination of the results obtained during this project on the WEB FORUM, discussions with the project partners, participation to congresses and scientific meetings.

vii) Continuing the epidemiological studies (relevant for the PART 2 of this Network).

viii) Dispatch to the National Cancer Registry of the Greek Ministry of Health of all HPV, CIN I, II, and III cases in order to be registered.

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 aim of this project is to continue to assess successful implementation of the most cost-effective communication system at national and European level. The experience accumulated in the previous projects will be re-used in the experimental implementation of a new "most cost-effective communication system". 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 improvement of the communication system which was implemented in the previous project (from December 2000 to 15. December 2001), will be based on the re-design

i) It is important to systematically assess the presence or absence of preconditions for the successful implementation. We will continue to determine these preconditions, the experiences of our previous projects will be elaborated and formulated in new developed tools like Internet-based questionnaires and other computer-based instruments.

ii) The new questionnaires, for those involved in the screening activities will, for example, contain questions concerning current and innovative practices, and barriers to and facilitators for implementation.

iii) Another example of a tool that will be improved, concerns a checklist that contains the elements of the pathology laboratory configurations for processing and storing PAP smear classifications and criteria for follow-up.

iv) The tools will be tested also in regions of the Netherlands that are interested in implementing our system.

v) 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.

vi) Following this new trials testing of the measurement instruments, the improved 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.

vii) The new implemented "most cost-effective system" to improve the follow-up will be disseminated on the Internet via WEB FORUM, and will be presented at national and European conferences.

ITALY: Unit of Cancer Epidemiology, Turin

The objectives of this project is to monitor the value of process indicators for cervical cancer screening in different screening programmes in Italy.

An Italian Group for Cervical Cancer Screening (GISCI) was founded in 1996 in Italy. 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.

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.
Following work will be performed in this project:

i) A random sample of some 10,000 women, which participate in the organised screening programmes of Torino, Firenze, Ravenna and Padova, will have a liquid cervical sample taken, tested for both thin layer cytology and for the presence of DNA form "high-risk" HPV types. If cytology and HPV are both negative, then the woman will be invited for a new screening round after 3 years.

ii) Women with HSIL cytology will be referred for colposcopy. Women with ASCUS or LSIL cytology and HPV positive will also be referred for colposcopy.
   • If cytology is ASCUS or LSIL but HPV test is negative, then the woman will be re-called for both tests after 1 year.
   • If the HPV test remains negative and the new cytology is normal the woman will be recalled for screening after 3 years.
   • Otherwise she will be referred for colposcopy. If cytology is negative but HPV test is positive and the woman's age is >= 35, then she will be directly referred for colposcopy. If age is <35 both tests will be repeated after 1 year.

iii) If HPV remains positive the women will be referred for colposcopy. The repeat has the purpose of reducing referral for colposcopy by excluding infections of short duration.

iv) The number of lesions positive to each test individually will be computed, in order to estimate the relative sensitivity. Also PPV for each test, the referral rate individually for each test and the proportion of tests to be repeated will be computed.

v) The obtained results will be disseminated on the Internet via WEB FORUM.

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

The aims of this project activities are:

i) Apply parameters in order to evaluate the efficiency of the Programme. Such parameters are based on European directives and computerization of the same, so that, by using similar technology to the other members of the network, results may be compared and diffused.

ii) Carry out monitoring of abnormal cytologies.

iii) Increase notification of cases of cervical cancer to the Registry of Gynaecological and Breast Cancer of Castilla and León.

iv) Carry out studies on recovery and death by cancer of the cervix of uterus.

v) Early detection of HPV viruses using PCR and hibridation procedures.

The region of Castilla y León is located in the middle of Spain. It has an area of 94.147 sq.km and has 2.5 million inhabitants distributed in nine provinces. The Regional Government of Castilla and León (Junta de Castilla y León) has eight departments, one of them is the Department of Health and Social Welfare (Consejería de Sanidad y Bienestar Social). The Head Office of Public Health of this Department is responsible
for the programme, carrying out, controlling and evaluating activities related to improving, protecting and restoring the population's health.

The Service of Health Promotion is committed to the elaboration, control and evaluation of health programmes aimed at improving the population's health and protecting it from hazards. Regional health policies are reflected in Castilla and León's 2nd Health Plan, a plan officially sanctioned as decree number 212198 and including health goals for the year 2007. The Plan proposes a number of actions against cancer. The Programme for the Prevention of Gynaecological Cancers and Infections has to be seen in the context of the Plan's headlines.

The functions of planning, co-ordination and management at a regional level are carried out in the Department of Health and Social Welfare of Castilla and León, the coordination at a provincial level by the Territorial Services of each of the nine provinces and the carrying out of the Programme in the Basic Healthcare Zones and public hospital services when needed.

PLANNED WORK

The Programme for the Prevention of Gynaecological Cancers and Infections of Castilla and León forms part of the European network of pilot programmes for the Screening of Cervical Cancer, and functions according to the European directives with the aim of improving the quality of Cervical Cancer Screening, and represents a work of great value to the European Community as this (1) involves the participation of various member states, (2) work will be carried out jointly in various member states and (3) work and results can be used in other member states as the standards used throughout will be uniform. This programme is also integrated with Primary Healthcare activities in Castilla and León, and, consequently, has an extensive application.

The activities of the Programme are now centred primarily on adequacy of Cytological Analysis Centre, co-ordination with hospital and primary healthcare services, so that abnormal cases may be followed up, and also to consolidate the Registry of Gynaecological and Breast Cancer of Castilla and León. A goal is the adaptation of the Computer Program controlling the parameters based on the European Conditions in such a way that the results will be presented identically to those of the other members of the network thereby making comparisons and dissemination much easier and increase coverage to 100% and participation to 85%.

Planned results
- Reduction of mortality through cervical cancer.
- Guarantee the quality of each and every activity in the Programme.
- Increase the participation of the target population.
- Apply parameters in order to evaluate the efficiency of the Programme. Such parameters are based on European directives and computerization of the same, so that, by using similar technology to the other members of the network, results may be compared and diffused.
- Carry out monitoring of abnormal cytologies.
- Increase notification of cases of cervical cancer to the Registry of Gynaecological and Breast Cancer of Castilla and León.
- Carry out studies on recovery and death by cancer of the cervix of uterus.
- Early detection of HPV viruses using PCR and hybridation procedures.
- Dissemination of the project results on the Internet via the WEB FORUM.
The aims of this project are

- To design and evaluate the introduction of secondary HPV screening as a public health care policy in Sweden.
- To evaluate the usefulness of primary HPV screening using an ongoing randomised trial.

**PLANNED WORK**

i) **PREPARATORY WORK:** A population-based sample of 12,496 women 35 years of age, resident in 5 regions in Sweden have been enrolled into a primary HPV screening trial and have been tested for HPV infection by PCR methodology, performed under a quality assurance programme financed by Europe against Cancer (already performed):

ii) **SECONDARY HPV SCREENING:** Together with the organised screening organisations in 2 Swedish counties, introduce secondary HPV screening as a randomised public health care policy. Randomisation will be at the colposcopy clinic level, and the clinics will be randomised to either the old referral policy of colposcopy of all low grade cytological abnormalities or to the new policy of either colposcopy of HPV-positive women or for HPV-negative women return to the ordinary screening programme without further gynaecological investigation. The policy will then be evaluated once per year for safety and cost.

- Safety: A database with the women with low-grade cytological abnormalities and their diagnosis dates will be built. The incidence of high-grade cervical disease (HSIL) will then be compared between the clinics using the old and the new policy and should not be significantly different. The incidence of high-grade cervical disease among the HPV-negative women that in the new policy are not submitted to colposcopy is compared with the incidence in the general population and should not be significantly different. Cost: The cost of HPV testing in the new policy is compared with the savings of reduced numbers of colposcopy and should compare favourably.

- Power considerations: Annually, about 1500-2000 women with low grade cytological abnormalities are expected to be affected by the new health care policy. After 1 year of follow-up, there will be conventional power to detect differences in HSIL incidence of >3-fold, after 2 years of >2-fold and after 4 years of >1.5-fold between the 2 different policies.

iii) **PRIMARY HPV SCREENING:** Follow-up of enrolled women by cytology and colposcopy. The randomised trial will during 2002 be focussing on 2 tasks:

- monitoring the incidence of the trial endpoint HSIL in the 2 trial arms by conventional cytology. The primary endpoint of the trial will be reached in February 2003.
- Colposcopy of persistently HPV-positive women, and of control women for comparison. Colposcopy-directed biopsies will be taken and, if no colposcopical abnormalities are present, there will be blind cervical biopsies. The histopathology of the biopsies will be compared to the
colposcopical images (stored as digital images on a DenVue™ computer-assisted colposcope) to establish the value of colposcopy for detecting cervical lesions in this high-risk group of women

**Tasks**

- Final design of secondary HPV screening randomised health care policy. Ethical committee approval (month 3).
- Start of the new health care policy. Database operational and continuously collecting cytological results, HPV testing results and health care resource usage in the 2 policies (month 3-month 11).
- Interim analysis of safety and cost-efficacy for the scientific report (month 11-month 11).
- Continued accrual of HSIL endpoints in primary HPV screening trial (month 1-month 12). The scientific report will contain data on total number of endpoint observations, as a measure of the progress of the trial, but the code will not be broken to reveal data on efficacy until 2003.
- Entering of digital colposcopy images and subsequent histopathological diagnoses into a HPV screening colposcopy database (month 1-month 11).
- Interim analysis for the scientific report of the value of colposcopy for predicting histopathological diagnoses in this particular group of women (month 11-month 12). Scientific publication, also taking the HPV DNA testing results into account, will be after the code has been broken in 2003.

**Project Results**

2. Establishment and maintenance of a database for monitoring of safety and cost-efficacy of the new and old policies. The database will ultimately generate knowledge of whether a routine health care policy aiming at increased specificity of cervical screening by secondary HPV testing of women with low-grade cytological abnormalities is safe and cost-efficient under real-life conditions.
3. Continued accrual of endpoint observations (HSIL incidence) for a randomised primary HPV screening trial. If the expected increased efficacy of HPV-based screening is indeed found, this could lead to new etiology-oriented cervical screening programs in Europe.
4. Establishment of a database of computerized colposcopic images of the cervix of women with persistent oncogenic HPV infection and, for comparison, from normal women, in relation to the histopathological diagnoses of the corresponding biopsies. This database may be useful for evaluation of the value of and continued improvement of colposcopy for this particular group of women.
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 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 recent key literature containing reviews, meta-analyses, general policy statements concerning new methods/techniques applicable in cervical cancer screening and follow-up.
2. Promote future research of high quality at sub-national, national and international level.
3. Promote international collaboration in general and within the Network in particular.
4. 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)
5. Implement the new method liquid cytology to prepare and analyse the smear test in a small sample of the screened women in conjunction with the conventional PAP smear test and with Artificial Intelligence Cytology (AIC).
6. We plan to conduct a study to determine the prevalence of HPV infection in a sub sample of the screened population and hybrid DNA analysis for HPV.
7. We plan to conduct a study combining liquid cytology, artificial intelligence cytology (AIC) and DNA analysis for HPV in a 1,000 patient random sample in order to assess the effectiveness of this diagnostic application in screening and early detection for Cervical Cancer and the feasibility of the combination of these new and promising technologies. If this new system of cervical cancer diagnosis proves effective, cohesive and feasible, it may be used as a model for other Centres within the European Network for Early Cervical Cancer Detection and in other European Cancer Control Centres.
8. We plan to conduct a preliminary study utilising IR. spectrometry as a cervical cancer diagnostic tool.

