

# Final Report

SPC.2002475

16. December 2002 to 15. December 2003

## Participants:

1.	GERMANY	Cytological Institute of the Bavarian Cancer Society, Munich (Co-ordinator)
2.	AUSTRIA	University of Vienna, Vienna
3.	BELGIUM	Scientific Institute of Public Health, Brussels
4.	FINLAND	Finnish Cancer Registry, Helsinki
5.	FRANCE	WHO – Int. Agency for Research on Cancer, Lyon
6.	FRANCE	Association EVE, Strasbourg
7.	GERMANY	South-west Saxony Tumorcentre Zwickau
8.	GREECE	Hellenic Society of Oncology, Athens
9.	GREECE	Our Lady Who Loves Mankind, Chalkidiki
10.	HOLLAND	University of Nijmegen, Nijmegen
11.	ITALY	Unit of Cancer Epidemiology, Turin
12.	PORTUGAL	Regional Oncology Centre, Coimbra
13.	SPAIN	Health and Social Welfare Council, Valladolid
14.	SWEDEN	Lund University at Malmö
15.	UK	Birmingham Women's Hospital

**15. January 2004**

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

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# Final Report

## 155 pages

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#### Attached:

15 Annexes (687 pages)

European Guidelines for Quality Assurance in Cervical Cancer Screening (267 pages)

**ANNEXES attached (687 pages):**

- Final Report No. 1 Germany: Cytological Institute of BKG, Munich (37 pages)
- Final Report No. 2 Austria: University of Vienna, Vienna (48 pages)
- Final Report No. 3 Belgium: Scientific Inst. of Public Health, Brussels (268 pages)
- Final Report No. 4 Finland: Finnish Cancer Registry, Helsinki (14 pages)
- Final Report No. 5 France: WHO – IARC, Lyon (19 pages)
- Final Report No. 6 France: Association EVE, Strasbourg (32 pages)
- Final Report No. 7 Germany: South-west Saxony Tumorcentre Zwickau (19 pages)
- Final Report No. 8 Greece: Hellenic Society of Oncology, Athens (4 pages)
- Final Report No. 9 Greece: Our Lady Who Loves Mankind, Chalkidiki (22 pages)
- Final Report No. 10 Holland: University of Nijmegen, Nijmegen (11 pages)
- Final Report No. 11 Italy: Unit of Cancer Epidemiology, Turin (23 pages)
- Final Report No. 12 Portugal: Regional Oncology Centre, Coimbra (4 pages)
- Final Report No. 13 Spain: Health and Social Welfare Council, Valladolid (31 pages)
- Final Report No. 14 Sweden: Lund University at Malmö, Stockholm (100 pages)
- Final Report No. 15 UK: Birmingham Women's Hospital (55 pages)

## 1. Summary

Cervical cancer is the second most common cancer among women, with more than 500.000 new cases/year, and more than 300.000 premature deaths a year. It is also the most common women cancer in the developing world, where about 80% of new cases arise. Infections with oncogenic human papillomaviruses (HPVs) causes cervical cancer with a long latency period of at least 10 to 15 years during which cervical cancer develops. Because of the long preclinical period cervical cancer can be prevented by screening, followed treatment of premalignant cervical lesions. Organised screening protects against cervical cancer, and screening programmes today identify women with abnormal cytology for further examinations by colposcopy and surgical removal of a histologically verified cervical intraepithelial neoplasia (CIN), the precursor to cervical cancer.

The European Network on Cervical Cancer Screening is operating in 12 Member States, and aims at

- improving the quality of laboratory work on "Cervical Cancer Screening"
- at using technological innovation for improving the screening process, and
- at using the statistical evidence in order to evaluate the impact of screening on cancer prevention.

The planned network work (contract SPC.2002475) on "Cervical Cancer Screening" from 16.12.02 to 15.12.03 is presented in section 2, and the previous work in section 5.

The performed work is presented in section 3, as follows:

1. Quality Assurance and Quality Control in screening process (in section 3.1).
2. "Monitoring, Epidemiology and Evaluation" (in section 3.2).
3. Experimental investigation of the "New Technologies" in cervical cancer screening, including HPV-tests, and discussion of their merits and limitations (in section 3.3).
4. The improvement of the WebForum for easy Internet-based communication and dissemination of the results, including the Guidelines (in section 3.4).

The network results were published in 91 publications in 2003, and 185 publications in 2000-2002.

The 2<sup>nd</sup> Draft of the "European Guidelines for Cervical Cancer Screening" (see the attached document of 267 pages) was released in December 2003. The electronic format of the guidelines is available in the Internet at [www.cancer-network.de](http://www.cancer-network.de).

The detailed results obtained in the 15 institutions of the Network are presented in the attached 15 Individual Final Reports (687 pages).

## 2. Planned Work

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

Objectives: To analyse the quality assurance and quality control practices (i.e. methods, techniques, tools, training) and to evaluate their impact on cervical screening with respect to their efficiency and costs. Improve the 1<sup>st</sup> version of the improved "European Guidelines for Quality Assurance in Cervical Cancer Screening" in accordance with the results obtained by the Network.

Leader: Prof. Ulrich Schenck

The work in this cluster integrates 15 projects from 12 Member States. The cluster activities aim at analysing, measuring, correcting and continuously improving the PRACTICES (i.e. methods, techniques, tools and training) in both organisational and technical processing in the health services related to 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 "Quality Control, Quality Assurance" (i.e. improvement of screening outcomes by using innovative methods, techniques and tools) and "Total Quality Management" (i.e. high quality of screening results by improving the skills of the persons) with the aim of ensuring high standards of patient care and protection.

The Quality Assurance and Control Practices (i.e. methods, techniques, tools, training) will be improved and their impact with respect to their efficiency and costs will be evaluated. The improved "European Guidelines for Cervical Cancer Screening" will be worked out, disseminated via the WebForum on the Internet and the 1<sup>st</sup> Version of the Guidelines will be released in November 2003. The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening will be discussed.

In this cluster 15 projects from 12 Member States produce the improved "European Guidelines for Cervical Cancer Screening". This cluster also includes 7 thematic projects from 6 Member States:

- AUSTRIA: University of Vienna
- BELGIUM: Scientific Institute of Public Health
- FRANCE: Association EVE, Strasbourg
- GERMANY: Cytological Institute of the Bavarian Cancer Society
- GREECE: (Ormylia-Chalkidike): Our Lady Who Loves Mankind
- GREECE: Hellenic Foundation of Oncology, Athens and
- UK: Birmingham Women's Hospital

This cluster will co-operate with 5 projects from Hungary, Poland, Romania and Slovenia.

Individual Member State Projects

**GERMANY:** Cytological Institute of the Bavarian Cancer Society

The planned work has three main objectives:

- i) to improve the Quality Assurance and Control Practices (i.e. methods, techniques, tools, training), and to evaluate their impact on cervical cancer screening in German laboratories with respect to efficiency and costs.
- ii) to improve and release the German version of the "European Guidelines for Quality Assurance in Cervical Cancer Screening"
- iii) to continue to investigate the "Continuous grading of intraepithelial lesions" and the study on DNA content of cases of intraepithelial lesions of mild and moderate dysplasia related to cytological / histological follow up (regression, persistence, progression)

**PREVIOUS WORK**

During the previous project (December 2001 - December 2002) work was performed as follows:

1. The Quality Assurance and Control Tools were improved. The improved tools were experimentally used for the screening work, and their impact on the cervical cancer screening process was evaluated, and the obtained quality improvements were quantified. The new working procedures by using the improved tools were documented and disseminated via the WebForum.
2. The first draft of the "Updated European Guidelines for Quality Assurance in Cervical Cancer Screening" was revised starting with December 2001. The up-dates were analysed and a new version of the Guidelines was scheduled for March 2002 on the WebForum in order to allow discussion with international experts working in this field. This new version of the Guidelines was scheduled to 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.
3. The study of "Continuous grading of intraepithelial lesions"  
The Study (300 cases) concerning the reproducibility of continuous grading was scheduled to be released in March 2002. The Study (600 cases) on the follow up of cases with mild or moderate dysplasia was scheduled to be released in June 2002. The Study related to the question: Do low risk HPV statistically protect against the risk of high risk HPV? was scheduled to be released in September 2002. The Study on DNA content of cases of intraepithelial lesions of mild and moderate dysplasia related to cytological / histological follow up (regression, persistence, progression) was scheduled to be released in November 2002.

**PLANNED WORK**

During this project (December 2002 - December 2003) the Quality Assurance and Control Practices (i.e. methods, techniques, tools, training) in German laboratories will be improved and their impact with respect to their efficiency and costs will be evaluated:

- i) the developed practices will be experimentally used for the screening work (until June 2003)
- ii) their impact on the quality of cervical cancer screening process will be evaluated with respect to their efficiency and costs. (in June 2003)
- iii) the improved Quality Assurance and Control Practices (i.e. methods, techniques, tools, training) will be documented and disseminated via the WebForum to the project partners (in November 2003)

The improvement of the German version 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 German version of the "Updated European Guidelines for Quality Assurance in Cervical Cancer Screening" will be revised (starting in December 2002).
- ii) Improved German and English versions of the Guidelines will be released (March 2003) on the WebForum and the opinions of the international experts working in this field will be incorporated (until May 2003).
- iii) This improved version of the Guidelines will be revised by the European Commission and released in November 2003.

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

- i) 2<sup>nd</sup> Study (200 cases) concerning the reproducibility of continuous grading (release in March 2003)
- ii) 2<sup>nd</sup> Study (400 cases) on the follow up of cases with mild or moderate dysplasia (release in June 2003)
- iii) 2<sup>nd</sup> Study related to the question: Do low risk HPV statistically protect against the risk of high risk HPV? (release in August 2003)
- iv) 2<sup>nd</sup> 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 October 2003.
- v) Comparison of the obtained studies results obtained in November 2002 (1<sup>st</sup> Study) and the 2<sup>nd</sup> study finished in October 2003 (planned in November 2003).

#### Information Dissemination.

- Work will be performed for improving the "European Guidelines for Cervical Cancer Screening", and for producing the Finish version of the Guidelines.
- The WebForum will be used for dissemination of the obtained project results.
- The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Germany will be discussed

**AUSTRIA:** University of Vienna, Department of Pathology

This new partner of the network will perform following activities:

- An experimental study of the new quality assurance and control practices of the Network will be carried out with the aim of ensuring high standards of cervical cancer screening in Austrian cytological and histological laboratories.
- An advanced quality management system will be developed for the laboratory, with the aim of introducing a certification audit, which should be held by a professional institution and has to be repeated every three years.
- The Austrian Guidelines for Cervical Cancer Screening will be adapted to the new methods and techniques elaborated by the Network.
- The consensus with the improved European Guidelines for Cervical Cancer Screening will be reached, and the Guidelines' recommendations will be implemented.
- The presentation of the performed work on the WebForum will facilitate the discussion with external experts and the dissemination of the obtained results world-wide via the Internet.
- The results obtained in the Network (from December 2002 to December 2003) will be presented, and their impact on cervical cancer screening in Austria will be discussed

**BELGIUM:** Scientific Institute of Public Health

The activities within the Network for improving the European Guidelines for Cervical Cancer Screening will be continued. The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Belgium will be discussed.