Following 6 projects from 6 Member States will participate to these activities:
- BELGIUM: Scientific Institute of Public Health – Louis Pasteur
- FINLAND: Finnish Cancer Registry, Helsinki
- FRANCE: Association EVE, Strasbourg
- GREECE: (Chalkidike): Our Lady Who Loves Mankind
- PORTUGAL: Centro Regional de Oncologia Coimbra
- SWEDEN: Lund University at Malmö

- The obtained results will be disseminated on the WEB FORUM to the other partners from the Member States.
BELGIUM: Scientific Institute of Public Health – Louis Pasteur

The main aim is to continue to evaluate the potential gain of sample quality and diagnostic validity of thin layer cytology combined with 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 cost benefit analysis will enable cytological laboratories and clinicians involved in cervical cancer screening to choose rationally between different screening methods.

Cost-effective modelling of alternative screening strategies: target age groups, screening frequency of screening, inclusion of new screening methods with MISCAN and alternative micro-simulation models.

FRANCE: EVE Association

The aim of the project is to continue 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 in 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 (Chalkidike): Our Lady Who Loves Mankind

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

i) Conduct a study to determine the prevalence of HPV infection in a sub sample of the screened population.

ii) We plan to conduct a preliminary study utilising IR. spectrometry as a cervical cancer diagnostic tool. This will involve a random sample of 15 pap smears that have already been diagnosed utilising conventional cytology practices and AIC quality control being analysed by the IR. spectrometer of our lab. This will occur in co-ordination with other leading centres in the USA who have pioneered this methodology and have demonstrated to some degree its accuracy and usefulness.

iii) Explore new technology in creating a communications link with European Centres of Excellence in the UK, Germany and other European Centres via the Internet.

FINLAND: Finnish Cancer Registry, Helsinki

The aim of this project is to perform a multi-arm randomised study on introducing new technologies in cervical cancer screening. We plan to:

- continue a randomised trial with neural network assisted analysis tool, Papnet, using capacity of 40,000 smears per year taken in the Finnish cervical cancer screening programme; and
- run a large-scale HPV-DNA testing in the organised cervical cancer screening programme.
- consider the ethical aspects according to the national rules. The Ethical Committees involved have given/are going to give their statement.

PLANNED WORK

The main aim of the randomised multi-arm trial is to evaluate the effectiveness of the proposed new technologies in preventing cervical cancer. We also analyse carefully the detection rates of cancerous and pre-cancerous lesions, colposcopic confirmation & treatment included (performance analysis), as well as concentrate on constructing a reliable quality control system within the national screening programme.

Papnet arm. More than 40 000 smears per year are scanned by Papnet and screened with review stations in each laboratory included in the trial arm. The study started with 6 laboratories in 1999, but now additionally two laboratories have entered the study. According to the present protocol, after accrual of three years (1999, 2000, 2001) 120,000 smears are to be included in the performance study on Papnet in late 2002. If the qualitative difference in detecting HSIL+ (moderate dysplasia or a more severe finding) lesions appear to similar than in the pilot, we have very good statistical power for comparing the performance of the method with the traditional screening (power 80%, alpha 0.05, two-sided to see differences even of 20% of magnitude in the cytopathological detection) and good statistical power even for differential detection of CIN3+ lesions (severe dysplasia or a more severe screening finding). After continuing the inclusion in the Papnet arm up to five years allows similarly sufficient statistical
power in detecting a marginal effect of about 50% in the prevention of the invasive cervical cancer which is expected based on the pilot results.

**HPV-screening.** We expect to finalise the HPV screening pilot using 2000 hospital smears already during the course of 2001. We plan to use Hybrid Capture II method developed by Digene in the primary HPV-DNA-based screening. The HPV-screening trial arm will be organised after the careful pilot analysed (provided that the pilot will be successful).

**HPV-vaccination.** Feasibility study on HPV-vaccination will also be continued in our country (Lehtinen et al. 1998, on-going) and the HPV-vaccination study will be coordinated with the new screening options.

**TASKS:** Randomisation for 2002 will be accomplished in December 2001. Sample collection will be continued throughout the activity period. A scientific study report (article) using the performance parameters will be written in September-December 2002, based on screenings during 1999-2001.

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**PORTUGAL:** Centro Regional de Oncologia Coimbra

The aim of this project is to continue the work of the previous project (16, December 2000 to 15. December 2001) on a combined study (Pap smear by ThinPrep Method and HPV testing) over a period of one 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 of ASCUS/ACFUS. The objective is to improve the 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.

This 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 BPV test with Hybrid Capture 11 (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.

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**SWEDEN:** Lund University at Malmö

The aim is to investigate the construction of a database of computerized colposcopic images of the cervix of women with persistent oncogenic HPV infection and, for comparison, from normal women, in relation to the histopathological diagnoses of the corresponding biopsies. This database may be useful for evaluating the value of and continued improvement of colposcopy for this particular group of women.
2.4 Planned Part 4: "Web Forum for Info Dissemination"

Objective: Development and use of WEB FORUM, the communication platform for teamwork, and Internet dissemination of the network results:

- Development of Multilingual User Interfaces
- Development of facilities for supporting images and voice data
- Development of an efficient Search Engine

Leader: Prof. Schenck (Co-ordination Centre)

The WEB FORUM is in daily use and allows teamwork and dissemination of the project information and results, including the intermediate results. Access is free of charge for all partners from the Member States:

- 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
- GERMANY: SWS Tumorcentre Zwickau
- GREECE: Hellenic Foundation of Oncology, Athens
- GREECE: (Ormylia-Chalkidike): Our Lady Who Loves Mankind
- HOLLAND: University of Nijmegen,
- ITALY: Unit of Cancer Epidemiology, Turin
- PORTUGAL: Centro Regional de Oncologia Coimbra
- SPAIN: Health and Social Welfare Council, Junta de Castilla y León, Valladolid
- SWEDEN: Lund University at Malmö
- UNITED KINGDOM: Birmingham Women's Hospital

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.

PLANNED WORK

Additional software development work will be performed by the Co-ordination Centre during this project (December 2001-December 2002), as follows:

- development of improved protection procedures in order to protect the "write access" to the forum data, and to avoid that data will be disrupted. (March 2002)
- improvement of the user access and of the navigation paths to the forum data (April-May 2002)
- development of multilingual facilities (June-August 2002)
- topic-oriented structuring of forum information, and implementation of facilities for supporting images and voice data (June-December 2002)
- Development of an efficient Search Engine (February-December 2002)
3. Obtained Results

Cervical cancer has now become the second most common cancer among women in the world, with up to 500,000 new cases/year and up to 300,000 premature deaths a year. It is the most common female cancer in large areas of the developing world where an estimated 80% of new cases arise. Because of the long preclinical period cervical cancer can be prevented by screening, diagnosis, and treatment of premalignant cervical lesions. 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 colposcopy.

Infection with oncogenic human papillomaviruses (HPVs) is the most important cause of cervical cancer worldwide. After infection there is a long latency period of at least 10 to 15 years during which cervical cancer develops in a small proportion of originally infected women. Prevention of HPV infections by vaccination may result in a 5–10% reduction of cancer mortality worldwide. Preventive HPV vaccines are entering clinical efficacy (phase III) trials:
- plain virus-like particles (VLPs),
- DNA free capsids comprising the major viral capsid (L1) protein, and
- chimeric VLPs (CVLP) containing various combinations of early viral proteins attached in different ways to the major L1 or the minor (L2) capsid proteins of the virus.

Randomised clinical trials will define the efficacy of the different vaccines against persistent HPV infection and other surrogate end points, such as cervical intraepithelial neoplasia grade II/III. Considerable gains at the individual and societal level would be obtained if cervical cancer could be prevented.

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 in "New Technologies", including HPV clinical detection. 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 of section 2, and the obtained results are here summarised. The detailed descriptions of the work and obtained results in 11 Member States are provided in the attached 13 Final Reports:

- Report No. 1 Germany, Munich
- Report No. 2 Belgium
- Report No. 3 Finland
- Report No. 4 France
- Report No. 5 Germany, Zwickau
- Report No. 6 Greece, Athens
- Report No. 7 Greece, Chalkidike
- Report No. 8 Holland
- Report No. 9 Italy
- Report No. 10 Portugal
- Report No. 11 Spain
- Report No. 12 Sweden
- Report No. 13 UK
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 (Munich), Belgium, France, Greece (Chalkidike), Holland, and UK

GERMANY: Cytological Institute of the Bavarian Cancer Society

The work in this reporting period had 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.

During the reporting period 16. December 2001 to 15. December 2002 laboratory work was performed as planned. The developed tools were experimentally used in the laboratory environment, and a number of 26,902 smears were analysed. The improvement of the quality of the laboratory screening was evaluated and re-screening work was performed for a number of 2,065 smears. The cost-efficiency of the screening work was analysed, and the computer-based recording of the screening work was improved and released in May 2002.

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.

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

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 based on the results of the Network Workshop "Guidelines for Cervical Cancer Screening" in Ormylia, Greece from 25-29. September 2001. The world wide access to WEB FORUM via Internet 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 Guidelines for Quality Assurance in Cervical Cancer Screening" (released in November 2001), was revised starting with December 2001, and a new draft was released for discussions on the WEBFORUM in April 2002.

The discussion documents of "ECCSN Terminology Group" of 5. May 2002, and about the "Cytopathology in Germany" of 28. April 2002 were released and made available for further discussion to the Network participants and external experts in the WEBFORUM.

The obtained results in updating the guidelines were presented at the 16th Workshop on Clinical Cytology (in German "16. Arbeitstagung für klinische Zytologie") on 10. May 2002 in Bad Ischl, Austria.
The Guidelines were re-structured, and the responsibilities of the Network partners were agreed. The Table of Contents of the Guidelines was released on 25. November 2002.

The first draft of the "Re-structured European Guidelines for Quality Assurance in Cervical Cancer Screening" was released as an Internet document, and collection of the contributions of the network partners was started in November 2002. The Guidelines Meeting on 16.-17. December 2002 in Luxembourg was planned, and the contributions of the partners were disseminated on the WEB FORUM.

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 Belgian work was concentrated on:
- Preparation of a case control study
- Application of HPV-DNA detection methods in (a) a primary screening setting, (b) triage of atypical or low grade cytological lesions, (c) follow-up of treated patients.
- Continuation of ongoing research concerning the comparison of liquid-based cytology versus conventional cytology.
- Trial of alternative therapeutic strategies for CIN-lesions: local surgery on cervix – topical application of immuno-modulators.

Work was performed on a case control study in co-operation with the Free University of Brussels, with the aim of correlating full rescreening of cytologically negative cervical smears with high-risk HPV testing and clinical outcome. The results were published as "Triage HPV versus primary HPV screening in combination with liquid-based cytology (the Brussels trial)".

A questionnaire for determining the attitude of women and gynaecologists towards the use of HPV tests in cervical cancer screening was developed in co-operation with the University of Liège.

The trial started in 1999 on "Application of HPV-DNA detection methods for triage of atypical or low grade cytological lesions" was continued, and 2,000 women were added. This trial was performed in co-operation with the Free University of Brussels.

Work was continued on the "Comparison of liquid-based cytology versus conventional cytology", and a systematic review of all articles published on this subject was produced.

Alternative therapeutic strategies for CIN-lesions (local surgery on cervix, topical application of immuno-modulators) were investigated and a trial was planned.

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

At the moment, results of the evaluation of thin layer techniques remain the same as in 2001. This study has already shown that Autocyte Prep® method improved specimen adequacy. An incidence of Low-grade Squamous Intraepithelial Lesion (LSIL) and of ASCUS-AGUS was also noticed with the two thin layer techniques (Autocyte Prep® and Cyteasy®). Both liquid based cytology techniques reduced the rate ASCUS-AGUS / LSIL.

Comparison of 3 years outcomes for adequate smears in the two laboratories and of diagnostic parameters of each technique need further follow-up.

2 447 smears coming from 4 pathology laboratories are involved in the long-term survey of ASCUS and AGUS. All cytological reports corresponding to these smears have been recoded regarding Bethesda 2001 classification. 76,7% are ASC-US, 14,1% are ASC-H, 8,9% Atypic Glandular Cells (AGC) and 0,3% show atypic glandular and squamous cells together.

To assess quality of cytologic results in this peculiar field of atypic smears, 10% of the smears involved in the study were blinded-reviewed. The temporary results of this review show that initial readers were probably too pessimistic. For example 42,3% of the smears initially coded ASC-US were re-evaluated as WNL.

A preliminary study of the outcomes was done by analysing subsequent smears and possible histological exams registered in our data base.

At the moment 8,1% of smears are lost of follow-up, 73,6% have a totally normal follow-up, 4,5% are followed by a histological lesion (at least CIN1), 11,5% have a cytologically confirmed lesion and 1,4% need further investigation in medical records.

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

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.

During the reporting period data on 5.520 examined women was processed including pap smear and gynecological examination, reaching a total of 18.579 women having been screened since the initiation of the screening program. Data for all these patients has been entered into the computer data base. During the past year the Center was successful in inviting and organizing groups of women from villages in the region that had never participated in the screening program before. These villages are extremely remote in the mountainous areas of Northern Greece. Of the 5.520 participating women whose data was analyzed in the framework of the Ormylia screening program, 1.426 (26%) were new participants.
The overall participation rate for all women screened in our program is 68.4% whereas the participation rate for the 25-64 age group is 85.4% and 89.6% for the age group 30-59 years.

The majority of tests performed during the previous period 30/08/99 to 15/12/2000 was negative for malignancy (99.862%) whereas 335 women were hysterectomised therefore no smear test was taken. Overall 26 women tested positive and were referred for colposcopy and 11 for biopsy. A number of 4 women tested positive underwent hysterectomy and conisation was performed on 8 women (CIN 3). A number of 6 women had a diagnosis of CIN I; 4 women had CIN II; and 1 woman had CIN III. A number of 5 repeat smear tests were taken in three months and 90 in six months respectively, whereas 2 women were diagnosed HPV positive. In 7 women the biopsy was negative for malignancy. All women followed the suggested treatment and are closely monitored by the screening program staff.

An additional number of 1,093 tests were classified as abnormal without any indications of malignancy, but presenting several types of vaginal infections and inflammations, which were treated according to the type of the pathogenic agent causing the abnormality. The majority of the detected pathogenic agents were fungi and cocci. In all cases women were advised by the gynecologist on further action they should take in order to finalize diagnosis and treatment of their condition. The majority of women presenting inflammation pertain to the 25-64 years age group.

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. 7.

HOLLAND: University of Nijmegen

In order to develop quality assurance and quality control tools, to evaluate their impact on cervical screening with respect to their efficiency and costs, and to educate cytotechnologists and pathologists in QA/QC, the following studies have been carried out:

- Evaluation of rapid prescreening in cervical cytology,
- Evaluation of the prevalence of squamous abnormalities in EEC-smears,
- Evaluation of the quality of smears taken by general practitioner’s assistants in a Dutch regional screening program,
- Development and implementation of virtual slide technology in electronic slide seminar on cervical cytology, and
- Automated regional evaluation.

Rapid Prescreening

Efficient quality assurance and improvement measures are essential ingredients in a well-organised cytology based programme for cervical cancer screening. Different Pap smear review procedures, aiming for optimisation of accuracy, are described throughout the literature. Evaluation and synthesis of those methods is needed. In a previous study,
data were pooled on diagnostic quality of rapid reviewing (RR) of cervical smears, initially reported as normal or unsatisfactory. In a cooperation with Brussels (dr M. Arbijn), and Munich (dr U. Schenck) we have contributed to a study to focus on rapid pre-screening (RPS) of unreported smears (Arbijn et al).

Six published studies, on the accuracy of rapid pre-screening relative to subsequent full screening, were pooled using meta-analytical methods. The pooled average sensitivity of rapid pre-screening was respectively 64.9% (95% confidence interval (CI): 50.7-79.1) for all abnormalities, 72.6% (CI: 60.6-85.2%) for ≥ low-grade lesions and 85.7% (CI: 77.8-93.6%) for ≥ high-grade lesions. The pooled specificity was estimated at 96.8% (CI: 95.8-97.8). The sensitivity increased significantly with duration of screening and decreased with workload. Almost three percent of all abnormal slides were detected only by RPS (2.8%, CI: 0.0-5.8%). This is comparable to the proportion of false-negative smears detected by RR.

RPS shows diagnostic properties that support its use as a quality control procedure in cytological laboratories. We showed previously that RR is superior to full reviewing of a 10% random sample of negative slides (10%FR). Since the yield of additional abnormalities found by RR and RPS is comparable, we expect RPS to be more efficient than 10%FR as well.

Prevalence of squamous abnormalities in ECC- smears
Purpose of this study was to determine the prevalence rate ratio of squamous lesions in smears without (ECC-) versus smears with endocervical component (ECC+) smears and to estimate the true prevalence of these lesions in women with ECC- smears by addition of short-term follow-up results of negative ECC- smears.

Results of smears in a 3 years period, as well as follow-up results of negative ECC-smears in the same period were retrieved. Smears were categorized into two groups: ECC- and ECC+ smears. The data were analysed for three outcome parameters, ASCUS or higher (ASCUS+), LSIL or higher (LSIL+) and HSIL or higher (HSIL+).

Squamous abnormalities occurred far less frequent in ECC- than in ECC+ smears. Prevalence rate ratio (PRR) was 0.28 for ASCUS+, 0.39 for LSIL+ and 0.36 for HSIL+. Addition of follow-up results of negative ECC- smears, results in PRR’s which are still significantly lower than 1, and most marked in sub-set HSIL+ (PRR=0.60). We conclude that the true prevalence of squamous lesions in women with ECC- smears is significantly lower as compared to ECC+ smears. These findings lent support to the decision to abolish the repeat of ECC- smears in the Dutch population screening program. During the present project period we have finalized the study and described the results in a paper which has now been accepted for publication in Cytopathology (Siebers et al).

Quality of smears taken by general practitioner’s assistants
The Dutch screening program has been reorganized in the mid-nineties resulting in an improved quality of the whole screening process (Hanselaar, Becker et al). To improve efficiency an increasing percentage of smears are now being taken bij GP assistents (GPA). Previous studies have shown that it is possible to train GPA such that an increase in quality parameters such as percentage of smears with endocervical component and adequate smears is feasible. Aim of the present study was to explore differences in the quality of smears taken by general practitioners (GP) and smears taken by GP assistants. Therefore thirteen general practices were selected where smears were made by the GP and thirteen practices where GPA performed the smear-taking. Quality of smears taken in a 3 years period in the selected practices were analysed. All
smear were made within the cervical screening program. Initial analyses show that the quality of the smears made by GPA are significantly more smears lacking endocervical cells and inadequate smears. The results will be described in a paper which will be submitted for publication in a medical journal (Verblackt et al).

“Virtual slide” technology in electronic slide seminar for cervical cytology
Theoretical and practical (post-)graduate education to cytotechnologists, pathologists and residents is limited by the availability and quality of microscopic slides. The archives of microscopic slides are needed for patient care, educational and QA/QC purposes. Because of damage of archival slides and rapid decline of stains, a considerable loss of slides occurs, especially of unique and important slides. We have co-worked with Zem Technology and Nikon Europe to develop a virtual microscope unit which is well equipped for a) digital representation of whole microscopic slides for (post-)graduate educational purposes, b) examination and reporting of virtual slides by a standardized procedure, and c) e-mail correspondence between remote user and seminar coordinator.
A “virtual slide” is a digital representation of a complete specimen that can be viewed on a PC. Virtual slide gives the look and feel of a microscope without the microscope being present. Virtual slide facilitates storage of microscopic images for use as reference, in databases or educational purposes. Use via internet-technology is feasible. In the first 6 months of this study period we have technically developed the system. In the second half of this period we have tested and implemented the system in an electronic seminar for cytotechnologists and pathologists. If successful, this technique will be made available to national and European slide seminars. The results will be described in a report which will be submitted for publication in a medical journal.

Automated regional evaluation
The purpose of evaluation of a cervical screening program is to obtain adequate instruments for monitoring and controlling of the program on a national (effect) and regional (process) level. The Dutch National Coordination Committee, responsible for organization and control of the screening program, felt the need to obtain a limited number of critical figures for monitoring by time trends and benchmarking. Based on these limited number of critical figures we developed an automated system for regional evaluation of the cervical screening program.
From the National Pathology Database (PALGA), we retrieved the results of all smears, made in 2001 in the cervical screening program in two Dutch screening regions with the results of succeeding pathology examinations. We also retrieved all histological diagnosed CIN and cervical carcinoma’s of women living in the two regions in question. With specially developed dedicated software, all data were imported into an MS Access-database. We automatically corrected for administrative fusions. With the software the data were transformed into several relevant tables and critical figures were calculated.
The produced tables can be categorized in 4 groups, each giving information for monitoring and benchmarking. The tables in group 1 (“Population, invitation and attendance”) provided information about the population, rate of invited women, attendance rate and coverage. Group 2 (“Screening results”) provided information about the results of screening for each regional laboratory, including short-term follow-up results (cytological and histological). Detection rates and positive predictive values were calculated for each regional laboratory. In this way the figures can be used for monitoring the quality of the regional laboratories by benchmarking. The tables in
group 2 provided also information for various age-categories, not only age-distribution of cytological detected abnormalities, but also age-distribution related to quality of the smear. Group 3 (“CIN and cervical cancer”) provided information concerning CIN and cervical carcinoma. Age distribution of CIN I/II/III and cervical carcinoma was given. The relation of the detected lesions with the screening program was established for 2 different cytological cut-off points (ASCUS or more and HSIL or more). Tables in group 4 (“Smears outside screening program”) provided information with respect to smears taken outside the screening program and their age distribution as well as information on logistics (various response times). Automated regional evaluation and production of relevant tables and critical figures has proved to be possible. Standardization of pathology data in the Netherlands is sufficient for automated analysis. The defined tables can provide adequate information for monitoring and benchmarking. The results of the regional evaluation are presented in the annual reports of the two screening regions (Annual reports of 2001; Foundations for Prevention of Cervical Cancer, East and South Netherlands).

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

UNITED KINGDOM: Birmingham Women's Hospital

The aims of British work were:

- To identify and record the quality of colposcopy training programmes in the 14 member states of the European Federation for Colposcopy (EFC), together with the National Colposcopy Societies of Poland, Hungary, Slovakia, Czech Republic, and Israel.
- To agree minimum standards of the training (Quality Assurance Standards) necessary for colposcopists to be competent to see, assess and, if necessary, treat women with pre-cancerous conditions of the cervix, vagina and anus.
- To agree ongoing standards of treatment (Quality Assurance Standards) thereby maximising the quality of treatment offered to women with pre-cancerous conditions of the lower genital tract. This will include audit of treatment.

The 14 countries were contacted and the results of the questionnaire were presented to the 11th World Congress of Cervical Pathology and Colposcopy 2002. In short there is very little organised colposcopy training throughout Europe. Training appears to be centred on individual institutions and the quality and period of training varies enormously. The only country with a nationally recognised colposcopy training programme is the United Kingdom. The results were published at the 11th World Congress of Cervical Pathology and Colposcopy in 2002, and in "Giornale Italiano di Obstetricia & Ginecologica 2002".