**RESEARCH WORK:**

- a. Continuation of ongoing randomised trial comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions. Randomisation of 2 x 1500 women in group A & B. All women in group A will receive liquid based cytology and Hybrid Capture II HPV testing; women in group B will receive LBC (all) and HC II only in case of ASCUS or LSIL is found in the thin layer smear. Follow-up, diagnosis and treatment is carried out according to earlier described protocols.
- b. Follow-up of 100 women treated for HSIL with repeat cytology, HPV testing with HC II and PCR, colposcopy and biopsy if necessary at months 1, 3, 6 and 12 after treatment. Outcome: prediction of recurrent disease. Timing: recruitment of HSIL cases over 12 months. End follow-up and reporting over the next 12 months.
- c. Triage of 400 cases if ASCUS/LSIL with concomitant repeat cytology and HPV testing (HC II and PCR using consensus primers for the L1 gene). Patients will be randomised into 2 groups. In group A: management will be oriented according to cytology and HPV. In group B: management will be decided according to cytology (HPV test results will be blinded). Timing: recruitment of HSIL cases over 12 months. End follow-up and reporting over the next 12 months.

**ADDITIONAL WORK:**

1. Development of a cervical cancer screening programme for the whole of Belgium. Creation of a steering group. Constitution of a steering group: first two months; elaboration of a Belgian programme in collaboration with the Communities and the Region of Brussels: months 3-12.



2. Statistical analyses of and reporting on the Belgian cervical screening data. Data collected in the framework of screening registration in the previous years. Statistical analysis and reporting during first 6 months.
3. Advanced statistical analyses of incidence and mortality trends concerning cervical and other uterine cancers: study of temporal and spatial variation in relation with influencing factors (age-period-cohort effects, spatial co-variables) for Belgium and other EU countries. Statistical analysis performed in collaboration with the Biostatistical Centre of the University of Limburg (Prof. G. Molenbergs); Leuven (Prof. E. Lesaffre) and the University of Aberdeen (Prof. A. Lawson). Activity will be spread over the 12 months of the year.
4. Cost-effectiveness modelling of alternative screening strategies: target age groups, screening frequency of screening, inclusion of new screening methods with MISCAN and Data Treeage micro-simulation models. Estimation of cost-effectiveness of the application of new screening techniques.
5. Surveys: (1) among gynaecologists and GP's concerning current knowledge, attitudes and practice concerning HPV testing and result communication, (2) among women concerning psychological aspects of HPV testing, need for information and communication. First: 3 months: development of questionnaires; month 4-5: pilot testing of questionnaires; month 6: elaboration of definitive questionnaires; month 9-10: sending of questionnaires to gynaecologists and interview of women; month 11 data entry and statistical analysis; month 12: reporting.
6. Collect data from structural databases available at sickness funds (health insurance agencies) containing detailed information on smear taking and smear reading for all assured individual members and compare this information with estimates of screening coverage derived from surveys such as the national Health Interview Surveys (HIS). Collection of health insurance data (1<sup>st</sup> 5 months). Data analysis (month 6-7). Comparison with coverage estimates from HIS-surveys (month 8-9). Reporting of 'validated' screening coverage ventilated over demographic, socio-economic and geographical determinants (months 10-12).
7. Work will be performed for improving the "European Guidelines for Cervical Cancer Screening", and for producing the Finish version of the Guidelines.
8. The WebForum will be used for dissemination of the obtained project results.
9. The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Belgium will be discussed

**FRANCE:** Association EVE, Strasbourg

The aims of the EVE Association during the current application in the European cervical cancer screening network are the following :

1. To finish the study started in December 2000 on evaluation of the thin layer technique used as a common practice within the framework of the campaign for cervical cancer screening in the Bas-Rhin region (project SI2.318240 (2001CVG2-002), running from 16. December 2000 to 15. December 2001).
2. To evaluate the diagnostic parameters of this technique we have already done a historical comparison of cytological results observed in the two laboratories one year before introduction of monolayers (August 1997-July 1998) and one year after (1999). A comparison for the same period with a control group where conventional Pap was still used is also achieved (intermediate report –period : 16. Dec. 2000 to 31. May 2001)
3. The diagnostic parameters (sensitivity, specificity, positive predictive value and negative predictive value) for conventional smears will be known, with a complete 3 year follow-up at

the end of 2002 but the same data will need 6 months more for monolayers as the end point is 31 December 2002.

4. The multivariate analysis will only be achieved at the end of this project, that is on 15 December 2003.
5. To continue the long term survey of ASCUS, AGUS and immature metaplasia in an organised regional screening program that is going to begin in December 2001.

Background: in 1997, ASCUS and AGUS were not very well known by physicians. On subjective reasons some of them will have been very aggressive, others will have considered these lesions as trivial. We'll try to provide objective facts for a better management of these smears.

Results schedule from 15 December 2002 to 15 December 2003 :

Review of smears and determination of proportion of misclassified smears should already be achieved.

In this phase of the project we will particularly focus on long term outcome at 5 years (end point is 31 December 2002).

A special study on follow-up patterns will be made. Gynaecologists will be asked about all exams and treatment carried out after the smears (e.g. colposcopy, histological exams and their results). This retrospective study on cases from 1997 will need consistent extra work from the gynaecologists and their association so we find it essential to remunerate them.

All these items on follow-up patterns together with age of women and precise type of initial cytological abnormalities will be included in the multivariate analysis which will be achieved at the end of the project (15 December 2003).

- The EVE Association will participate with all the other members of the screening network in the improvement of the European Guidelines for Quality Assurance in Cervical Cancer Screening.
- We will also contribute to the project of creating a uniform reporting scheme for cytological results in the European community in order to make evaluation data comparable in EC countries. The results obtained in the Network (from December 2000 to December 2003) will be presented, and their impact on cervical cancer screening in France will be discussed
- Finally the EVE Association will participate in the project on evaluation of the effects of screening on cervical cancer incidence and mortality in Europe run by the European cervical cancer screening network. We will transmit our monitoring data concerning the Alsace region and national data when available.

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

Work will be carried out in co-operation with the University of Athens with the aim of improving the European Guidelines on Cervical Cancer Screening. For the project we will incorporate the data that is created from the clinical trials the University of Athens performed in collaboration with the Hellenic Cytology Society.

The Clinical trials include:

1. The investigation of clinical utility of the Thin Prep System for specimen collection and processing. For these purposes we have developed two main projects. One concerning a split study and the other a direct to vial study. In the latter, a correlation amongst the results found in cytology, colposcopy, micro-colposcopy and biopsy is performed.
2. The evaluation of HPV Testing and Typing in the screening program for cervical cancer. In this project we compare the data from three different techniques for HPV detection, i.e. Hybrid Capture, Home PCR and PCR ELISA.
3. We currently develop a database that incorporates the processing of the clinical data and the cytological report for each case involved in our screening program. We will incorporate a Pan European method – standard for acquiring and reporting cytological information and enhance our knowledge base to cover a more complete investigation system.
4. The results obtained in the Network (from December 2000 to December 2003) will be presented, and their impact on cervical cancer screening in Greece will be discussed

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

Work will be carried out with the aim of improving the quality assurance and control practices in Greek laboratories, and a Greek version of the European Guidelines on Cervical Cancer Screening will be released. The research activities are as follows:

- To continue the study utilising IR. spectrometry as a cervical cancer diagnostic tool. This will involve a random sample of a smears that have already been diagnosed utilising conventional cytology practices and AIC quality control being analysed by the IR. spectrometer of our lab (duration of 6 months).
- To continue the study to determine the prevalence of HPV infection in a sub sample of the screened population (month 3, 6, and 9).
- To continue to 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 (every 3 months).
- Closely follow up of the women tested positive and regularly update their screening files with all the available data on further assessment and treatment (months 4, 8, and 12).
- Continue the 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, (every 3 months).

- 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 (every 3 months).
- Continue our screening public education initiatives and out reach 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).
- The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Greece will be discussed.

#### **UNITED KINGDOM:** Birmingham Women's Hospital

The aims of this project activities are:

- i) To evaluate 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 on common 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.
- iv) To work out the recommendations for the Guidelines for Cervical Cancer Screening

#### PLANNED WORK

1. The European Federation for Colposcopy (EFC) has set up a Working Party under the auspices of the British Society for Colposcopy and Cervical Pathology to assess the status of colposcopy training throughout member states of the European Community, Poland, Hungary, Slovakia, Czech Republic, Israel, Romania, Yugoslavia, Croatia and Lithuania. This working party is chaired by Dr. J. A. Jordan and consists of representatives from the UK, France, Italy, Spain, Germany, Greece and the Netherlands.
2. The Working Party presented its preliminary findings to the First European Congress for Colposcopy in Greece on the 4 – 6 October 2001. At this meeting it was agreed that all member Societies will work towards the introduction of agreed standards of training for all colposcopists.
3. An Executive Board will meet on an ongoing basis during the period of the grant and will monitor the effective use of the grant in meeting the objectives. The Executive Board will call a Regional Conference to monitor the progress made by each member Society, and to encourage each Society to introduce a system of accreditation of training. The Executive Board will also encourage each member Society to evaluate ways in which the outcome of the treatment of cervical pre-malignant disease can be monitored.

4. The EFC meets every 3<sup>rd</sup> year. The Second European Congress for Colposcopy will be held. At this meeting member Societies will be expected to report on progress towards the introduction of agreed standards of training for all colposcopists.
5. Societies will also be asked to report on progress towards the introduction of a programme to assess the outcome of treatment of women with cervical pre-malignant disease. In liaison with WHO training courses will be held in Eastern European countries
6. Information collected during the period of study will be communicated to all member Societies by direct communication and via a website currently operated by the British Society for Colposcopy and Cervical Pathology.
7. To work out the recommendations for the Guidelines for Cervical Cancer Screening.
8. The impact of the project work on the improvement of the Colposcopy practices in the UK will be presented, and the WebForum will be used for dissemination of the obtained project results..
9. The results obtained in the Network (from December 2001 to December 2003) will be presented, and their impact on cervical cancer screening will be discussed

## 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. Ahti Anttila

In this thematic cluster are 7 projects from 7 Member States:

- BELGIUM: Scientific Institute of Public Health
- FINLAND: Finnish Cancer Registry, Helsinki
- FRANCE: WHO – International Agency for Research on Cancer, Lyon
- GERMANY: SWS Tumorcentre Zwickau
- ITALY: Unit of Cancer Epidemiology, Turin
- SPAIN: Health and Social Welfare Council, Junta de Castilla y León, Valladolid
- SWEDEN: Lund University at Malmö

### Individual Member State Projects

**BELGIUM:** Scientific Institute of Public Health

The aims of this project are:

- Advanced statistical analyses of incidence and mortality trend
- Statistical analyses and reporting of data from the Belgian Cervical Screening Registers.

### PREVIOUS WORK

During the previous project (16. December 2001 to 15. December 2002) work was performed as follows

- 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.

### PLANNED WORK

1. Statistical analyses and reporting of the Belgian cervical screening data.  
Data collected in the framework of screening registration in the previous years.  
Statistical analysis and reporting during first 6 months.

2. Advanced statistical analyses of incidence and mortality trends concerning cervical and other uterine cancers: study of temporal and spatial variation in relation with influencing factors (age-period-cohort effects, spatial co-variables) for Belgium and other Member States. Statistical analysis performed in collaboration with the Biostatistical Centre of the University of Limburg (Prof. G. Molenbergs); Leuven (Prof. E. Lesaffre) and the University of Aberdeen (Prof. A. Lawson). Scheduled: month 1 to 12
3. Cost-effectiveness modelling of alternative screening strategies: target age groups, screening frequency of screening, inclusion of new screening methods with MISCAN and Data Treeage micro-simulation models. Estimation of cost-effectiveness of the application of new screening techniques. Collaboration with Erasmus University of Rotterdam and with European Organisation for Research and Treatment of Cancer (Brussels). Scheduled: month 6 to 12
4. Surveys will be performed as follows:
  - (1) among gynaecologists and GPs concerning current knowledge, attitudes and practice concerning HPV testing and result communication,
  - (2) among women concerning psychological aspects of HPV testing, need for information and communication.
    - month 1 to 3: development of questionnaires;
    - month 4 to 5: pilot testing of questionnaires;
    - month 6: elaboration of definitive questionnaires;
    - month 9 to 10: sending of questionnaires to gynaecologists and interview of women;
    - month 11 data entry and statistical analysis; and
    - month 12: reporting.
5. Collect data from structural databases available at sickness funds (health insurance agencies) containing detailed information on smear taking and smear reading for all assured individual members and compare this information with estimates of screening coverage derived from surveys such as the national Health Interview Surveys (HIS).
  - month 1 to 5: Collection of health insurance data
  - month 6 to 7: Data analysis
  - month 8 to 9: Comparison with coverage estimates from HIS-surveys
  - month 10 to 12: Reporting of 'validated' screening coverage ventilated over demographic, socio-economic and geographical determinants

The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Belgium will be discussed.