In October 2002 the minimum standards of training for colposcopy were agreed. Although colposcopy is performed for a variety of different reasons and in different settings throughout Europe the prime objective, the detection of pre-cancerous cervical disease, and the required core skills are the same. It was decided to use a competence-based approach which would aim to deliver those competencies needed to practice
colposcopy rather than adopt a traditional knowledge-based approach. The method chosen was the Delphi technique. A 4-round iterative questionnaire survey was used and the competencies rated using a 5-point Likert scale. Competencies raised as 4 or more by at least 90% of the respondents were regarded as necessary for the core curriculum. Eighteen participants took part in all 4 rounds and 27 were active in each of the last 3 rounds. Fifty-one core competencies were selected from a list of 76 competencies collated by the group as a whole. The majority (44) of the selected core competencies received a score of 4 graded in each round. Overall there was evidence of increasing consensus but the individual shift in opinion was slight. The Delphi technique was found to be an effective tool for obtaining an expert consensus and enabled group “ownership” of the identified core curriculum. The final number of agreed core competencies was 51.

Quality Assurance Standards of treatment
Techniques used for the elimination of cervical premalignant disease fall into 2 categories – excision and destruction (ablation.) There is variation from centre to centre throughout Europe but the end result is intended to be the same, namely the elimination of premalignant disease. In the United Kingdom each centre treating women with premalignant disease must submit an audit of its work on an annual basis. This is not the case in any other country and at this stage it would be impossible for every centre to submit an audit of its work. The study group plans to target major centres in every country. The first stage will be to identify the methods of treatment. The second stage will be to identify ways in which the success of treatment, as measured by the elimination of disease at follow-up, can be determined.

Introduction of agreed standards of training in colposcopy for each Member State.
The agreed core curriculum for minimum standards of training has been circulated to all Member States of the European Federation for Colposcopy together with the national colposcopy societies of Poland, Hungary, Slovakia, Czech Republic, Israel and Romania. The project during 2003 will be to follow through and to ask each country how it intends to introduce the standards of training with a view to reporting in January 2004.

Identification of ways in which the quality of treatment can be measured, the aim being to ensure that all European women obtain the best possible quality of treatment for their premalignant disease. Major centres in Europe will be targeted to give an analysis of methods of treatment and the success of treatment as measured by freedom from disease following treatment. This is ongoing.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 13.
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, Finland, Germany (Zwickau), Greece (Athens), Holland, Italy, Spain, and Sweden

BELGIUM: Scientific Institute of Public Health

Work was performed on:

- Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection.
- Support to cytological laboratories in uniform registration of cytological and histological data on cervical lesions. Computer support for data-entry, extraction and transmission.
- Advanced statistical analyses of incidence and mortality trend concerning cervical and other uterine cancer: study of temporal and spatial variation in relation with influencing factors (screening, age-period-cohort effects, treatment, survival).
- Organisation of the Symposium on Cervical Cancer Screening by the Belgian Society of Clinical Cytology.

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

FINLAND: Finnish Cancer Registry, Helsinki

A planning meeting was held in the IARC, Lyon, together with Dr E.Weiderpass and the staff of the ENCR in December, and the study protocol has been produced for analysing historical cervical cancer incidence and mortality trends as to the impacts of screening in the European countries. The activity will continue with Dr Weiderpass and ENCR during 2003.

Unlike in our original proposal this analysis will include all European countries, not only those with high-quality cancer incidence and mortality information. Our first proposal was to concentrate on those countries who have reliable data on the cancer
incidence and mortality (and no corrections for the diagnostic or registration limitations would have been required). The role of the cervical cancer screening network will be to coordinate and implement data collection on screening parameters and on some related exposures.

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

GERMANY: SWS Tumorcentre Zwickau

We have performed statistical analyses and reporting of data from the Saxony Cancer Register concerning cervical and other uterine cancers. A handbook (of 26 pages in German) on data evaluation for clinical cancer registries was published, and is available on the web.

Juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection was offered to 10 hospitals in the south-west Saxony region.

Support was provided to cytological laboratories in the south-west Saxony region for uniform registration of cytological and histological data on cervical lesions.

We have performed statistical analyses of incidence and mortality trend concerning cervical and other uterine cancer: study of temporal and spatial variation in relation with influencing factors (screening, age-period-cohort effects, treatment, survival). We presented the obtained results to the network participants to the meeting in Munich on 5-6. September 2002.

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

GREECE: Hellenic Society of Oncology, Athens

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

i) Implementation part of the 6th round of the screening programme in Ilia, and part of the 5th round of the screening programme in Messinia.

ii) Follow-up of the women with non negative smears (HPV, CIN I, II, III, invasive cancer) through the Control Unit that is located in the central offices of the Hellenic Foundation of Oncology

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) Optimise cervical cancer early diagnosis.

vi) Dissemination of the results obtained during this project on the WEB FORUM, discussions with the project partners, participation to congresses and scientific meetings.
vii) Continuing the epidemiological studies
viii) Dispatch to the National Cancer Registry of the Greek Ministry of Health of all HPV, CIN I, II, and III cases in order to be registered.
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. 6.

HOLLAND: University of Nijmegen, University Medical Centre St Radboud

In a previous study, as a member of the EC Network for Cervical Cancer Screening, this group has developed a general practice-based call system in a population based screening programme for cervical cancer. This resulted in an increased participation of at-risk women, and a protection rate of 85% in the population.
A way to optimise the compliance to follow-up of abnormal smears is to improve the communication between smear taking general practice and the cytological laboratory, because the difficulties with follow-up are primarily difficulties of communication. Therefore, a communication between the smear taking GP and the cytological laboratory has been developed in the Netherlands. The outcomes of this project were comprised in a multi-annual study, to implement and evaluate, at local level, the effectiveness of two different communication systems, particularly based on the European guidelines for the Quality Assurance in Cervical Cancer Screening, between general practices and two cytological laboratories, to monitor positive screening results. This project will detect the most cost-effective system.
The specific aim of this project was to develop a systematic assessment of the presence or absence of preconditions for successful implementation of the most cost-effective communication system at national and European level. In this manner the study further contributes to an evidence based screening practice in routine primary care.
In our previous reports of the project (ending 15 December 2001) we have reported preliminary findings. During the present project period we have finalized the study and described the results in a paper which is submitted for publication in an international medical journal.
Briefly the results indicate that in the Netherlands, the comprehensive system with monitoring and reminding of all abnormalities by the cytopathology laboratory appears to be more effective than leaving the follow-up to GPs and using the laboratory as a safety net (selective system). The performance of the system is a minimal intervention with relatively low labour intensity and low cost.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 8.
ITALY: Unit of Cancer Epidemiology, Turin

Part of the Italian work was related with the monitoring of process indicators for cervical screening. Purpose of the project was defining indicators that measure aspect of the screening process that are crucial for effectiveness and for human and economic costs, comparing different programmes, providing reference values and finding out situations needing correction.

A first list was defined and an Italian “Manual” (indicators, rationale, methods for data collection, interpretation, preliminary standards) was prepared. This manual was published as a supplement to the Journal for Epidemiology and Prevention.

Data were collected in a standardised manner from the large majority of Italian organised programmes. Since most of such programmes were in a starting phase in such a period this allowed building their information and computer registration systems in such a way that they were able to provide the needed data.

This allowed computing national figures and making comparisons between programmes. This also allowed eliciting areas and specific programmes needing improvement. A synthesis has been published in 2002 in “Osservatorio Nazionale per la prevenzione dei tumori femminili. Primo rapporto”.

Such an experience can be used at a European level, in particular in the preparation of the new Guidelines for quality assurance, in order to define more comparable monitoring systems.

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 area of the performance of the Programme is the most extensive region in Europe, the Autonomous Community of Castilla y León, that, with an area of 94,147 square kilometres, has 6,145 towns distributed in nine provinces. The population of Castilla y León is 2,545,926 inhabitants, of which 1,283,600 are women. Of the 243 Health Basic Zones in Castilla y León, in the period 61-12-2001 / 15-12-2002, 99,2% of the Health Basic Zones have the necessary human and material resources to perform the Programme. The target population to which this Programme is aimed at are women in Castilla y León aged 25 – 65, as well as those women who do not belong to this age group but have risk features. In 2002, 98,4% of the target population in Castilla y León have access to the service (553,768 women)

The screening procedure includes the performing by the health professionals of Primary Care of the clinical history and the smear taking to do a Papanicolaou test in the reading centres of the Programme. It has been established that the two first smear tests are to be done in an interval of one year. Subsequently, the screening interval following a negative result is three years.

Analysing the 64,132 women with smear test in this period, 57,446 are women between 25 and 65 years old (89,57%), and 10,43% are younger than 25 or older than 65: of these, 6,62% (4,248) are women younger than 25 and 3,8% (2,438) belong to women older than 65.

The percentage of women with more than one smear test, 7,26% is lower than the percentage of women with abnormal smear test, 12,05%. The smear tests per woman in the age group 25-65 is 1,04. Of the 64,132 women who took part in the Programme...
55,859 (87.10%) did not have any pathology; the 10.83%, 6,946 women had infections and only in 653 cases morphological disorders were found in the smear test.

Follow up of 97.24% of the anomalous cases including viruses and CIN has been performed; 342 (52.37%) with final results and 293 (44.87%) were not available in February 2003. 166 of the 342 cases with final results after the follow up are positive (48.54%) and 234 cases (68.42%) are negative. Distribution of the positive cases: 4 invasive carcinomas, 1 microinvasive carcinoma, 11 carcinomas in situ, 120 dysplasia and 30 different morphological disorders.

Some techniques of HPV detection have been introduced in the diagnosis and treatment protocol of women with morphological disorders in the screening smear tests in the provinces of Ávila and Valladolid. Results in:

Ávila:
3.57% of the women with morphological disorders in the screening smear tests are HPV + and 25% are waiting for the test results.
25% of the women with morphological disorders have not done the HPV test in this province.

Valladolid:
48.09% of the women with morphological disorders in the screening smear tests are HPV + and 9.48% are waiting for the test results.
Only 0.55% of the women with morphological disorders have not done the HPV test in this province.

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 56,373 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 the unit of gynaecological cytology of the University of Valladolid, in 2002, the reading of 56,373 screening smear tests has been done. Those smear tests were done in the provinces of Avila, León, Palencia, Salamanca, Segovia, Soria, Valladolid y Zamora:

- Reception, labelling and record of 56,373 extensions.
- Preparation and colour of the extensions.
- Reading of the extensions.
- Double screening of the abnormal samples and a percentage of the samples chosen at random among the takings considered to be normal.
- Working out of the cytological report.
- Study of HPV by means of hybridisation and PCR in takings performed for diagnosis and treatment of women who showed morphological disorders in the screening smear tests performed in the provinces of Ávila and Valladolid.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 11.
SWEDEN: Lund University, Malmö

Following work was performed in the period 16. December 2001 to 15. December 2002:

- Final design of secondary HPV screening randomised health care policy. Ethical committee approval (month 3).
- Start of the new health care policy. Database operational and continuously collecting cytological results, HPV testing results and health care resource usage in the 2 policies (month 3-month 11).
- Interim analysis of safety and cost-efficacy for the scientific report (month 11-month 11).
- Continued accrual of HSIL endpoints in primary HPV screening trial (month 1-month 12). The scientific report contains data on total number of endpoint observations, as a measure of the progress of the trial, but the code will not be broken to reveal data on efficacy until 2003.
- Entering of digital colposcopy images and subsequent histopathological diagnoses into a HPV screening colposcopy database (month 1-month 11).
- Interim analysis for the scientific report of the value of colposcopy for predicting histopathological diagnoses in this particular group of women (month 11-month 12). Scientific publication, also taking the HPV DNA testing results into account, will be after the code has been broken in 2003.