**FINLAND:** Finnish Cancer Registry, Helsinki

We plan to start a completely new and comprehensive quality assurance and feed-back system for the cervical cancer screening programme. It will include follow-up of screening coverage based on individual screening invitations and visits records maintained at the mass screening registry of the Finnish cancer registry, as well as of screening attendance and detection rates based on the individual screening visit data. The screening data can be linked with the nation-wide population and cancer registries, since we have access to a systematic data collection and registration infrastructure within the cervical cancer screening programme in Finland

**PREVIOUS WORK**

During the previous project (16. December 2001 to 15. December 2002) we studied in which magnitude the different screening policies in Europe affect cervical cancer incidence and mortality rates, as follows

- 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.

We have demonstrated the recent developments and the overall impact of screening in the European Union as an entity, as well as for various nation-wide modalities that are in action in Europe and potential sources of heterogeneity between different programmes and settings in contributing screening effectiveness.

**PLANNED WORK**

We plan to start organising and assessing, utilising this infrastructure, a completely new and comprehensive quality assurance and feed-back system for the cervical cancer screening programme. The scope of the activity will be to systematically survey cervical cancer and any CIN3+ cases by screening invitational status - to be able to monitor and also give feed-back if needed e.g. by municipality area, if significant numbers of target age groups are left uninvited by a group of municipalities or if there was a low participation rate among invited - and also by screen-detected findings. In case of new cases diagnosed, either in screening or otherwise, a systematic re-review of the programme smears will be done with an automation-assisted cytological screening tool, Papnet, along with disease-free neighbouring slides serving as a negative control;



in collaboration and involvement of the primary screening cytology laboratories in the final re-diagnosis. We'll also consider reviewing a sample of false positive primary screening smears. Then we expect to give significant feed-back information related to diagnostic criteria and screening practice.

Ethical aspects:

The study will be performed according to the stipulations of legislature and ethical principles on health care in our country. Statements from ethical committees and permissions from the authorities on cancer registration and sample collection are needed. The process includes also acceptance from authority on personal data secrecy and protection.

Study materials:

There are annually about 260,000 invitations and some 190,000 smears taken within the programme. Women aged 30 to 60 years are invited with a five-year interval (if with normal results; we use a shorter interval for women with any suspicious results). The age-specific coverage in 1996 was about 90% and attendance rate 72%. In some age groups such as 30 and 35 year old women the invitational coverage varied between 70%-90% and attendance rate was only 60%-65% among those invited; among the best-screened ages (40, 45, 50 years) we had 100% coverage and attendance varying around 75% to 80%.

On an estimate, the overall pap smear screening activity may prevent some 600 cervix cancer cases per year in the Finnish female population, but about 170 new cases are diagnosed each year; 100 cases are among screening ages (30-64 years old women). Most of these cancer cases occur among those women who were invited in the programme, but who did not attend. There appears still to be some space for marginal improvements in screening effectiveness also with an improved cytological quality. We have estimated, based on preliminary linkages between mass screening and cancer registry files, that there would be some 100 cases of CIN3+ diagnosed during the year 2000 (likely to be the most recent available year in the cancer registry during the activity period) in the re-reviewing process, and additionally 200 controls. Additionally some 700 smears will be included in a sample of false positive smears.

Work will be performed for improving the "European Guidelines for Cervical Cancer Screening", and for producing the Finnish version of the Guidelines.

The WebForum will be used for dissemination of the obtained project results.

The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Finland will be discussed.

**FRANCE:** WHO- International Agency for Research on Cancer, Lyon

#### PLANNED WORK

The International Agency for Research on Cancer (IARC) is an international cancer research organisation located in Lyon, France. It is part of the World Health Organisation (WHO), but with a separate administration and budget, supported by 16 participating countries (Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Russian Federation [membership suspended], Sweden, Switzerland, United Kingdom and the United States of America).

In addition to 135 staff employed on the regular budget, the Agency has visiting scientists, fellows and graduate students. The Agency currently employs around 270 staff from 39 countries.

The Unit of Field and Intervention Studies of the IARC is a new partner, and will participate in the "European Cervical Cancer Screening Network", in the following way:

1. developing comparable data for incidence, mortality and survival for cervical cancer sites in the applicant European countries.
2. compiling data on HIV infection prevalence and time trends and cervical screening practices in the participating European countries.
3. analyse the information above, relating cervical cancer incidence, mortality, and survival, with information on cervical cancer screening practices and HIV infection in the participating European countries.
4. work will be performed for improving the "European Guidelines for Cervical Cancer Screening".and the WebForum will be used for results dissemination .

**GERMANY:** SWS Tumorcentre Zwickau

The aims of these project activities are to continue the work on statistical analyses and reporting of data from the Saxony Cancer Register concerning cervical and other types of uterine cancers and to participate to the network activities for improving the "European Guidelines for cervical Cancer Screening Network".

#### PREVIOUS WORK

During the previous project (16. December 2001 to 15. December 2002) following work was performed:

- 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.
- Support to cytological laboratories in uniform registration of cytological and histological data on cervical lesions. Computer support for data-entry, extraction and transmission.
- 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 International Symposium on Oncology in Zwickau.

#### PLANNED WORK

Our work will be continued in monitoring as follows:

1. continuation of the statistical analyses and reporting of data from the Saxony Cancer Register concerning cervical and other types of uterine cancers
2. developing appropriate procedures for supporting juridical advice concerning the development of data-collection and call-recall systems with respect to the new regulations on privacy protection in Germany, and
3. analyse the information above, relating cervical cancer incidence, mortality, and survival, with information on cervical cancer screening practices and HIV infection in the Saxony region.
4. work will be performed for improving the "European Guidelines for Cervical Cancer Screening".
5. the WebForum will be used for dissemination of the obtained project results
6. The results obtained in the Network (from December 2001 to December 2003) will be presented, and their impact on cervical cancer screening in Saxony will be discussed

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

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

The final aim of this study is evaluating if HPV testing alone can be used for primary cervical cancer screening at intervals longer than the 3 years currently adopted in many EU countries, with an equal or better protection. The short term objective is comparing the sensitivity of HPV testing and conventional cytology, used as primary screening tests, in identifying women with histologically confirmed high-grade cervical intraepithelial lesions (CIN+) and estimating the costs of these technologies in terms of tests to be repeated, referral rate and positive predictive value (PPV). On a longer term the purpose is evaluating if HPV testing results in a strong reduction of histologically confirmed high-grade CIN at the subsequent screening round, three years after.

**PREVIOUS WORK**

Previous studies showed higher sensitivity (but lower specificity) of "high risk" HPV testing as a "primary" screening test for cervical cancer than conventional cytology. There is previous experience in Turin in studies of HPV testing as a method of "triage" of low-grade/borderline lesions and a cross-sectional study on the prevalence of HPV infection by age is on-going.

A trial on HPV testing for cervical cancer screening is on-going (from December 2001 to December 2002) in Sweden as well as an Italian multi-centric study comparing HPV testing and liquid-based cytology.

**PLANNED WORK**

This project is part of a larger Italian trial on HPV testing, with recruitment over 2 years, which is promoted by the Italian Ministry of Health. Following work will be performed in this project:

1. Some 20.000 women coming for cervical screening in organised programmes in Italy will be randomised to a two arm ("conventional" and "experimental") controlled trial. An equal number of women will be randomised to each arm (10.000 to each). In addition to Torino, collaborating centres will be: Firenze, Padova and of the Region Emilia Romagna.
2. Women in the "conventional" arm will have conventional cytology. They will be managed according to current protocols. Women in the "experimental" arm will have HPV testing. We will use Hybrid Capture 2. Only probe B (for intermediate-high risk types) will be applied.

- If HPV test is negative, then the woman will be invited for a new screening round after 3 years. If HPV test is positive and the woman is at least 35 years old, then she will be referred for colposcopy. If HPV test is positive and age is <35 then the woman will be tested for cytology and referred for colposcopy if cytology is ASCUS or more severe.
  - Otherwise both cytology and HPV test will be repeated after one year. If at such a control cytology is ASCUS or more severe or HPV is still positive, the woman will be referred for colposcopy. Otherwise she will be advised for a new test after 3 years.
  - The number of histologically confirmed lesions positive in each arm will be computed, in order to estimate the relative sensitivity. Also PPV, the referral rate and the proportion of tests to be repeated will be computed in each arm.
3. These activities will allow studying the detection rate of histologically confirmed intraepithelial lesions at the next screening round, three years after (after the end of the present project). A strong reduction in the experimental arm will show that excess lesions found by HPV are not regressive and that using longer screening intervals is safe.
  4. The Italian centre will collaborate to the preparation of new "European Guidelines for Cervical Cancer Screening".
  5. The obtained results will be disseminated on the Internet via the WebForum.
  6. The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in the Piemonte region of Italy will be discussed.

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

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 2<sup>nd</sup> 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

**PREVIOUS WORK**

The previous work was concentrated on

- Carrying out studies on recovery and death by cancer of the cervix of uterus
- Early detection of HPV viruses using PCR and hybridisation procedures
- Applying 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 could be compared and diffused.
- Reduction of mortality through cervical cancer.

PLANNED WORK

The Programme for the Prevention of Gynaecological Cancers and Infections of Castilla and León (the most extensive region in the EU) forms part of the European Network for the Screening of Cervical Cancer. The planned work of the Programme is centred primarily on:

1. Improving the quality of the Cytological Analysis Centre in the University of Valladolid.
2. Improve co-ordination with hospital and primary healthcare services, so that abnormal cases detected by the programme may be followed up.
3. Consolidating a Registry of Gynaecological Cancer of the region, so that the changes in cancer incidence and efficacy of the programme could be evaluated.
4. Implement a regional health survey, including questions related to the use of cytology, to estimate the coverage of cervical screening, inside and outside the programme.
5. Adaptation of the computer software controlling the parameters based on the European Conditions in such a way that the results will be presented identically to other programmes.
6. Work will be performed for improving the "European Guidelines for Cervical Cancer Screening".
7. The obtained results will be disseminated on the Internet via the WebForum.
8. The results obtained in the Network (from December 2000 to December 2003) will be presented, and their impact on cervical cancer screening in the region of Castilla y León of Spain will be discussed.

**SWEDEN:** Lund University at Malmö

The main aims of this project are to:

- Establish a nation-wide individually identifiable cervical mass screening register in Sweden.
- Identify causes of cervical cancer in Sweden that may be attributable to deficits in the cervical screening strategies.
- Quantify the relative importance of such deficits in terms of relative risk and number of cervical cancer cases attributable to these deficits.
- Inform the regional screening organisations of the results of their screening programmes and suggest possible improvements.
- Explore the feasibility of starting a cervical treatment registry, to enable follow-up of the modes of treatment that are used and what their effectiveness is.
- Explore the possibility of establishing a sentinel system within the organised cervical screening programme for measuring population-based trends over time of the major cervical cancer risk factors in Sweden.
- Explore the possibility to implement primary HPV screening as a randomised health care policy in Sweden.

**PREVIOUS WORK**

Work was performed for designing and evaluating the introduction of secondary HPV screening as a public health care policy in Sweden. The evaluation the usefulness of primary HPV screening was based on a randomised trial, and the performed work is as follows:

- Implementation of a randomised health care policy of secondary HPV testing in Sweden.
- 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 may be useful for evaluation of the value of and continued improvement of colposcopy for this particular group of women

**PLANNED WORK****Establishment of a cervical cancer mass screening register in Sweden: Evaluation of cervical screening efficacy**

Background: Organised cervical cancer screening was implemented in Sweden in the mid-1960s. A marked decline in cervical cancer incidence could be attributed to the time-point of start of screening. Squamous cell carcinoma has declined by 60%, whereas adenocarcinoma has increased. About 950 000 papanicolaou (Pap) smears are taken annually. Only 31% of the smears are taken in the organised screening programme. As of 1998, the screening guidelines are 3-yearly tests between 23 and 50 years of age and 5-yearly tests between 50 and 60 years of age. However,

health care in Sweden is organised by autonomous counties and there are about 30 different regional autonomous cervical cancer screening programs in Sweden. There is no regular follow-up regarding whether the different regions actually implement screening, whether the guidelines are followed, what the population coverage and smear usage is and what the reasons are for the continued existence of cervical cancer in Sweden in spite of organised screening. For a review of how cervical screening is organised in Sweden, please see *Dillner, J.: Cervical cancer screening in Sweden, European Journal of Cancer, 36, 2255-2259 (2000)*.

For about 80% of Sweden, computerised files of organised and spontaneous Pap smear usage by each individual are collected, but these files are not fused to generate nation-wide data on screening usage and are not used for linkage with cancer registries to determine whether the screening has the desired effects for the reduction in incidence and mortality of cervical cancer.

#### 1. PREPARATORY TASKS ALREADY PERFORMED:

The applicants constituted a working group for the establishment of a cervical cancer Mass Screening Registry in Sweden. A planning grant has been awarded from the Swedish National Board of Health and Welfare. The regional screening organisations have been asked to link regional screening files with the cancer registry to determine causes of cervical cancer related to smear usage. To date data from 16 regional organisations have been obtained, indicating that files are in sufficiently good shape to allow linkage and that there is in general willingness to collaborate on this issue in Sweden. Dr. Dillner also co-ordinates nation-wide efforts to modernize cervical screening in Sweden using Human Papilloma Virus testing within organised screening programs. Evaluation of the implementation of new screening technologies is not possible without a registry to monitor usage and effects.

2. MASS SCREENING REGISTRY. I) Finalization of a document with the policies, statutes and administrative structures of the new mass screening registry. The managers of regional screening programs in Sweden as well as the National Board of Health and Welfare will be asked to comment on this document before it is finalised. II) Decision on which data items that are necessary to be kept in the Mass Screening Register and the format for supplying files. III) Obtaining of permissions from the Ethical Committees and the Data Inspection Board. IV) Collection of regional files into a national register. V) Linkage with the cancer register and conducting statistical analyses. VI.) Feed-back with results to the regional screening organisations.
3. EXPLORATORY TASKS. I) For optimal monitoring of cervical screening programs, it would be preferable to know whether there has been treatment and which form of treatment has been given following detection of a cervical abnormality. Such data is not registered at all today, but the applicant group will explore the feasibility to start registering also the treatment. II) For evaluation/prediction of effects in absence of screening, it would be preferable to know whether there are trends over time in the exposure to major cervical cancer risk factors such as papilloma virus (HPV) infection. The possibility to use a part of the screening program to monitor HPV prevalence by HPV testing will be explored. III) Randomised trials of HPV screening are ongoing and have so far shown promising results. The next step will be evaluations of the effect of screening when applied as a real-life public health policy. The most reliable evaluation of a health care policy is by randomised implementation. The new mass screening registry will explore the possibilities to introduce HPV screening in Sweden in a nation-wide, randomised fashion.

#### EXPECTED RESULTS

1. Finalization of a document with the policies, statutes and administrative structures of the new mass screening registry. The managers of regional screening programs in Sweden as well as the National Board of Health and Welfare will be asked to comment on this document before it is finalised. (month 1 to 3).

2. Decision on which data items are necessary to be kept in the Mass Screening Register and the format for supplying files (month 1 to 3).
3. Permissions from the Ethical Committees and the Data Inspection Board. (Month 3 to 6).
4. Collection of regional files into a national register (month 6 to 9).
5. Linkage with the cancer register and statistical analyses(month 7 to 11).
6. Feed-back with results to the regional screening organisations(month 12).
7. Explore the feasibility to start registering also the treatment (month 6). If positive, start registering at selected sites The possibility to use a part of the screening program to monitor development of population-based HPV prevalence over time by HPV testing will be explored. If positive, collection of samples for HPV testing will be performed (month 7 to12).
8. All regional health care organisers will be asked if they are willing to introduce HPV screening. If so, they will be randomised either to addition of HPV screening or to conventional screening only (month 12). The HPV screening policy will exactly follow the procedures used in the ongoing, soon completed Swedish randomised trial (For details see: Dillner, J.: Primary screening for Human Papillomavirus infection. *Ballière's Best Practice & Research in Clinical Obstetrics & Gynaecology*, 15, 743-758 (2001)). The proportion of the country that will be willing to participate will be crucial for the power of the evaluation and for further planning of whether this approach is feasible.
9. Improving the "European Guidelines for Cervical Cancer Screening".
10. The obtained results will be disseminated on the Internet via WebForum.
11. The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Sweden will be discussed.



### 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. Marc Arbyn

The work will be concentrated on following topics:

1. To continue the randomised trials comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions and follow-up.
2. Randomisation of 2 x 1.500 women in group A & B. All women in group A will receive liquid based cytology and Hybrid Capture II HPV testing; women in group B will receive LBC (all) and HC II only in case of ASCUS or LSIL is found in the thin layer smear. Follow-up, diagnosis and treatment will be carried out.
3. To start a completely new and comprehensive quality assurance and feed-back system for the cervical cancer screening programme. It will include follow-up of screening coverage based on individual screening invitations and visits records maintained at the mass screening registry of the Finnish cancer registry, as well as of screening attendance and detection rates based on the individual screening visit data.
4. To conduct a detailed study utilising IR spectrometry as a cervical cancer diagnostic tool , and to compare the obtained results with the available preliminary results.
5. To determine the diagnostic value (detection rate ratio, gain in sensitivity, specificity, positive predictive value, ROC-curves) of the ThinPrep method as compared to conventional screening.
6. To determine the cost-effectiveness of the ThinPrep method as compared to conventional screening.
7. To determine the additional qualitative advantages of the ThinPrep Method as compared to conventional screening.
8. The High Risk HPV type identify the risk to progression but cannot predict the outcome of each individual lesion. This goal may be achieved by the planned study of biological intermediate progression markers, while the appearance of H-SIL is the ultimate marker of progression.
9. To conduct a combined study (Pap smear by ThinPrep Method and HPV testing) 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/AGUS.
10. All regional health care organisers in Sweden will be asked if they are willing to introduce HPV screening. If so, they will be randomised either to addition of HPV screening or to conventional screening only .

Following 7 projects from 7 Member States will participate to these activities:

- BELGIUM: Scientific Institute of Public Health
- FINLAND: Finnish Cancer Registry, Helsinki
- GREECE: (Ormylia/Chalkidike): Our Lady Who Loves Mankind
- HOLLAND: University of Nijmegen
- ITALY: Unit of Cancer Epidemiology, Turin
- PORTUGAL: Centro Regional de Oncologia Coimbra

- SWEDEN: Lund University at Malmö

**BELGIUM:** Scientific Institute of Public Health

The main aims are:

- To continue the randomised trials comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions.
- Follow-up of 100 women treated for HSIL with repeat cytology, HPV testing with HC II and PCR, colposcopy and biopsy if necessary.
- Triage of 400 cases if ASCUS/LSIL with concomitant repeat cytology and HPV testing (HC II and PCR using consensus primers for the L1 gene).
- Development of a cervical cancer screening programme for the whole of Belgium.
- Statistical analyses and reporting of the Belgian cervical screening data.
- Cost-effectiveness modelling of alternative screening strategies.
- Collect data from structural databases available at sickness funds (health insurance agencies) containing detailed information on smear taking and smear reading .

PLANNED WORK

1. Continuation of ongoing randomised trial comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions. (Project in collaboration with Free University of Brussels).
2. Randomisation of 2 x 1500 women in group A & B. All women in group A will receive liquid based cytology and Hybrid Capture II HPV testing; women in group B will receive LBC (all) and HC II only in case of ASCUS or LSIL is found in the thin layer smear. Follow-up, diagnosis and treatment is carried out according to earlier described protocols
3. Women recruited since 2000 will undergo further follow-up. Work to be carried out in co-operation with the Free University of Brussels. Timing: recruitment of new women (first six months; follow-up and reporting: months 6-12).
4. Follow-up of 100 women treated for HSIL with repeat cytology, HPV testing with HC II and PCR, colposcopy and biopsy if necessary at months 1, 3, 6 and 12 after treatment. Outcome: prediction of recurrent disease. Work to be carried out in co-operation with the University of Liège (Laboratory of Prof. P. Delvenne). Timing: recruitment of HSIL cases over 12 months. End follow-up and reporting over the next 12 months.
5. Triage of 400 cases if ASCUS/LSIL with concomitant repeat cytology and HPV testing (HC II and PCR using consensus primers for the L1 gene). Patients will be randomised into 2 groups. In group A management will be oriented according to cytology and HPV. In group B management will be decided according to cytology (HPV test results will be blinded). Work to be carried out in co-operation with the University of Liège (Laboratory of Prof. P. Delvenne). Timing: recruitment of HSIL cases over 12 months. End follow-up and reporting over the next 12 months.
6. Development of a cervical cancer screening programme for the whole of Belgium. Creation of a steering group. Constitution of a steering group: first two months; elaboration of a Belgian programme in collaboration with the Communities and the Region of Brussels: months 3-12.
7. Statistical analyses and reporting of the Belgian cervical screening data. Data collected in the framework of screening registration in the previous years. Statistical analysis and reporting during first 6 months.

8. Advanced statistical analyses of incidence and mortality trends concerning cervical and other uterine cancers: study of temporal and spatial variation in relation with influencing factors (age-period-cohort effects, spatial co-variables) for Belgium and other EU countries. Statistical analysis performed in co-operation with the Biostatistical Centre of the University of Limburg (Prof. G. Molenbergs); Leuven (Prof. E. Lesaffre) and the University of Aberdeen (Prof. A. Lawson). Activity duration: from month 1 to 12.
9. Cost-effectiveness modelling of alternative screening strategies: target age groups, screening frequency of screening, inclusion of new screening methods with MISCAN and Data Triage micro-simulation models. Estimation of cost-effectiveness of the application of new screening techniques. Collaboration with Erasmus University of Rotterdam and with European Organisation for Research and Treatment of Cancer (Brussels). Timing: from months 6 to 12.
10. Surveys: (1) among gynaecologists and GP's concerning current knowledge, attitudes and practice concerning HPV testing and result communication, (2) among women concerning psychological aspects of HPV testing, need for information and communication. First: 3 months: development of questionnaires; month 4-5: pilot testing of questionnaires; month 6: elaboration of definitive questionnaires; month 9-10: sending of questionnaires to gynaecologists and interview of women; month 11 data entry and statistical analysis; month 12: reporting.
11. Collect data from structural databases available at sickness funds (health insurance agencies) containing detailed information on smear taking and smear reading for all assured individual members and compare this information with estimates of screening coverage derived from surveys such as the national Health Interview Surveys (HIS). Collection of health insurance data (1<sup>st</sup> 5 months). Data analysis (month 6-7). Comparison with coverage estimates from HIS-surveys (month 8-9). Reporting of 'validated' screening coverage ventilated over demographic, socio-economic and geographical determinants (months 10-12).
12. Work will be performed for improving the "European Guidelines for Cervical Cancer Screening".
13. The obtained results will be disseminated on the Internet via the WebForum.
14. The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Belgium will be discussed.