We have obtained following results:

2. Establishment and maintenance of a database for monitoring of safety and cost-efficacy of the new and old policies. The database will ultimately generate knowledge of whether a routine health care policy aiming at increased specificity of cervical screening by secondary HPV testing of women with low-grade cytological abnormalities is safe and cost-efficient under real-life conditions.
3. Continued accrual of endpoint observations (HSIL incidence) for a randomised primary HPV screening trial. If the expected increased efficacy of HPV-based screening is indeed found, this could lead to new etiology-oriented cervical screening programs in Europe.
4. Establishment of a database of computerized colposcopic images of the cervix of women with persistent oncogenic HPV infection and, for comparison, from normal women, in relation to the histopathological diagnoses of the corresponding biopsies. This database will be useful for evaluation of the value of and continued improvement of colposcopy for this particular group of women.

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

BELGIUM: Scientific Institute of Public Health

The work performed in this part is closely related with the reported work in the section "Performed work on Quality Assurance and Quality Control".

Our aim was to continue to evaluate the potential gain of sample quality and diagnostic validity of thin layer cytology combined with HPV DNA detection using the Hybrid Capture kit II in comparison with the classical Pap smear.

This research was executed in collaboration with the Free University of Brussels. This is the continuation of the research started in 1999 “Primary versus triage based HPV detection in combination with thin layer cytology. A randomized trial”. A number of 2000 women were added to the trial in 2002.

Methodology: Two time one thousand extra women have been added for the year 2002. These women consulting at the gynecological department of the Hospital of the Free University of Brussels are 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 is limited to those showing atypical or low grade cytological lesions (triage setting).

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

FINLAND: Finnish Cancer Registry

According to the study plan and contract for the current activity period, the main Finnish activity was related to evaluation and implementing new technologies in the cervical cancer screening programme. The Finnish Cancer Registry has continued a very large-scale public-health trial on the automation-assisted screening methodology (fourth year of the overall project), and started a large-scale primary screening trial.
using HPV-DNA testing. They have also finalised biostatistical analyses of the HPV-DNA pilot study and of second to third year results on screening process indicators on the automation-assisted screening trial. The first-year results on the automation-assisted screening were published in the IJC journal. They have also planned a complete audit system within the Finnish cervical cancer screening programme that includes also testings and other programme aspects of both of the new technology arms. They have negotiated with the Finnish and international study groups on HPV vaccination; to integrate the screening trials with the emerging research on vaccines in the future.

The main activity has been to evaluate new technologies in cervical cancer screening. They have obtained the following results from the beginning of the project up to the end of the current activity period:

**Automation-assisted screening**

They have randomised up to 222,206 women in the automation-assisted screening arm and a two-fold number in the control arm during the first four years of the trial (1999-2002). In addition 34,839 women were randomised during 2002 for the automation-assisted screening arm. Biostatistical analysis on the screening during the first three years (1999-2001, on which years there exist at the moment screening records at the mass screening registry) were restricted on 157,187 women randomised in the Papnet arm and 317,753 women randomised in the control arm, respectively. Women randomised in the area of one cytology laboratory included originally in the study (Laboratory of the Finnish Cancer Society in the Vaasa municipality) were excluded from the final analysis, because the laboratory could not follow the study protocol adequately throughout the study period.

109,712 women were screened in the automation-assisted screening arm and 317,753 women in the control arm during the first three years of the trial within the cytology laboratories included in the final analysis; in addition 36,554 smears of women in the automation-assisted screening arm were scanned during 2002 (screening results not yet available). The study included six cytology laboratories in the Finnish cervical cancer screening programme. According to the preliminary results the participation rate was 70% in both arms, and the proportion of smears screened actually with the methods for which the woman had been randomised (Papnet) was 89%. The latter proportion was 72% in the year 1; 96% in the year 2; and 98% in the year 3; the remainder (not screened with Papnet) being scanning errors.

One can conclude that the study protocol was followed well in the laboratories and also that the registration was successful for the study purpose. Laboratories coped with the new system during the three first years.

The results of the first year have been published in a scientific journal (Nieminen et al. 2002). According to the results automation-assisted screening was at least as sensitive and specific in finding pre-cancerous lesions as manual screening, when assessed in the well-controlled and highly effective organised screening programme existing in Finland. Comparisons of the test sensitivity and specificity, where the status of the histologically confirmed lesions is used as the gold standard, on the three first years will be published in a scientific paper.
Concerning 2003 (the fifth year) they plan to integrate the complete feedback and audit process to the screening arm(s) as well as to measure for the cost-effectiveness purposes details on working time consumption, capacity, etc. in the cytology laboratories. Time is now mature for that as there are experiences using the automation-assisted instruments in the laboratories. They also plan that the automation-assisted screening methods runs in the routine without any extra financial demands (other than caused by the depreciation cost of the instrument).

**Primary HPV screening**

We have finalised the biostatistical analysis of the HPV screening pilot study (Nieminen et al., submitted). The results have suggested that the cross-sectional sensitivity of HPV-DNA test was somewhat higher than that of the cytological screening methods; and that the independent double screening with HPV-DNA test and cytology does not increase the cross-sectional sensitivity compared to HPV-DNA test alone. However, cytology appears highly more specific and they propose cytological test analysed posterior to the HPV test to increase the programme specificity. The results of the pilot study will become available in detail when the manuscript will be published.

We have organised and started a large-scale primary HPV screening trial running within the Finnish cervical cancer screening programme. During the current activity period they have planned the design in detail after accomplishing the analysis of the pilot. Thereafter they acquired ethical permissions from the Finnish authorities and ethical committees to run and evaluate the primary HPV screening trial. This work has included also production of detailed information materials for the individual women in the HPV or control arms. These materials have been approved by the ethical committees. They made agreements with 7 municipalities on starting the HPV screening trial. They randomised 7,000 women in the HPV-screening arm in these municipalities while inviting (7,000 are in the automation-assisted screening and 7,000 in the conventional screening arm, respectively, making 21,000 altogether in the HPV screening trial); they expect 5,000 of the women invited in the HPV screening arm to be screened. No results on HPV screening are available yet. They also trained sample takers; there were 1 to 6 sample-taking units in the study area per municipality; trained also the laboratory staff on the testing system and started the HPV analyses; as well as produced all the written instructions and other documents required.

HPV screening arm has started as planned; but for the next years they have to pay much attention on how to enlarge that screening arm to the same size as the Papnet arm (i.e. recruit more municipalities and laboratories). There are various difficulties in this because HPV screening logistics and costs as well as screening capacity are different. The plan is to expand the trial first to other municipalities of the first HPV-laboratory and in the same time also to large cytology laboratories within the Finnish programme. They need to consider later on also how to integrate smaller laboratories in the study.

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

The aims of the project were:

- To continue the evaluation of thin layer techniques as common practices within the framework of the campaign for cervical cancer screening in the Bas-Rhin region.
- To run a long term survey of ASCUS and AGUS in our organized screening programme.

At the moment, results of the evaluation of thin layer techniques remain the same as in 2001. This study has already shown that Autocyte Prep® method improved specimen adequacy. An incidence of Low-grade Squamous Intraepithelial Lesion (LSIL) and of ASCUS-AGUS was also noticed with the two thin layer techniques (Autocyte Prep® and Cyteasy®). Both liquid based cytology techniques reduced the rate ASCUS-AGUS / LSIL.

Comparison of 3 years outcomes for adequate smears in the two laboratories and of diagnostic parameters of each technique need further follow-up.

2 447 smears coming from 4 pathology laboratories are involved in the long-term survey of ASCUS and AGUS.

All cytological reports corresponding to these smears have been recoded regarding Bethesda 2001 classification. 76,7% are ASC-US, 14,1% are ASC-H, 8,9% Atypic Glandular Cells (AGC) and 0,3% show atypic glandular and squamous cells together.

To assess quality of cytologic results in this peculiar field of atypic smears, 10% of the smears involved in the study were blinded-reviewed. The temporary results of this review show that initial readers were probably too pessimistic. For example 42,3% of the smears initially coded ASC-US were re-evaluated as WNL.

A preliminary study of the outcomes was done by analysing subsequent smears and possible histological exams registered in our database.

At the moment 8,1% of smears are lost of follow-up, 73,6% have a totally normal follow-up, 4,5% are followed by a histological lesion (at least CIN1), 11,5% have a cytologically confirmed lesion and 1,4% need further investigation in medical records.

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

Professor Rigas (Scientific Chief of Centre Panagia Philanthropini) and his team have pioneered a novel means of cancer detection and experiments that have been performed in the USA are in the process of being replicated in the Center of Ormylia basic science laboratory which is fully equipped with Spectroscopy and Chromotography equipment.

Until recently, the main way to distinguish a cancer cell from a normal healthy cell was by its appearance. Magnified many hundreds or thousands of times under a light
microscope, a cell can be examined by pathologists experienced in recognising and characterising structural anomalies. But in recent years an additional technique for screening cancer cells has begun to emerge, known as Fourier transform Infra Red (or FT-IR) spectroscopy.

**FT-IR spectroscopy** uses electromagnetic radiation of wavelengths longer than visible light (that is from approximately 0.7) and shorter than microwaves (up to around 1000 micrometers). This radiation is 'fired' at the substance being investigated. When absorbed by that substance, the energy causes its constituent molecules to vibrate and rotate. This effect, when collected and mathematically analysed - using the so-called 'Fourier transform' function - yields a 'spectrum' of peaks and troughs, the height and position of which reveal the molecular structure and composition of the substance being studied.

One promising use of this technique is discussed by Menashi Cohenford of Bio-Rad, Cambridge, Massachusetts, and Professor Basil Rigas in the 22 December 1998 edition of the *Proceedings of the National Academy of Science*. The duo report that FT-IR spectroscopy seems to reveal extensive structural abnormalities in cervical cell samples which, when judged only by light microscopy, would be deemed 'normal'.

Cohenford and Rigas used Fourier transform Infra Red spectroscopy to examine over 2000 individual cervical cells taken in the customary way from 10 healthy women, 7 women with some misshapen cells ('dysplasia') and 5 women diagnosed with cancer of the cervix. They found that the spectra of the apparently normal cells from samples of dysplastic or malignant tissue differed significantly from the spectra of normal cells from normal cervical tissue. This process has been replicated to a certain degree at the Centers lab in Ormylia providing further data based upon the smears from the screening program.

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

**PORTUGAL Centro Regional de Oncologia Coimbra**

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 33,277 women independently of the phase of the programme.

**Conventional method**
Cervical smears taken from patients using a Cervix-Brush, and were prepared in two ways. Firstly, a Pap smear was done.

From 16/12/2001 until 15/12/2002 we performed 33,277 smears. We found the following results:

### Cytological results Conventional Method

<table>
<thead>
<tr>
<th></th>
<th>Total smears 33 277</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory</td>
<td>269</td>
</tr>
<tr>
<td>Negative</td>
<td>31,993</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>744</td>
</tr>
<tr>
<td>LGSIL</td>
<td>523</td>
</tr>
<tr>
<td>HGSIL</td>
<td>138</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>10</td>
</tr>
</tbody>
</table>

#### ThinPrep method
After performing the Pap smear, in 8,645 smears out of a total of 33,277 smears, the rest of the sample was rinsed into a vial of PreservCyt solution and prepared as a slide, using the ThinPrep processor.

### Cytological results ThinPrep Method

<table>
<thead>
<tr>
<th></th>
<th>Total smears 8,645</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory</td>
<td>37</td>
</tr>
<tr>
<td>Negative</td>
<td>8,324</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>146</td>
</tr>
<tr>
<td>LGSIL</td>
<td>122</td>
</tr>
<tr>
<td>HGSIL</td>
<td>12</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>4</td>
</tr>
</tbody>
</table>

#### HPV test
From 16/12/2001 until 15/12/2002 we performed the HPV TEST by HYBRID CAPTURE II in 114 women.
We realised the test not only in cases classified as ASCUS, but also in some NORMAL, LGSIL and recidive of scamous carcinoma and adenocarcinoma, and we found the following results:

**HPV TEST by HYBRID CAPTURE II.**

<table>
<thead>
<tr>
<th>TOTAL CASES</th>
<th>AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>114</td>
<td>&gt; 20 and &lt; 78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEGATIVE -- 31</th>
<th>8-AR+</th>
<th>25.80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS -- 63</td>
<td>26 - AR+</td>
<td>41.26%</td>
</tr>
<tr>
<td>LGSIL -- 20</td>
<td>16 - AR+</td>
<td>80%</td>
</tr>
</tbody>
</table>

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

**SWEDEN:** Lund University, Malmö

Following work was performed in the period 16. December 2001 to 15. December 2002:

1. Final design of secondary HPV screening randomised health care policy. Ethical committee approval (month 3).
2. Start of the new health care policy. Database operational and continuously collecting cytological results, HPV testing results and health care resource usage in the 2 policies (month 3-month 11).
3. Interim analysis of safety and cost-efficacy for the scientific report (month 11-month 11).
4. Continued accrual of HSIL endpoints in primary HPV screening trial (month 1-month 12). The scientific report contains data on total number of endpoint observations, as a measure of the progress of the trial, but the code will not be broken to reveal data on efficacy until 2003.
5. Entering of digital colposcopy images and subsequent histopathological diagnoses into a HPV screening colposcopy database (month 1-month 11).
6. Interim analysis for the scientific report of the value of colposcopy for predicting histopathological diagnoses in this particular group of women (month 11-month 12). Scientific publication, also taking the HPV DNA testing results into account, will be after the code has been broken in 2003.

We have obtained following results:

- Establishment and maintenance of a database for monitoring of safety and cost-efficacy of the new and old policies. The database will ultimately generate knowledge of whether a routine health care policy aiming at increased specificity of cervical screening by secondary HPV testing of women with low-grade cytological abnormalities is safe and cost-efficient under real-life conditions.
• Continued accrual of endpoint observations (HSIL incidence) for a randomised primary HPV screening trial. If the expected increased efficacy of HPV-based screening is indeed found, this could lead to new etiology-oriented cervical screening programs in Europe.

• Establishment of a database of computerized colposcopic images of the cervix of women with persistent oncogenic HPV infection and, for comparison, from normal women, in relation to the histopathological diagnoses of the corresponding biopsies. This database will be useful for evaluation of the value of and continued improvement of colposcopy for this particular group of women.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 12.
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 (Munich, Zwickau), Greece (Athens, Chalkidiki), Holland, Italy, Portugal, Slovenia, Spain, Sweden, UK

All individual projects have access to the WEB FORUM. Dissemination of the obtained Network results is performed world wide, and facilitates the feedback from a large number of specialists in cervical screening and public health authorities.

Following software development work was performed by the Co-ordination Centre during the reporting period (December 2001-December 2002), as follows:

- development of improved protection facilities in order to protect the "write access" to the forum data, and to avoid that data will be disrupted.
- development of the "Guidelines" section
- improvement of the user access and of the navigation paths to the forum data
- access to the current Network activities and documents (meetings, Guidelines documents, etc.)
- further development of multilingual facilities
- topic-oriented structuring of forum information, and implementation of facilities for supporting images and voice data. A test video was integrated and is available for demonstration in the section "Activities".
- development of an efficient Search Engine

Implemented Services of WEB FORUM:

- Multilingual access in 6 languages
- Installation of the "access permission codes" for network administration
- Installation of the administrative data and financial data
- 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 61 publications of the Network (see chapter 4).

The URL of the WEB FORUM is: http://www.cancer-network.de
Cervical Cancer Screening Network
Duration: 16.12.01 – 15.12.02
Welcome page (in ENGLISH)

Partner description (in ENGLISH)
Section Guidelines (in ENGLISH)

Guidelines Documents (in ENGLISH)
Network Meeting in Munich, 5-6. September 2002 (in ENGLISH)

Cervical Cancer Screening Network

Duration: 16.12.01 – 15.12.02
Project description (in SPANISH)

Descripción del Proyecto
Las actividades de la red de 13 proyectos en los Estados miembros y de 4 proyectos en los países candidatos se coordinan por el centro de la coordinación (Instituto Científico de la Sociedad Bávara del Cáncer), y agudizadas en partes temáticas, como sigue:

- **PARTE 1**: Garantía de calidad de control de calidad
  Lider: Prof. Ulrich Scharck
  El desarrollo y la mejora de las herramientas innovadores de la garantía de calidad y de control de calidad y la evolución de su impacto para mejorar estrategia de la garantía de calidad en la investigación cervicov agendizado por la escuela del laboratorio y el funcionamiento individual por una agencia independiente.

- **PARTE 2**: Epidemiología y evaluación de la invasión c eraseal
  Lider: Dr. Ali Amilla
  Continuación de vigilar del largo plazo y evaluación epidemiológica de la investigación c eraseal en varias regiones europeas, con el objetivo de establecer indicadores reales de los resultados, y estimar costes-y-ventas y reducir al máximo los errores medicos.

- **PARTE 3**: Nuevas tecnologías en la investigación c eraseal
  Lider: Dr. Marc Arby
  Investigación de la innovación tecnológica. La incorporación continua de la innovación técnica permitirá para mejorar la calidad de la investigación cervicov europea. Los resultados ayudarán a determinar los patrones de diagnóstico de nuevas tecnologías en la investigación cervicov en término de la sensibilidad, de la especificidad, de valores predictivos y de la reproducibilidad.

- **PARTE 4**: Trabajo en equipo y difusión de la información via Internet

Partners (in ITALIAN)

**della rete “Guidelines”**

5. **Franca-Strasburgo**
   Association FVE - Campagne De Depistage Du Cancer Du Col De L’Utèris Dans le Bas-Rhin
   3, Place de Cypres, 67000 Strasbourg
   Descrizione
   Telf.: 0033-388-25 77 17, Fax: 0033-388-25 77 21
   e-mail: asscoocurit@ofat.fr

6. **Germania Monaco di Baviera**
   Istituto Científico della Società Bavarese del Cancer
   Troperi, 38
   8165 Monaco di Baviera
   Cytological Image Gallery
   Descrizione
   Telf.: 0049-89-114 350, Fax: 0049-89-4919 3515
   e-mail: utric@schreick.de
   URL: http://cytologic.schreick.de

7. **Germania Zwickau**
   SWS Tumorecentre Zwickau
   Karlsruhe Str. 35, 08600 Zwickau
   Descrizione
   Telf.: 0049-735-56 99 100, Fax: 0049-735-54 99 111
   e-mail: tzw@tumorzentrum.z.uart.de

8. **Grecia Atene**
   Hellenic Foundation of Oncology
   11 Valtzis St., 10600 Atene
   Descrizione

9. **Grecia Creta**
   The Center for Public Health “Paraske” (Our Lady Who Loves Mankind), Chania
   Via di Kalkidikis
   Descrizione
   Telf.: 0030-771-44 488, Fax: 0030-771-44 488

10. **Italia**
    Azienda Sanitaria Locale I Torino, Unità di Epistemologia dei Tumori
    Via San Francesco di Paola, 31
    Descrizione
    Telf.: 0031-41 020, Fax: 0031-41 020
    e-mail: brcella@tin.it
4. List of Publications


5. C. Davister. Attitudes et représentations face au virus HPV dans le cadre du dépistage du cancer du col. (Phase exploratoire novembre-décembre 2002.)


Meta-analysis of the diagnostic properties of rapid pre-screening of Pap smears.  
24th International Congress, organised by the International Academy of pathology, Amsterdam (The Netherlands), 5-11 October 2002.

Triage of women with minor cytological lesions of the uterine cervix using HPV DNA testing: a meta-analysis.  
16th World Congress of Epidemiology, organised by the International Epidemiological Association, Montreal (Canada), 18-22 August 2002.

Triage of women with minor cytological lesions of the uterine cervix using HPV DNA testing.  
Cochrane Reviewers’ Day, organised by the Dutch Cochrane Centre, Amsterdam (The Netherlands), 11 October 2002.

12. M. Arbyn  
HPV testing and its role in cervical cancer screening.  
Institute of Oncology, Ljubljana (Slovenia), 14 October 2002.

13. M. Arbyn  
HPV et cancer du col de l'utérus.  
Serninary organised by the Centre Anti-Cancéreux de l'Université catholique de Louvain. (lecture)  
Clinique Universitaire Saint-Luc, Brussels (Belgium), 16 may 2002.

14. Support to the Flemish technical Working Parties, Flemish administration of Health Care, Attendance to the meeting of 24.January 2002 organized by a Belgian insurance agency (Partena) to promote the screening

15. Statistical analyses and reporting of data from the Flemish Cervical screening register (meetings)

16. Advanced statistical analysis of incidence and mortality trend concerning cervical and other uterine cancer (meetings)

17. M. Arbyn, H. Geys.  

18. M. Arbyn.  

19. M. van Ballegooijen, M. van den Akker, T. Cool, M. Arbyn.  
20. Development of a Belgian policy to negotiate with the different Belgian authorities at the Federal and Community level.
M. Arbyn, G. Marchant
Recommandations techniques pour des frottis du col satisfaisants.

Classification trees and its application to cervix cancer screening in the Belgian health Interview Survey.
Arch Public Health 2002; 60, 275-294

Thin-layer liquid-based cervical cytology and PCR for detecting and typing human Papillomavirus DNA in Flemish women.
British Journal of Cancer 2003, in press.

23. Training
Course in SPSS, an informatics programme to realise statistics.
Place: Leuven, Belgium
Date: 17-18/6/02. Participant: Ginette Marchant


25. M. Arbyn
Potential clinical use of molecular markers predicting progression of cervical cancer precursors.

26. M. Arbyn
Evaluation of new methods for cervical cancer screening: methodologies in quantitative research. (lecture)
Workshop Application of Research methodologies in Reproductive Health Projects, organised by the International Centre for Reproductive Health, University of Ghent (Belgium), 1-5 July 2002.


28. Pekka Nieminen, Sirkku Vuorma, Merja Viikki, Matti Hakama, Ahti Anttila
Comparison of HPV test vs. conventional and automation assisted pap-screening as potential screening tools for preventing cervical cancer (submitted).


31. J-J. Baldauf


33. J-J. BALDAUF.

34. M. FENDER, C. PETERS.

35. J-J. BALDAUF.

36. J-J. BALDAUF.

37. J-J. BALDAUF.

38. J-J. BALDAUF.

39. J-J. BALDAUF.
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40. M. FENDER, J. SCHOTT, J-J. BALDAUF, J. MULLER, E. SCHLUND, P. DELLENBACH.
41. J-J. BALDAUF, D. HAMID, P. WALTER, J. RITTER. 

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December 2002
5. Previous work


Quality Assurance and Quality Control

In Germany a number of 41,561 screening patterns with new features were acquired. New software modules were developed and integrated in the running Screening System in order to allow the on-line analysis and display of screening patterns with the selection of different demonstration modes of the on-line screen viewer. In this way the cytotechnologists have the option to chose whether they wish to see their screening patterns while it develops or have it just stored for continuous documentation for quality assurance and consumer protection. The software features for supporting fast access to screening patterns (over 150,000) were developed.

Diversity of reporting schemes in cytology remain a major problem for the acquisition of reliable data for international comparison of screening data. Principles of translatable reporting despite diverging views on terminology and reporting were worked-out and a system was developed for a continuous grading of intraepithelial lesions, which we have applied to a large series of squamous intraepithelial lesions, in which HPV testing has been performed. Reporting schemes from other countries are now available in the Internet at the web site http://zytologie.schenck.de. Online image support for reporting was developed, and a fire wall was installed for data protection.