#### **FINLAND:** Finnish Cancer Registry, Helsinki

We plan to start a completely new and comprehensive quality assurance and feed-back system for the cervical cancer screening programme. It will include follow-up of screening coverage based on individual screening invitations and visits records maintained at the mass screening registry of the Finnish cancer registry, as well as records of screening attendance and detection rates based on the individual screening visit data.

We will perform a large-scale public-health study on evaluating new technologies in cervical cancer screening. The aim is to provide evidence on the effectiveness of the proposed new technologies in preventing cervical cancer, and test thus for future routine screening technologies for programme screening.

#### PLANNED WORK

- We will perform a large-scale public-health study on evaluating new technologies in cervical cancer screening, which will implement a randomised multi-arm design on the various feasible technologies.

- For the planned activity period, from December 16, 2002 to December 15, 2003, we will recruit about 40,000 women to automation-assisted pap smear screening, and 5,000 women to the HPV-DNA screening design within the Finnish cervical cancer screening programme.
- Women with manual pap smear screening practice will serve as the reference.
- The randomisation is performed in the invitation process.
- Data on the screening invitations and visits, including histologically confirmed findings, are collected via mass screening registry and cancer registry files.
- We will evaluate the screening process parameters such as coverage, compliance and detection parameters for screening using the new technologies.
- The ultimate aim of the randomised design is to provide evidence on the effectiveness of the proposed new technologies in preventing cervical cancer, and test thus for future routine screening technologies for programme screening. The follow-up of women invited will be continued after the recently-planned inclusion period, to be done in later years. If the qualitative difference in detecting CIN3+ (severe dysplasia or a more severe finding) lesions appear to similar to the pilots, we have good statistical power for comparing the performance of the new methods with the traditional screening (power 80%, alpha 0.05, two-sided).
- Work will be performed for improving the "European Guidelines for Cervical Cancer Screening".
- The obtained results will be disseminated on the Internet via the WebForum.
- The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Finland will be discussed.

#### **GREECE (Ormylia/Chalkidike): Our Lady Who Loves Mankind**

Work will be continued in order to determine the prevalence of HPV infection in a sub sample of the screened population. The results obtained by a preliminary study in December 2002 will be compared with the obtained results of this project.

#### **PLANNED WORK**

We intend to perform following project activities:

- To continue the study work in order to determine the prevalence of HPV infection in a sub sample of the screened population.
- We plan to conduct a detailed study utilising IR spectrometry as a cervical cancer diagnostic tool. This will involve a random sample of 30 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 leading centres in the USA who have pioneered this methodology and have demonstrated to some degree its accuracy and usefulness.
- The results of the preliminary study (obtained in December 2002) will be compared with the results of the "Detailed Study" (obtained in October 2003).
- Apply the new technology in creating a communications link with European Centres of Excellence in the UK, Germany and other European Centres via the Internet.
- The obtained results will be disseminated on the Internet via the WebForum.
- The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Greece will be discussed.

#### **HOLLAND: University of Nijmegen**

The project aims are:

- To determine the diagnostic value (detection rate ratio, gain in sensitivity, specificity, positive predictive value, ROC-curves) of the ThinPrep method as compared to conventional screening.
- To determine the cost-effectiveness of the ThinPrep method as compared to conventional screening.
- To determine the additional qualitative advantages of the ThinPrep Method as compared to conventional screening.

#### PLANNED WORK:

This prospective research project will be carried out in GP and gynaecology practices and at pathology departments in the Eindhoven and Nijmegen areas, the Netherlands. The research population will consist of a two year screening population in the adjoining regions of Eindhoven and Nijmegen (N=60,000 smears/women). This number is sufficient (power = 0.8, alpha = 0.05) to indicate an increase in sensitivity of 24% (ASCUS+) and 27% (HSIL+). In several studies an increase has been indicated of 10-25% (LSIL+) (Ferenczy, Sheets, Carpenter, Bolick).

The GP practices are randomly distributed between ThinPrep- and conventional smears. All smears will be taken with the Cervex Brush by participating general practitioners (GP's). There will be a two year follow-up period.

Women are referred to the gynaecologists for colposcopy according to the national Dutch guidelines. All referred women will have a cervical biopsy taken for histopathological evaluation. In the removed material a routine histological classification will be determined. The reference test is a blinded review of all histological follow up material. This histological assessment will be done by an experienced pathologist who will be blinded as to the original used screening methods, screening results, routine histological diagnosis, and previous routine histopathological diagnosis. Discrepancies will be determined by a third pathologist.

In case of ASCUS and LSIL with only normal follow-up smears in the follow-up period the follow-up will be considered negative. If follow-up smears are abnormal but histological follow is absent, the case will be disregarded.

The cross-sectional diagnostic value in terms of gain in sensitivity, specificity, and positive predictive values of the Thinprep technique relative to conventional cytology will be determined for the subgroups ASCUS+, LSIL+, and HSIL+ for different levels of histopathology (atypical squamous (metaplastic) mucosa, CIN1+, CIN2+).

The costs of conventional screening and Thinprep will be evaluated considering among others costs of disposables, the adequacy of the smear, preparation time, screening-times for cytotechnologists and pathologists, transportation, stocking and disposing of rest materials.

Short-term cost and effects in terms of incremental cost per additional abnormal case detected will be calculated. The long term consequences of implementation of Thinprep, provided differences in test performance, in the Dutch cervical screening programme will be simulated using the MISCAN-model. Both the health effects (invasive cancers prevented, life years gained), and cost-effectiveness will be assessed. Also other possible (dis-)advantages of Thinprep such as user satisfaction, possible use of additional techniques, such as immunocytochemistry, HPV and automated screening will be evaluated.

#### PLANNED TASKS

- Information of all relevant regional organizations (Regional cervical cancer screening organization; GP organizations and gynaecologists) about the project. Elaboration of draft and final protocol. Sample size calculations.

- Randomization of all participating GP practices in two comparable groups.
- Design of questionnaire between the participating GP's that will measure user satisfaction of current conventional screening method and Thin Prep method.
- Instruction of participating GP's in the Thin Prep method.
- Design of registration sheet for the measurement of all relevant screener activities
- Definition of research database to include all test results, screener activities and follow-up data, final diagnosis and additional used qualitative advantages or disadvantages of the Thin Prep method.
- Distribution, collection and analysis of initial GP questionnaires.
- Training of cytotechnologists and pathologists in the Thin Prep method.
- Inclusion of first 20.000 cervical samples: Registration of results, screener activities and all other relevant activities relating to the use of the both methods (use of additional techniques on Thin Prep preparations)
- The obtained results will be disseminated on the Internet via the WebForum.
- The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Holland will be discussed.

#### FUTURE ACTIVITIES

- Registration of follow-up data of first 20.000 samples.
- Inclusion of 30.000 new cervical samples: Registration of results, screener activities and all other relevant activities relating to the use of the both methods
- Blinded review and registration of the results of all histological follow-up data. Setting final follow-up diagnosis.
- Distribution, collection and analysis of definitive GP questionnaires
- Evaluation of test results including calculation of diagnostic value parameters and measurement of cost-effectiveness using MISCAN model.
- Evaluation of the questionnaires.
- Assessment of impact of sample taker effects on the diagnostic outcomes.

#### EXPECTED RESULTS:

This study will be a methodological improvement of the existing published studies which showed a variety of methodological problems such as the absence of a good reference test, observer variability in histological grading, non-blinded evaluation of index- and reference tests.

The final report will be prepared containing the outcome of the project. The project will result in:

1. Establishment of the diagnostic value of the ThinPrep method in primary screening as compared with the conventional screening method using a robust golden standard.
2. Determination of the cost-effectiveness of the ThinPrep method as compared to conventional screening.
3. Determination of the additional qualitative advantages of the ThinPrep Method as compared to conventional screening.
4. Design of a proposal for implementation of ThinPrep in the new guideline of the European Cervical Cancer Screening Network for European screening programs, taking into account the cost-effectiveness and other quality-parameters.
5. This secondary prevention project aims to combat cervical cancer in Europe by assessing a new screening instrument that may be more sensitive (without loss of specificity) and cost-effective. The results of the project will give evidence based support for the implementation of this technique in European countries.
6. Conclusions of the study will orient the updating of the European Guidelines on Cervical Cancer Screening as far as the use of new technologies is concerned.

**ITALY:** Unit of Cancer Epidemiology, Turin  
in co-operation with the University of Ferrara

### PLANNED WORK

Bio-molecular progression markers in HPV-related cervical tumorigenesis.

- study of biological intermediate progression markers in HPV-related cervical tumorigenesis
- patient management, to support early detection and prevention project, to depict a bio-pathological cancerogenetic pathway of cervical carcinoma

The cervical tumorigenesis begins by the initiating role of HPV oncogenic type and proceeds throughout multiple steps characterised by derangement of cell cycle control, immortalization and progression to invasive carcinoma. The manifest HPV productive infection has a well known morphology, which allows the assessment and management of infection itself; however, the morphology can identify clinically relevant lesions but cannot distinguish between Low or High Risk HPV type infection, at this moment of the natural history. HPV DNA testing is a useful test to differentiate HPV types responsible of the infection. However, the High Risk HPV type identify the risk to progression but cannot predict the outcome of each individual lesion. This goal may be achieved by the study of biological intermediate progression markers, while the appearance of H-SIL is the ultimate marker of progression. Moreover, this study may be useful to the appropriate patient management, to support early detection and prevention project, to depict a bio-pathological cancerogenetic pathway of cervical carcinoma.

**OBJECTIVE:** Aim of the study is to evaluate the biological intermediate markers predictive of progression in normal samples, in HPV related lesion, dysplasia and infiltrating carcinoma of uterine cervix. The study will be developed in two steps:

First step: analysis of the most informative progression marker(s) in archival histological samples.  
Second step: application of the results to screening-collected cytological liquid phase cervical samples, showing evidence of HPV infection.

### METHODOLOGY

The first step: Histological archival samples from formalin-fixed, paraffin embedded archival specimens, negative for precursors lesions and carcinoma, and with confirmed diagnosis of moderate dysplasia, severe dysplasia, in situ carcinoma, invasive squamous carcinoma, will be preselected.

Simultaneously, we will begin the recruitment of cytologic liquid phase cervical samples from patients submitted at the same time to surgical procedures. In these patients also previous smears will be evaluated. The tumour markers selected are:

- FHIT gene ( Fragile Histidine Triad, 3p14.2) LOH by Fluorescent in Situ Hybridization
- Genetic instability by microsatellite analysis (the panel will be defined)
- Expression of p53 and p16 gene products by monoclonal antibody immunohistochemistry
- High Risk HPV by in situ Hybridization.

The second step consists of

- Selection of the most informative panel to progression
- Application of the results to liquid phase samples in screening detected abnormalities.
- The obtained results will be disseminated on the Internet via the WebForum. The results obtained in the Network (from December 2002 to December 2003) will be presented, and their impact on cervical cancer screening in Italy will be discussed.