In Belgium rapid reviewing has proven to be a good quality method. Research was performed in collaboration with the Research Working Party: “Implementation of HPV screening in combination with thin layer cytology in the framework of early detection of cervical cancer“.

The diagnostic accuracy of liquid based cytology as compared with the conventional Pap smear is assessed with a clinical trial. The initial protocol is adapted according to the possibilities that were not foreseen at the first introduction of the project. In addition, an application of HPV detection by the use of Hybrid capture tests was performed.

The obtained results show that the detection rate of biopsy proven high grade lesions by primary screening cyto+HPV is 1.42% (95% CI: 0.88-2.17). For the screening by cytology + HPV conditioned by a low-grade cytological result this detection rate is 1.08% (95% CI: 0.62-1.74). 32% more lesions were found in the first arm. This difference is not significant. The detection rate ratio is 1.32 (CI: 0.69-2.52). One is included in the confidence interval.

HPV primary screening is more sensitive, but less specific than primary cytological screening. 54% of women with ASCUS/low grade SIL can be sorted out as being not carrier of high risk HPV. Among the 46% carriers of HPV one over five women appear to harbour +CIN2 pathology.

In the Netherlands two reminder systems were investigated (focussing on different categories of abnormal smears) that aim at maximising follow-up of abnormal and unsatisfactory smears, based on the European guidelines for the Quality Assurance in Cervical Cancer Screening, the National guidelines of the Dutch College for General
Practitioners concerning cervical smears, and the guidelines for Pathology Laboratories. The research questions concern the assessment of the effects of the two reminder systems on the follow-up of abnormal and unsatisfactory smears, the costs of the two systems and the experiences of the practices with the reminder systems, focusing also on barriers.

A study is performed in which two different reminder systems - a maximal and a minimal variant- are evaluated to maximise follow-up of abnormal and unsatisfactory smears. All general practices in the area of two Pathology Laboratories in the region of Nijmegen (n = 132) are randomised into the two different reminder systems. Each system consists of a patient specific reminder of the lab to the GP if a recommended repeat smear was not performed. The two systems focus, however, on different categories of abnormal smears. The evaluation study consists of an effect and process evaluation.

Two laboratories in the region of Nijmegen and all general practitioners in their catchment area (n = 132) participated in the study. In the effect evaluation, all women registered in the 132 practices who were invited for cervical screening in the framework of the nation-wide screening programme (and who had no recent history of abnormal smear results) were included. Every woman was followed up for at least one year after the first abnormal or unsatisfactory smear was known: in the maximal variant 1226 women, in the minimal variant 1034 women, with a total of 2260 women.

With regard to the effectiveness of the two reminder systems, in the maximal variant 49.8% of the women had a follow-up within the recommended period plus a delay interval of 10 weeks (this is before the sending of the reminder); in the minimal variant this was 44.5%. After sending reminders from pathology laboratories to general practitioners, in the maximal variant 70.5% of the women had still a smear taken; for the minimal variant this was 54.7%. The overall follow-up (=% of follow-up examinations at least one year after the first abnormal or unsatisfactory smear was known) was 85.2% for the maximal variant and 74.9% for the minimal variant: a 10% difference between both variants.

Concerning the results of the follow-up examinations, from the unsatisfactory to mild/moderate abnormal initial smears in the maximal variant, 27.4% showed progression to a more severe abnormality; from the unsatisfactory to mild/moderate abnormal initial smears in the minimal variant, 33.1% showed progression to a more severe abnormality.

In the process evaluation, experiences of the general practices with the two reminder systems are assessed. Remarkable was that 14% percent of all practices did not know for which smear classifications they received reminders. Furthermore, 74% of the practices in the maximal variant knew that they received reminders for all unsatisfactory and abnormal smears, while only 23% of the practices in the minimal variant knew that they received reminders for moderate and severe abnormalities. In addition, for 82% it was important to receive reminders and 64% indicated that the reminders supported them to improve their performance concerning the follow-up. Regarding the ideal follow-up method, ‘follow-up monitoring of all unsatisfactory and abnormal smears by the general practitioner and when a follow-up examination was not performed, only reminders from the laboratory by moderate or severe smears (=minimal variant)’ was preferred by 46% of the practices in the maximal variant and 63% in the minimal variant. ‘Follow-up monitoring of all unsatisfactory and abnormal smears by the laboratory’ (==maximal variant) was preferred by 39% of the maximal variant practices and 35 % of the minimal variant practices.
The main barriers of the participating general practices with the performance of the reminder systems were the lack of registration skills for performing the follow-up in general practice, the current reimbursement and the fact that the GPs think that the benefit of the follow-up of slightly abnormal and unsatisfactory smears was not evidence based and the fact that they think that the follow-up is the responsibility of the patient.

To assess the costs of the reminder systems, the time to perform the systems (i.e. the input) has to be measured and multiplied by the cost/prices. Unfortunately, the cost/price analyses are running now and can not be reported in this report. Therefore, only the necessary time to apply the systems is reported, both from the laboratory’s and general practitioner’s viewpoint.

The project provided insight into the effectiveness and time investments of implementing two different reminder systems to improve the follow-up of abnormal and unsatisfactory smears. It also described the barriers and experiences in the general practices during the implementation of the systems. With these insights, it is possible to improve cervical screening programmes by surmounting barriers and improving follow-up rates of women. The results will be disseminated through the EC Network for Cervical Cancer Screening, and through international publications. The next step in the set up of an optimal integrated screening of cervical cancer is to implement the most cost-effective system at national and European level. For this step, tools for successful implementation of a reminder system between smear-taker and cytological laboratory are necessary. Therefore, the specific aim of our next project is to develop a systematic assessment of the presence or absence of preconditions for successful implementation of the most cost-effective communication system at national and European level. In this manner the study further contributes to an evidence based screening practice in routine primary care.

Monitoring, Epidemiology and Evaluation of Cervical Screening

In Germany the co-operation with M. Ballegooijen (Rotterdam), A. Linos (Athens) and L. von Karsa (Cologne) relating to the different national concepts of screening programs was continued during the project duration. A joint paper has been published in the European Journal of Cancer. Locally, in Bavaria, our institution was involved in the discussion on a new law to improve cancer registries.

Analysis work was performed on data concerning the tables suggested in the “European Guideline for Quality Assurance in Cervical Cancer Screening”. One of the surprising facts is that the rate of unsatisfactory smears is very low (below 0.1%). About 94% of the Pap smears have been analysed within 12 days. Follow-up is related to the suggestion by the cytopathologist. In cases of mild or moderate dysplasia less than 20% are without follow-up cytology in our institution.

In Belgium an advanced system of central registration of all cervical screening activities in the Flemish Region was established, and activities of the Working Party were performed for Uniformisation of Cytology, in accordance with the programme "Europe Against Cancer", and the creation of the multidisciplinary Research Working Party was promoted. The annual meeting of the Belgian Society took place. Results of the current European project could not be presented because of the lack of a contract at that time between the Flemish Cervical Cancer Screening Programme and the European Commission.
In Greece data on 7,408 examined women was processed including pap smear and gynecological examination, reaching a total of 15,770 women having been screened since the initiation of the screening program. Of the 7,408 participating women from villages whose data was analyzed in the framework of the Ormylia screening program, 2,809 (26.372%) were new participants.

Following the Center’s successfully developed invitation methodology, the participation rate has greatly increased. The overall participation rate for all women screened in our program is 68.4% whereas the participation rate for the 25 - 64 age group is 85.4% and 89.6% for the age group 30-59 years. The majority of tests performed during the reporting period was negative for malignancy (99.862%) whereas 378 women were hysterectomised therefore no smear test was taken.

An additional number of 1,093 tests were classified as abnormal without any indications of malignancy, but presenting several types of vaginal infections and inflammations, which were treated according to the type of the pathogenic agent causing the abnormality.

The majority of the detected pathogenic agents were fungi and cocci. In all cases women were advised by the gynecologist on further action they should take in order to finalize diagnosis and treatment of their condition. The majority of women presenting inflammation pertain to the 25 -64 years age group.

In Italy data were collected in a standardised form from 44 organised programmes, about women invited for screening in 1999. The same process indicators computed for the EU project “Setting standards for process indicators in cervical cancer screening” (Agreement N° SOC 98 200263 05F02Q) were computed. Data confirmed the picture obtained from the previous survey. Results about Detection Rate in the present survey seem to identify a geographic cluster at increased baseline risk, and suggest that differences in DR are not the result of differences in screening sensitivity.

In Sweden most of the enrolment activity took place in the cities of Stockholm (Karolinska Institute/Dr. Dillner), Gothenburg (Gothenburg University/Dr. Ryd) and Malmö (Lund University/Dr. Hansson).

Stockholm enrolled about 6,000 women, Gothenburg 2,500 women and Malmö 1,000 women. Gothenburg entered the trial late and enrolled all 2,500 women between November 1999 and 15. March 2000, when the study was finally closed for enrolment with a total of 12,500 women.

Most of the HPV testing was performed in Malmö (Laboratory of Dr. Hansson). The coordinating activities were done in Stockholm (Laboratory of Dr. Dillner).

The overall prevalences of HPV infection in the Swedish general population were 6.6%, with the most oncogenic HPV type (HPV 16) also being the most common infection. Thirteen different types of infections were found. HPV types that are only rarely associated with cancer, such as HPV 39, 51, 52, 56, 59 and 66 were found in almost 2% of the population, raising questions of which HPV types that should be tested for in cost-effective screening programs.

Overall, the HPV test was found to be robust and generally well suited to large-scale use. HPV testing was also well accepted by the general population of women in Sweden (the results are detailed in the “Appendix 8: Swedish Final Report”).

The population-based prevalence of HPV infections that are persistent, that is, that can be detected again 12 months later was also a major deliverable of the project. The results are not described in the submitted "Annex 8: Swedish Final Report", but this
testing has indeed been done. 47% of infections were persistent, resulting in that the population-based prevalence of persistent HPV infections in Sweden is 3.1%.

As indicated by previous cost-efficiency modelling, prevalences of this magnitude would tend to favour HPV screening as a cervical screening modality and the results so far thus seem promising. However, conclusive results will not be obtained until the magnitude and duration of the protective effect of HPV testing has been quantified 3 years later.

As it was clearly stated in the proposal that population-based prevalences of infections and of persistent infections were the deliverables that could be achieved during the contract time, the project has achieved its goals both in terms of the deliverables and in terms of promoting exchange of experiences, collaboration and standardisation between different EU countries.

A number of 20,000 women aged 30-55 years were included by the University of Amsterdam (the Dutch subcontractor of the Swedish partner), and about 10,000: women belonged to the intervention group, and high risk HPV detection by GP5 +/-6+ PCR-EIA was performed for all women. Evaluation at the end of this project resulted in an equal distribution of the different cytology groups in the intervention and control groups. High risk HPV prevalences were found to be 4, 26, 74, 90 and 100% in Pap 1, 2, 3a1, 3a2 and 4, respectively. Follow up samples after 6 months after intake were obtained from approx. 50-60% of the women. One third of the HPV positives women with normal cytology cleared their infection after 6 months. Interestingly, a substantial number of high risk positive cytomorphologically normal women (11%) developed cervical dysplasia after 6 months, of which CIN3 (3%). At present, data from the second follow up (15 to 18 months after intake) are being analysed. Furthermore, HPV negative abnormal cytology showed regression after 6 months. Above mentioned results are preliminary and the final results of the Dutch HPV screening trial can be expected in 2002.

Parallel HPV analyses were here performed, showing very high levels of agreement with the collaborating partner laboratories. Furthermore, PCR primers and probes and reagents were validated here, and these validated reagents were used by partner laboratories.