**PORTUGAL:** Centro Regional de Oncologia Coimbra

The aim of this project is to continue the work of the previous project (16. December 2001 to 15. December 2002) on a combined study (Pap smear by ThinPrep Method and HPV testing) on women whose first cytological test was 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 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 conducted in 17 counties of the Central Zone that are remote from urban centres and whose health-care systems are not yet incorporated into the Cervical Screening Programme, meaning that screening is only done occasionally and on a small scale.
- The target population are women aged between 20 and 64, those under 20 who have already had sexual intercourse, and those over 64 that have not had previous cytological tests. Excluded from the study are women who have had hysterectomies and those with previous diagnoses of intra-epithelial lesions or cervical carcinoma.
- The smears are taken by GPs after a gynaecological examination, using the Cervex-Brush that is rinsed directly into PreservCyt vials and sent to the Cytopathology Laboratory of the Cancer Institute. The slides are prepared with the ThinPrep 2000 device, and screened and classified according to the Bethesda System.
- All the smears classified as ASCUS or AGUS are reviewed by two cytopathologists, submitted to a HPV test with Hybrid Capture II (HCH) and referred for colposcopy. The colposcopies will be done by the same two Gynaecologists, experts in Colposcopy. The biopsies are also studied by two pathologists expert in cervical pathologies.

**SWEDEN:** Lund University at Malmö

- To explore the possibility of establishing a sentinel system within the organised cervical screening programme for measuring population-based trends over time of the major cervical cancer risk factors in Sweden.
- To explore the possibility to implement primary HPV screening as a randomised health care policy in Sweden.

**PLANNED WORK**

- All regional health care organisers will be asked if they are willing to introduce HPV screening. If so, they will be randomised either to addition of HPV screening or to conventional screening only. The HPV screening policy will exactly follow the procedures used in the ongoing, soon completed Swedish randomised trial (For details see: Dillner, J.: Primary screening for Human Papillomavirus infection. *Ballière's Best Practice & Research in Clinical Obstetrics & Gynaecology*, 15, 743-758 (2001)). The proportion of the country that will be willing to participate will be crucial for the power of the evaluation and for further planning of whether this approach is feasible.
- Work will be performed for improving the "European Guidelines for Cervical Cancer Screening".
- The obtained results will be disseminated on the Internet via the WebForum.



- The results obtained in the Network (from August 1999 to December 2003) will be presented, and their impact on cervical cancer screening in Sweden will be discussed.

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

- Objective: Development and use of WebForum, the communication platform for teamwork, discussions and dissemination of the network results in Internet
- Development of Multimedia Interactive User Interface
  - Development of Document Management Facilities
- Leader: Prof. Schenck (Co-ordination Centre)

The WebForum 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:

1. AUSTRIA: University of Vienna
2. BELGIUM: Scientific Institute of Public Health
3. FINLAND: Finnish Cancer Registry, Helsinki
4. FRANCE: WHO – IARC, Lyon
5. FRANCE: Association EVE, Strasbourg
6. GERMANY: Cytological Institute of the Bavarian Cancer Society
7. GERMANY: SWS Tumorcentre Zwickau
8. GREECE: Hellenic Foundation of Oncology, Athens
9. GREECE: (Ormylia-Chalkidike): Our Lady Who Loves Mankind
10. HOLLAND: University of Nijmegen,
11. ITALY: Unit of Cancer Epidemiology, Turin
12. PORTUGAL: Centro Regional de Oncologia Coimbra
13. SPAIN: Health and Social Welfare Council, Junta de Castilla y León, Valladolid
14. SWEDEN: Lund University at Malmö
15. UNITED KINGDOM: Birmingham Women's Hospital

### Individual Member State Projects

All individual projects will have access to WebForum. Discussions within the project team will improve the team work. Dissemination of the obtained project results will be performed world wide via Internet, and will facilitate the feedback from a large number of specialists in cervical cancer screening.

### PLANNED WORK

Additional software development work will be performed by the Co-ordination Centre during this project (December 2002 - December 2003), as follows:

- Development of Document Management Facilities for supporting large size documents on the WEB. These facilities are requested for the presentation of the "European Guidelines for Cervical Cancer Screening" on the WEB.
- Development of Multimedia Interactive User Interface in order to allow the direct access of medical staff to multimedia data (text, tables, images, electronic patient data, laboratory patient results, microscope images, etc) for research and training reasons.
- Display of the of the "European Guidelines for Cervical Cancer Screening" on the WEB

### 3. Obtained Results in 2003

During the reporting period 16. December 2003 to 15. December 2003 the 2<sup>nd</sup> draft of the integrated "European Cervical Cancer Screening Network" (267pages) was released, and is available in Internet (at [www.cancer-network.de](http://www.cancer-network.de) ).

The Guidelines document on paper (267 pages) is attached to this report.

The work performed on "Quality Assurance and Quality Control" of cervical screening ensures high standards in laboratory practice, and is presented in section 3.1.

The performed work on "Monitoring, Epidemiology and Evaluation" is presented in section 3.2. In section 3.3 we present the experimentally used "New Technologies in Cervical Cancer Screening". The dissemination of the obtained results is presented in section 3.4 together with the WebForum (our Internet platform for information dissemination).

The detailed descriptions of the performed and obtained results by 15 institutions in 12 Member States are provided in the attached 15 Final Reports (687 pages):

Report 1	Germany-Munich
Report 2	Austria
Report 3	Belgium
Report 4	Finland
Report 5	France-Lyon
Report 6	France-Strasbourg
Report 7	Germany-Zwickau
Report 8	Greece, Athens
Report 9	Greece, Chalkidike
Report 10	Holland
Report 11	Italy
Report 12	Portugal
Report 13	Spain
Report 14	Sweden
Report 15	UK

### 3.1 Quality Assurance and Quality Control 2003

This cluster has produced the Guidelines Chapters 4, 5, 6, 7, 8, 10 and 12. This cluster has also integrated the 1st and 2nd draft of the "European Guidelines for Cervical Cancer Screening. The Guidelines documents are available at the WebForum via the Internet ([www.cancer-network.de](http://www.cancer-network.de)).

Work was continued on analysing the quality assurance and quality control practices (i.e. methods, techniques, tools, training) and for evaluating their impact on cervical screening with respect to their efficiency and costs. This cluster includes 7 thematic projects from 6 Member States:

- AUSTRIA: University of Vienna
- BELGIUM: Scientific Institute of Public Health
- FRANCE: Association EVE, Strasbourg
- GERMANY: Cytological Institute of the Bavarian Cancer Society
- GREECE: Hellenic Foundation of Oncology, Athens,
- GREECE: (Ormylia-Chalkidike): Our Lady Who Loves Mankind
- UK: Birmingham Women's Hospital

**GERMANY:** Cytological Institute of the Bavarian Cancer Society

This partner co-ordinates the Network, has produced the Chapters 4, 5, 8 and 10, and has integrated the 2<sup>nd</sup> draft of the "European Guidelines for Quality Assurance in Cervical Cancer Screening".

Work was performed with 3 main objectives:

- i) to improve the quality control and quality assurance, and to evaluate their impact on cervical cancer screening process, and
- ii) to update the European Guidelines for Quality Assurance in Cervical Cancer Screening, and to produce the Chapters 4, 5, 8, and 10.
- iii) to continue to investigate the "Continuous grading of intraepithelial lesions" and the study on DNA content of cases of intraepithelial lesions of mild and moderate dysplasia related to cytological / histological follow up (regression, persistence, progression)

The tools developed during the previous reporting periods were improved and experimentally used in the laboratory environment, and a total number of 30.156 smears were analysed. The improvement of the quality of the laboratory screening was evaluated and re-screening work was performed for a number of 1.424 smears. The cost-efficiency of the screening work was analysed, and the computer-based recording of the screening work was improved and released in June 2003.

The study "Continuous grading systems for the diagnosis of intraepithelial lesions" was continued in co-operation with the Technical University of Munich, and the obtained results were published at the 27th Conference of the German Association of Pathology, in Bamberg on 11-14. June 2003.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 1 of 37 pages.

**AUSTRIA:** University of Vienna, Department of Pathology

This partner has produced the Chapters 6 and 7 of the Guidelines, and has performed following work (from 16. December 2002 to 15. December 2003):

- An experimental study of the new quality assurance and control practices of the Network was carried out with the aim of ensuring high standards of cervical cancer screening in Austrian cytological and histological laboratories.
- A new quality management system was developed for the laboratory, with the aim of introducing a certification audit, which should be held by a professional institution and has to be repeated every three years.
- The Austrian Guidelines for Cervical Cancer Screening were adapted to the new methods and techniques elaborated by the Network.
- The consensus with the improved European Guidelines for Cervical Cancer Screening was reached, and the Guidelines' recommendations were implemented in the chapters 6 and 7 of the Guidelines.
- The performed work on Guidelines chapters 6 and 7 is presented on the WebForum and can be accessed via Internet

The new quality management program was carried out in an area concentrated on the work of gynecopathohistology and cytology, based on a work load of 7.500 histology cases and 60.000 cytology cases preparatory work for primary and repeated certification audits. The quality assurance program included research activities within the Austrian unit like the evaluation of clinical HPV-testing, DNA in situ Hybridisation, fluorescence in situ hybridisation (FISH), different techniques for immunohistochemistry, the investigation of angiogenesis and lymphangiogenesis in different types of cancer.

The entire process was accompanied by questionnaires of people engaged in the process. Regular intra-laboratory meetings were also used for evaluation of advantages and disadvantages of the quality assessment procedure under investigation.

Final charts demonstrated that preparatory processes and certification via audit highly influences the quality of entire working process, collegiality and motivation of the personnel. Norms in the certification/quality management system have to be adapted, especially for the diagnostic procedure in histology and cytology. The experience gained entered discussions at all meetings of the European cervical cancer screening network and are bases for chapters 6 and 7 of the Guidelines.

The Austrian partner participates actively in the "ARGE Qualitätssicherung" of the Austrian Society of Cytology. Meetings with the other members of this committee were organised. Based on the network meetings the Austrian situation of cervical screening was re-discussed and effort was undertaken to find a reorganized way of self-control for laboratories working in the field of gynaecological cytology. In co-work with all the other members a revised version of the "Leitfaden zur Beteiligung an der freiwilligen Selbstkontrolle zytologischer Laboratorien" (Guideline for participating in the voluntary auto-control of cytological laboratories) was newly established and adapted for the Internet.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 2 of 48 pages.

**BELGIUM:** Scientific Institute of Public Health

The research work was performed as planned.

- Continuation of ongoing randomised trial comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions. Randomisation of 2 x 1500 women in group A & B. All women in group A received liquid based cytology and Hybrid Capture II HPV testing; women in group B received LBC (all) and HC II only in case of ASCUS or LSIL was found in the thin layer smear. Follow-up, diagnosis and treatment was carried out according to earlier described protocols.
- Follow-up of 100 women treated for HSIL with repeat cytology, HPV testing with HC II and PCR, colposcopy and biopsy if necessary at months 1, 3, 6 and 12 after treatment. Outcome: prediction of recurrent disease. Timing: recruitment of HSIL cases over 12 months. End follow-up and reporting over the next 12 months.
- Triage of 400 cases if ASCUS/LSIL with concomitant repeat cytology and HPV testing (HC II and PCR using consensus primers for the L1 gene). Patients were randomised into 2 groups. In group A: management was oriented according to cytology and HPV. In group B: management was decided according to cytology (HPV test results will be blinded). Timing: recruitment of HSIL cases over 12 months. End follow-up and reporting over the next 12 months.

Work was performed for improving the "European Guidelines for Cervical Cancer Screening", the Chapter 3 of the Guidelines was produced by this partner. The Chapter 3 is available at the WebForum via the Internet.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 3 of 268 pages.

**FRANCE:** Association EVE, Strasbourg

Work was performed as planned from 16. December 2002 to 15. December 2003:

Long Term Survey of ASCUS and AGUS in the EVE Screening Programme:

2 446 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, 9,0 % Atypical Glandular Cells (AGC) and 0,2% show atypical glandular and squamous cells together. To assess quality of cytological results in this peculiar field of atypical smears, 10 % of the smears were reviewed. First blinded, this review showed great discrepancies (66% of cases). Category Kappa values were under 0,41. Discordant cases were re-evaluated. At the end of the reviewing procedure 235 cases were assessed; 120 were classified as ASC-US, 9 as ASC-H, 10 as glandular atypia, 9 as ASC+AGC, 2 as inadequate, 61 as within normal limits, 4 as LSIL and 4 as HSIL or more severe lesions. This review appeared clinically relevant.

A study of outcomes at 5 years of atypic smears was done using data routinely registered in our screening data base and extra questionnaires sent to smear-takers.

Results of this survey, for cases not lost of follow-up with a completed questionnaire, showed 8,5 % confirmed CIN1, 4,5 % high-grade lesions and 0,3 % invasive cancers.

Only age of patients and result of previous smear were statistically related with outcomes. Younger women and those with an anterior abnormal smear had more lesions. Recoding cytologic

reports in 4 categories did not predict outcomes in term of total lesions detected but more high grade lesions were observed in case of ASC-H and glandular atypia than in case of ASC-US.

Evaluation of liquid-based cytology methods as common practices was performed within the framework of the campaign for cervical cancer screening in the Bas-Rhin region: The objective of the study is to evaluate liquid-based cytology as a common practice within the framework of the Eve cervical cancer screening campaign.

Population and methods : The Eve programme collects data on all smears taken in women aged 25 to 65 and living in the Bas-Rhin region. 2 laboratories have introduced liquid-based cytology in 1998. Lab A uses Autocyte Prep ®, Lab B, Cyteasy ®. First cytology results obtained by conventional Pap (August 1997-July 1998 : 46 199 smears) are compared to those by thinlayers (1999 : 48 943 smears). Results in the two labs are pooled because they show same trends. The same comparison is done in a control group where conventional Pap was used during both periods.

In the two labs diagnostic parameters of each cytological method are assessed by comparing outcomes at 40 months of adequate smears. Positive threshold is ASCUS+. Distinction between true negative, false negative, true positive and false positive cases is made on colposcopic and histological findings or on results of subsequent smears. Actually in routine screening, not all smears are followed by diagnostic exams.

Specimen adequacy improves with liquid-based cytology : inadequate smears drop by 40 %. An increase of LSIL (2,6 % versus 1,1 %) and ASCUS (4,0 % versus 3,6 %) with a reduction of ASCUS/LSIL rate is also noticed with thinlayers whereas distribution of cytological results remains stable in the control group.

Sensitivity of liquid based cytology is better than conventional Pap's one (71,7% versus 64,8%) but it has a lower specificity (94,7% versus 95,5 %). Positive and negative predictive values do not differ statistically. Among all histologically confirmed lesions, interval lesions drop from 34,7 % with Conventional Pap to 29,5 % with liquid-based cytology. Interval CIN1 decrease statistically (45,9 % versus 36,1 %) whereas interval CIN2+ do not (26,1 % versus 23,0 %). Thinlayers seem to be more sensitive and less specific but these results must be taken cautiously since at the moment more information on histological data are available for conventional smears.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 6 of 32 pages.

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

Following results were obtained from 16. December 2002 to 15. December 2003:

- The 5<sup>th</sup> round of the Cervical Cancer Screening programme of the county of Ilia with a target population of women 25-64 years of age, who are permanent residents of the above mentioned county, has been completed.
- The preparation of the 5<sup>th</sup> round of Messinia county has been finished. The programme has started and it continues to run at the present time. The target population is women of 25-64 years of age, permanent residents of Messinia county.
- The Hellenic Foundation of Oncology has decided to start a new programme for the screening for cervical cancer in the Municipality of Aharnon in the county of Attiki. Apart from the local population in these Municipality there are gypsies and a large number of asylum seekers who are considered as permanent residents. All relative preparations have already been started in order for this programme to commence in 2004.

- The follow-up of women with abnormal results (ASCUS, LGSIL, HGSIL, invasive Ca) continues with repeat pap-test and full collection of data in relation to their subsequent therapy or surgical intervention.

The primary reading is performed only by cytopathologist doctors who actively participate to seminars and congresses so as to keep up with the state of the art. One reading is performed. For the results quality assurance, re-screening is performed for the abnormal smears (ASCUS, LGSIL, HGSIL) and a second opinion requested from the Cervical Assessment Steady Unit in Athens (11, Valtetsiou str.). In smears with pathological findings, analogous treatment is suggested. For insufficient or inappropriate smears, repetition of the Pap-Test examination is suggested after three (3) months. One cytopathologist screens 15-20 cervical smears daily.

In Greece there is no external agency checking the laboratory results of reports, for the purpose of promoting a high standard of performance and comparability between laboratories. Proficiency testing is not performed.

A gynaecologist studies the follow-up of the screened women. She (all gynaecologists who have contact with the women are female, since some Greek husbands in rural areas will not allow their wives to be examined by male gynaecologists) personally communicates, by phone or mail, with each woman, who had a abnormal smear (with ASCUS, LGSIL, HGSIL or invasive cancer) at the previous rounds of screening program.

During the clinical assessment a project manager together with the gynaecologist discuss with the women who had abnormal smears. They try very diligently, to explain to them the nature of their existing problem and to persuade them to go through with the treatment.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 8 of 4 pages.

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

Work was carried out with the aim of improving the quality assurance and control practices in Greek laboratories, and contributions were made to the Chapters 8 and 10 of the European Guidelines on Cervical Cancer Screening.

The research activities were continued as follows:

- the study "utilisation of IR spectrometry as a cervical cancer diagnostic tool" was continued. This has involved a random sample of a smears that have already been diagnosed utilising conventional cytology practices and AIC quality control being analysed by the IR spectrometer of our lab.
- The study for determining the prevalence of HPV infection in a sub sample of the screened population was continued.
- We have continued to 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 was done in order to better target persons who have not been screened, especially in the more rural and remote villages.
- We have continued to closely follow up the women tested positive and regularly update their screening files with all the available data on further assessment and treatment.
- We have continued the reliability study of the slide test reading by selecting a stratified random sample, (10%) of smear tests previously read by the cytology laboratory.
- We have continued 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.



During the period from period 16/12/2002 to 15/12/2003 data on 5,979 examined women was processed including pap smear and gynaecological examination

- Our public "screening and education initiatives" were continued, and we have recruited 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 has continued 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.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 9 of 22 pages.

#### **UNITED KINGDOM:** Birmingham Women's Hospital

This partner has produced the Chapter 12 of the European Guidelines for Quality Assurance in Cervical Cancer Screening. The performed work during the reporting period 16. December 2002 to 15. December 2003 had following aims:

- To evaluate 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 on common 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.
- To work out the recommendations for the Guidelines for Cervical Cancer Screening

#### Implement the guidelines for minimum standard of training in colposcopy

Through the auspices of the European Federation for Colposcopy (EFC) minimum standards of training for colposcopy have been agreed by all member states of the EU and East European countries. In total 25 countries have been involved, namely Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Irish Republic, Israel, Italy, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, the U.K., and Yugoslavia.

A competence-based curriculum was formulated using the Delphi technique. Fifty-one competencies have been identified by expert consensus. Agreement between Member societies was reached in October 2002. The guidelines have been circulated to all 25 Member organisations of EFC with a view to initiating a programme to introduce the standards during 2003-2004. So far 6 countries (Croatia, Germany, Greece, Irish Republic, Netherlands and the U.K.) have confirmed that the guidelines have been accepted and will be introduced. The situation with other Member countries is being established at this time.

#### Identify treatment methods for cervical premalignant disease (CIN)

Members of the steering committee met 5 times in 2003 (Hamburg 20<sup>th</sup> February, Krakow 6<sup>th</sup> June, Athens 21<sup>st</sup> June, Hamburg 19<sup>th</sup> September 2003 and Paris 4<sup>th</sup> December) to discuss ways in which the programme could identify how CIN was treated across Europe.

Each Member country was sent a series of questionnaires asking for information on the optimum way to manage various problems related to management of CIN. A representative from each country was given the same 10 evidence based guidelines (based on the U.K. National Health

Service Screening Programme, U.K. NHSCSP Guidelines, and asked to grade agreement with the guidelines on a scale of 1 (disagree completely) to 4 (agree completely.) To date 19 countries have responded and there is broad agreement with the NHSCSP guidelines. The preliminary results were presented at the 3<sup>rd</sup> European Meeting for Colposcopy in Paris on the 25<sup>th</sup> January 2004. A further questionnaire has been distributed and the results will be presented formally at the next meeting of the British Society for Colposcopy and Cervical Pathology (BSCCP) Cardiff 23<sup>rd</sup> April 2004.

Implement a programme to audit the results of treatment of CIN

A link has been established with the Cancer Registry in Birmingham (known as the Cancer Intelligence Unit – CIU – West Midlands, U.K.) This Cancer Registry has been in existence since 1937. It serves 10% of the population of England and Wales. A simple software package is being developed which will allow treatment centres throughout Europe to audit the results of the treatment of CIN.

When the software has been developed major centres in Europe will be asked for an audit of their treatment of CIN.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 15 of 55 pages.

### 3.2 Monitoring, Epidemiology and Evaluation

This cluster has produced the Guidelines Chapters 2, 9 and 11 of the "European Guidelines for Quality Assurance in Cervical Cancer Screening. The Guidelines documents are available at the WebForum via the Internet ([www.cancer-network.de](http://www.cancer-network.de))

Work was performed as planned during the reporting period 16. December 2002 to 15. December 2003. Long-term monitoring and epidemiological evaluation of the cervical screening were performed in several European regions, with the objective of establishing realistic results outcome indicators, and to estimate costs, benefits and adverse effects.

This cluster includes 7 thematic projects from 7 Member States:

- BELGIUM: Scientific Institute of Public Health
- FINLAND: Finnish Cancer Registry, Helsinki
- FRANCE: WHO – International Agency for Research on Cancer, Lyon
- GERMANY: SWS Tumorcentre Zwickau
- 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

This partner has produced Chapter 3 and commented on Chapters 2, 9 and 11 of the Guidelines. Work was performed on statistical analyses of incidence and mortality trend, and statistical analyses and reporting of data from the Belgian Cervical Screening Registers.

##### Evaluation of Cervical cancer mortality in Belgium (1954-94):

The Belgian partner investigated the evolution of mortality from cervical cancer in Belgium between 1954 and 1994 in terms of absolute number of deaths, and standardised and age-specific mortality rates. Changes over generations were summarised using the standardised cohort mortality ratio. Trend studies of cervical cancer mortality were hampered by certification problems. The number of deaths due to cancer of the uterine cervix is not known exactly since a substantial proportion of death causes are coded as cancer of the uterus without specifying the anatomic site: cervix or corpus uteri. This inaccuracy in codification has been corrected using distribution tables derived from countries where this certification problem is minimal. Trends in mortality from certified and corrected cervical cancers were compared. The corrected age-standardised mortality rate decreased continuously over the last 4 decades, from over 14 to 5 per 100,000 woman-years (slope -0.26/100,000 woman-years, 95% CI -0.28 to -0.24). Its slope is 3.1 times (95% CI 2.9-3.5) more important than for the rate of mortality from certified cervical cancer. In addition to the almost linear decrease, substantial nonlinear cohort influences were observed in certified and corrected mortality rates. The tendency of increasing mortality in women born after 1935 required particular attention. Nevertheless, the slope of the corrected recent cohort effect remained limited in Belgium, probably as a consequence of screening.