A prospective primary HPV-DNA screening pilot was started in September 2000 by the Finnish subcontractors of the Swedish partner:

- Mass Screening Registry, Finnish Cancer Registry, Helsinki, Finland
- Tampere School of Public Health, University of Tampere, Tampere, Finland
- Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland

in order to evaluate the clinical and diagnostic aspects of HPV testing in Finland for its use in screening for cervical cancer.

In the Finnish context, hospital smears are especially suitable for the pilot study since their background rate of histologically confirmed cancerous and precancerous lesions is much higher than that in routine mass screening; sufficient statistical power in differential detection can be obtained with a smaller study population.

During the period September 2000 to 15th December 2000, altogether 1,450 HPV and liquid-based samples were collected and processed as follows. One VCE sample (taken
with a brush and a wooden spatula) per woman was taken for the conventional pap-smear and for the liquid-based smear (Cytyc Thinprep) and one additional brush sample for HPV-detection with Hybrid capture II. In addition to the manual reading of the conventional and liquid-based smears also the automation-assisted pap smear screening device (Papnet) are used the analysis of the smears. HPV-DNA analysis will also be processed for each of the women. The women with positive cytological results, or with repeated suspicious results, with any of the methods, or with clear symptoms, will be sent to colposcopic examination including histological confirmation.

There are five different methods (routine manual, automation-assisted manual, liquid-based manual, liquid-based automation-assisted, and HPV-DNA detection) to be compared in a split-sample and prospective designs. The four different cytological screening methods are processed in Finland. For the HPV-DNA analysis the samples have been shipped to the Digene's laboratory in the United States for analysis.

The overall study size will be 2,000 women. The rest of the study material has been collected during the period 16. December 2000 to January 2001. No results of the cytological, histological nor HPV-DNA are available yet.

New Technologies in Cervical Cancer Screening

In Belgium it was concluded that the evaluation of new screening methods is potentially very valuable, but the cost/effectiveness still has to be documented, especially for public health outcomes. New screening methods (HPV detection, thin layer cytology, automated screening) can possibly contribute to the improvement of the quality of screening tests (less false negatives, less false positives). Unfortunately the current knowledge does not allow to say this regarding the “reduction of life-years lost”, the decrease in incidence of invasive cancers and the decrease in cause-specific mortality. Mathematical modelling of the natural history of the disease combined with a simulation of the effects of different screening methods still is necessary for the estimation of their impact.

In Finland the main activity was concentrated on evaluating and implementing new technologies in cervical cancer screening. Pilot studies were performed on automation-assisted screening, and a large-scale randomised trial using these new methods available was started.

Altogether 41,160 smears were assessed with the automation-assisted device, Papnet, during the activity period in the randomised design on primary screening. Bio-statistical analysis with the histologically confirmed results is available yet from the first year of the trial. According to the first-year results 58,400 women were randomised in the automation-assisted arm and 116,900 in the manual screening arm, respectively, in 1999 while invited. Altogether 42,100 women were screened in the automation-assisted arm and 84,200 in the manual screening arm. Participation rate was 72% in both arms. There was a clearly positive cytological finding (Papanicolaou groups III-V) in the automation-assisted arm for 260 women (0.6% of those screened); and in the manual screening arm for 600 women (0.7%). Histologically confirmed invasive cervical cancer was detected for three women in the automation-assisted arm, and for four in the manual screening arm (odds ratio 1.50, 95% confidence interval 0.30-6.80). For detecting cervical intraepithelial neoplasia grade III or a more severe screening outcome (CIN3+), the corresponding detection rates were 55 and 115; odds ratio 0.96 and the confidence interval 0.69-1.31. Specificity of pap smear group I within the
Papnet arm was 92.9% and within the manual screening arm 93.3%, respectively, and the positive predictive value 55% for any CIN1+ outcome among cytology positives within the Papnet arm and 51% in the manual screening arm. In conclusion, the first-year results on the primary screening use of Papnet suggest that the automation-assisted screening technique studied is as sensitive and specific in finding pre-cancerous lesions as manual screening, assessed in the well-controlled and highly effective organised screening programme in Finland. We are going to continue the trial as planned.

Concerning the other activities than the large-scale public-health trial, re-reading of smears both in the organised programme and taken for opportunistic screening is also taking place with Papnet. The results are not available yet. Planning on human papillomavirus (HPV) based screening trial have also taken place.

In Italy the performance of the AUTOPAP system was evaluated in the setting of an organised screening programme in Italy. in particular: (a) the proportion of histologically confirmed lesions identified by conventional screening that would also be identified when applying AUTOPAP, (b) if the use of maps provided by the system could reduce the time of interpretation and (c) its impact in terms of diagnosis and recommended action. Before the start of the programme 4,856 smears from the screening programme of Turin and 3,260 from Ivrea were scanned. Women from Turin were followed-up for further cytological and histological results. In both areas a sample of scanned smears was drawn and interpreted with and without maps and interpretation time measured. Other samples were taken and interpreted with maps. The diagnosis was compared to that without maps. In Turin interpretation with maps was strictly limited to the areas identified by maps while in Ivrea, if they showed some abnormality, the entire smear was examined.

All scanned smears from the 7 women who had a histologically confirmed diagnosis of CIN were classified as “review” or “process review” (95% ci 65%-100%). Interpretation time was reduced by 48% in Ivrea and by 38% in Turin. The weighted kappa for diagnosis was 0.971 (95% c.i. 0.951-0.992) in Ivrea and 0.745 (95% c.i. 0.687-0.804) in Turin. In Turin some overall under-grading of smears with maps, compared to the original diagnosis, was observed.

The obtained data suggest a substantial saving in interpretation time by use of maps. They also suggest that they can be safely used but that, when abnormal areas are observed the entire smear must be examined.

In Portugal a number of 48,966 smears were analysed in the period of 30 August 1999 to December 2000. When an unsatisfactory smear occurs it is repeated approximately three months later.

A number of 9,650 cervical smears were done by the THINPREP PAP Test during the reporting period, not in the population from the screening programme, but in the women that frequent the Gynaecologic consultation of the Oncological Centre of Coimbra.

The used THINPREP method ensures a significant decrease of unsatisfactory smears. There is also a decrease in the number of cases that are considered satisfactory but limited by inflammation of 11% to 0,2%

About the smears "satisfactory but limited by the absence of endocervical/metaplastic cells" we have a decrease of about 3,6%, but if we compare the results of some doctors, for the conventional method we found about 28% of smears without endocervical/metaplastic cells and in the THINPREP method they have only 8,2% of these cases.
The problem is not the way how they collect, but how they do the smear. Although the number of women in these series is very different we can observe an improved detection in ASCUS and LSIL. The improvement in the diagnosis of these lesions implies a reduction of the false negative rate of the Pap smear.

A very important benefit of the THINPREP method that we must consider is the possibility that with the same sample we can realise different smears, analyse other infections, detect HPV (very important and actual subject in cervical cancer screening) and apply other techniques such as immunostaining.

Dissemination of the Network results

The project WEB was developed 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). Additional partners from France, Greece, Spain and Slovenia have joined the Network, and a Proposal for the continuation of the Network activities from 16. December 2001 to 15. December 2002 was submitted to the European Commission.
5.2 Previous results (Dec. 2000 - Dec. 2001)

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 Iliia. 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 ratio 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 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.

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

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

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

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

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

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

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

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

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

- Age specific incidence rate of CIN III with the peak in the age 30-34 in the period 1994-1998,
- Age specific incidence rate of invasive cervical cancer started to increase in younger women aged 30-39,
- Age specific incidence rates by birth cohorts, distribution of cervical cancer by stage at diagnosis with an increase in the age group 35-49 years,
- Relative 5-year survival rate of cervical cancer patients,
- Mortality trend (5,1 per 100.000)

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

In Belgium work was performed as planned, and in co-operation with the Free University of Brussels on the randomised trial on "Primary versus triage based HPV detection in combination with thin layer cytology". A number of 3,000 women, consulted in 2000 at the gynaecological department of the Hospital of the Free University of Brussels were randomised into two experimental arms A and B. From all women a liquid based cervical smear was taken using the AUTOCYTE preparation system. Samples from all women in group A were used for ancillary high risk Human Papillomavirus DNA detection using the HYBRID CAPTURE II method (primary screening setting). HPV testing in material from women in group B was limited to those showing atypical or low grade cytological lesions (triage setting). All women, being HPV positive or showing squamous high grade (HSIL+) or glandular abnormalities (AGUS+) or worse, were called in for further diagnostic exploration. Detection of histologically confirmed CIN-2/GIN-2 or worse was the main study outcome. The cross-sectional sensitivity and specificity of cytology and virology were assessed within each experimental arm. Cases that are co-negative for HPV and cytology were assumed being true negatives without histological verification.

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

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

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

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

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

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

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

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

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

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

- a historical comparison for each of the laboratories of the distribution of smear tests according to the cytological result during two 12-month periods before and after the introduction of the new technique. The training period of the thin layer technique of 6 months was excluded. A control group of laboratories still using conventional Pap was also included.

- a study of the positive predictive value of the thin layer method relative to conventional Pap smear for high-grade smears where the systematic taking of a histological sample is compulsory.
- the comparison of the degree of cytological-histological correlation for the two methods for low grade smears followed by histological examination. For those followed by cytology only, results of subsequent smears have also allowed a comparison of the two methods.

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

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

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

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

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

➔ **Improving Screening of pap-smears:** Measures to reduce errors were identified thorough the Center’s research and also in consultation with USA and European experts. A number of specific measures have been implemented to the degree that is feasible within the limited finances of the institution in order to correct the problem of false-negative Pap smears. These have included recommendations on the optimal technique in performing a Pap smear and improved methods to harvest cells from the entire transformation zone (e.g., using a cytobrush with a plastic Ayre spatula). Cytopathology laboratories have been asked to establish procedures to optimize quality assurance. For example, lab chiefs were asked that the guidelines be implemented for workload limitations requiring a cytotechnologist to screen no more than 100 slides per
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:
TOTAL CASES 832
AGE > 20 and < 78

| NORMAL -- 200 | AR+ 48 | 24% |
| ASCUS -- 380 | AR+ 130 | 34.2% |
| LGSIL -- 245 | AR+ 152 | 62.04% |
| CARCINOMA/RECIDIVE -- 7 | AR+ 7 | 100% |

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 VIDEOM (Video-communication workplace) was performed with the aim of promoting the co-operation with these European projects, and for providing a direct access world-wide of the medical staff via Internet to the project results.

The Network results were made available to the specialists in international conferences and medical journals and books by 78 publications (41 publications from Germany, 21 from Belgium, 4 from Finland, 9 from Italy, and 3 from Sweden).

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

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

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

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


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Annexes

Following annexes are attached:

- Final Report 1 of Cytological Institute of the Bavarian Cancer Society Munich, Germany (48 pages)
- Final Report 2 of Scientific Institute of Public Health – Louis Pasteur Brussels, Belgium (492 pages)
- Final Report 3 of Finnish Cancer Registry Helsinki, Finland (13 pages)
- Final Report 4 of Association EVE, Strasbourg, France (20 pages)
- Final Report 5 Germany: South-west Saxony Tumorcentre Zwickau, Germany (46 pages)
- Final Report 6 of Hellenic Foundation of Oncology Athens, Greece (14 pages)
- Final Report 7 of Our Lady Who Loves Mankind Chalkidike, Greece (16 pages)
- Final Report 8 of University of Nijmegen Nijmegen, Holland (6 pages)
- Final Report 9 of Unit of Cancer Epidemiology Turin, Italy (22 pages)
- Final Report 10 of Centro Regional De Oncologia de Coimbra Coimbra, Portugal (5 pages)
- Final Report 11 of Junta de Castilla y León Valladolid, Spain (32 pages)
- Final Report 12 of Lund University Malmö, Sweden (26 pages)
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