##### Virologic versus cytologic triage of women with equivocal Pap smears: a meta-analysis of the accuracy to detect high-grade intra-epithelial neoplasia:

In co-operation with the Swedish partner, the Belgian partner performed a meta-analysis to assess the accuracy of human papillomavirus (HPV) DNA testing as an alternative to repeat cytology in

women who had equivocal results on a previous Pap smear of the uterine cervix. Data were extracted from papers published between 1992 and 2002 that contained results of concomitant virologic and cytologic testing followed by colposcopically directed biopsy in women with an index smear showing atypical cells of undetermined significance (ASCUS). Fifteen studies were identified in which HPV triage and the histologic outcome, presence or absence of a cervical intra-epithelial lesion of grade II or worse (CIN2+), was documented.

The sensitivity and specificity were 84.4% (95% CI = 77.6% to 91.1%) and 72.9% (95% CI = 62.5% to 83.3%), respectively, for HPV testing overall and 94.8% (95% CI = 92.7% to 96.9%) and 67.3% (95% CI = 58.2% to 76.4%), respectively, for HPV testing in the eight studies that used the Hybrid-Capture-II assay. Sensitivity and specificity of repeat cytology at a threshold for abnormal cytology ASCUS was 81.8 % (95% CI = 73.5% to 84.3%) and 57.6% (95% CI = 49.5% to 65.7%), respectively. Repeat cytology considering higher thresholds yielded a substantially lower sensitivity but higher specificity than triage with the Hybrid-Capture-II assay. The ratio of the sensitivity of Hybrid-Capture-II assay over that of repeat cytology at threshold ASCUS pooled from four studies that documented both triage tests was 1.16 (95% CI = 1.04 to 1.29). The specificity ratio did not differ significantly from unity.

Evidence is available indicating improved accuracy (higher sensitivity, similar specificity) of the Hybrid-Capture-II assay in comparison with the classical repeat Pap smear using the threshold of ASCUS for an outcome of CIN2+ among women with equivocal cytologic results.

A contract with the National Union of Socialistic Health Insurers was made to obtain data concerning cervical cancer screening follow-up and treatment of cervical cancer. This partner received data for 1996-2002 from the National Health Insurance on expenses and the number of cervical cancer related performances. 13 million records concerning Pap smear taking and reading, colposcopy, cervical biopsy, conisation, hysterectomy were compiled, merged, and included in the data management system.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 3 of 268 pages.

#### **FINLAND:** Finnish Cancer Registry, Helsinki

This partner has produced the Chapters 2 and 9 of the Guidelines

Work was also performed on the study on a comprehensive quality-assurance and feed-back programme for the national cervical cancer screening programme.

The current monitoring procedures of the programme include follow-up of screening coverage, attendance, and detection rates. A nation-wide annual statistical publication on the programme is based on individual screening invitation and visit (including histological confirmations) data. The screening records are maintained at the mass screening registry of the Finnish Cancer Registry and they can be linked with the nation-wide population and cancer registries. These infrastructures have been used in a number of earlier studies evaluating effectiveness. Now the Finnish partner has started in the current project to utilise it in a completely new way: by launching a study on a comprehensive quality-assurance and feed-back programme for the national cervical cancer screening programme.

The scope of the activity is to systematically survey cervical cancer and CIN3 cases by screening invitation and attendance status -- to monitor and also give feed-back when necessary, for example, if significant numbers of target age groups were left uninvited by a group of municipalities, or the attendance rate has been alarmingly low -- and also by screen-detected findings. Feed-back is given both in terms of sensitivity and specificity errors.

There are annually some 260,000 invitations and 200,000 visits in the programme, and the registration coverage is above 95%. The age-specific coverage has been in earlier years in the region of 90% and has now increased in the 2000s up to 95%. The attendance rates have been in the region of 70% and the attendance has also increased up to 72-73%.

However, in several municipalities (and particularly among 30 and 35 year old women when invited) the attendance rates are very low, the national rate varying from 60 to 65% and municipality-specific rates could even be only 50%. We have estimated (and supported e.g. by the Cancer Society of Finland) that an attendance rate of approximately 80% would decrease population cancer rates still meaningfully. The attendance rates have not yet improved as targeted.

The registered proportion of inadequate smears is <0.1%. Follow-up information e.g. on the histologically confirmed findings from referrals of the screening laboratories is complete. We linked during the activity period some 2,281,000 screening invitations and 1,561,000 screening visit records from 1990-1999 with the files of the national cancer registry. The availability of the archived smears varied by laboratory from 1990 to 1994 as the starting year. Smears from earlier years were not available.

There were very few cancer cases after a negative screening visit in the programme. Thus far nine large screening laboratories have been included in the audit files. The audit materials during the current activity period consist of 600 cases (200 previous slides from cervical cancer cases, and 400 from CIN3 cases; approximately half of the cancer case slides are from adenocarcinomas and half from squamous cell carcinomas) and of about 1200 control slides. All these case and control slides have been evaluated in a blinded phase in the reference laboratory, and a similar blinded assessment is on-going in the original screening laboratories. Thereafter the two blinded assessments are compared and a panel will check those with a major (big) discrepancy, and the screening laboratories will be capable of reviewing the slides also with knowing the details of the cancer case information.

The final goal of the project is to assess whether the audit programme helps in decreasing cancer cases in the future, and also simultaneously decrease false-positive screening results. The research experience indicates that the screening laboratories are willing to co-operate in the comprehensive audit programme. Feed-back is an important tool also to correct errors in the screening policies as quickly as possible.

There is an obvious error in the municipality-specific decision-making procedures concerning the operational aspects related, for example, to attendance. Changing the screening policies within municipalities is, however, a very long-term process and we cannot say yet how much additional effectiveness could be as a result from the feed-back programme.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 4 of 14 pages.

**FRANCE:** WHO- International Agency for Research on Cancer, Lyon

This partner has reviewed the Chapter 3 and contributed to Guidelines Chapter 2.

The first step IARC took was to obtain information on cervical cancer mortality from the WHO mortality database (last updated in December 2002). For cervical cancer incidence, data from the EUROGIN database (available at IARC) was utilised. For the cancer mortality databases, only countries were included in the analysis countries that have at least 11 years of observation (not necessarily continuous).

Similarly, for the cancer incidence database, IARC only included those countries or regions that have cancer registries reporting at least 11 years of observed cancer incidence, and that were included in at least 3 consecutive volumes of the book "Cancer Incidence in 5 Continents" from IARC. Inclusion of information in this book implies that the cancer registries collecting the information do meet a series of minimal quality criteria, and therefore have reliable information.

Following these criteria, the European countries that contributed both mortality and incidence data to this study were the Czech Republic, Denmark, Estonia, Finland, Hungary, Iceland, Lithuania, Luxembourg, Netherlands, Norway, Switzerland, and UK.

EU countries contributing incidence data only (but not mortality data) to this study were Slovakia, Slovenia, Sweden, France (regional only), Italy (regional only), Spain (regional only), Germany (Saarland only), Poland (Cracow only).

Inconsistencies and problems in the database were identified, such as missing values, missing number of deaths, missing population data, and invalid codes for diseases. The IARC group checked all information, and whenever needed, contacted country representatives in Europe for clarification/complementation of information.

For several countries (for different calendar periods) the codification of cancer of the uterus was not specified as "cervical cancer" or "corpus (endometrial) cancer". This causes an important problem in the analysis. The working group developed rules for reallocation of NOS (not otherwise specified) cases, inputting missing data for specific periods in countries where such problems were observed.

A common format of data on cervical cancer screening process values was developed and requested from each EU country. Information was obtained about: presence or absence of an organised screening program, target age group, intervals, coverage, incidence of screen-detected lesions by age, invitational design, and historical changes in the program. For countries with regional data on cervical cancer trends only, region-specific information on cervical screening process values were requested. Screening experts were contacted in each relevant country or region.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 5 of 19 pages.

**GERMANY:** SWS Tumorcentre Zwickau

The aims of the performed work during the reporting period 16.12.02 - 15.12.03 was to continue the work on statistical analyses and reporting of data from the Saxony Cancer Register concerning cervical and other types of uterine cancers and to participate to the network activities for improving the chapters 8 and 10 of the "European Guidelines for cervical Cancer Screening Network".

Statistical evaluation work: The endometriosis carcinoma with an incidence of 25 cases per 100.000 women and year represents the most malignant female genital disease. Typically the incidence is within postmenopausal phase; the mean age is 68 years, with a maximum between the 65th and 70th year. The investigation includes 381 cases of invasive and 6 cases of a non-invasive endometriosis carcinoma which were registered in southwest Saxony within the period of observation (including first-emerged and multiple emerging tumours).

The number of 31.6 diseases/ 100.000 women and year, is above the German and the Saxonian average (28.5 diseases / 100.000 women and year). Also the mean age of incidence is 2 years above the average. The fact that the endometrial carcinoma belongs to the prognostically auspicious malignomes results from their diagnosis in the first stage. This is confirmed by our analysis with an average quota of 70.5 % in the T1- stage. This convenient trend can also be seen in the entire region except in Zwickau-City.

In a total 85,8% of all cases, an operation was performed primarily. Additionally, for 54% an adjuvant radiotherapy was given. In 8,5% of the cases a radiotherapy was given primarily and 26 times (6,7%) no therapy was documented. These ratios are stable over the complete period of investigation.

The removal of the primary tumour is done by hysterectomy. The removal of the lymph nodes by LNE (=pelvis, some cases paraaortal lymphonodectomy). The in the operation concept and in the practice guidelines usually included adnectomy was not implemented in 18% of cases or was not documented.

Altogether, the numbers show, that unattached by the spread of tumours and other criteria (like forecast considerations, collateral morbidity), the main tumour was merely removed by hysterectomy in 60 % of all cases and in 40 % of all cases by the additional removal of the regional lymph nodes.

Due to the number of incidences in context with the numbers of the Workgroup of Population-Oriented Cancer Registries in Germany, the Zwickau partner starts from the assumption of a high amount of completeness for the registered cases. This is also confirmed by the representative composition of the stages. The assessment of the compliance with practice guidelines was by several factors more complicated as it was for instance possible in case of the cervix carcinoma. The concept of the therapy of the endometriosis carcinoma can be configured more individually. This is caused by the age structure with its resulting higher multi-morbidity. After all we clearly see from the number of records of the well occupied stage T1, that with increasing extension of the tumour, the rate of hysterectomy and LNE and the rate of adjuvant radiotherapy rises, which reflects the compliance with the advised practice guidelines of therapy.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 7 of 19 pages.

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

This partner has produced the Chapter 11, contributed to Chapter 2, and reviewed Chapters 2 and 9 of the Guidelines.

The objective of this partner was to continue to monitor the value of process indicators for cervical cancer screening in different screening programmes in Italy. The aim of the performed study is to evaluate "if the HPV test alone can be used for primary cervical cancer screening" at intervals longer than the 3 years currently adopted in many EU countries, with an equal or even better protection. The short term objective is to compare the sensitivity of HPV testing and conventional cytology in identifying women with histologically confirmed high-grade cervical intraepithelial

lesions (CIN) and estimating the costs of these technologies in terms of tests to be repeated, referral rate and positive predictive value (PPV) for histologically confirmed high grade lesions.

The Italian partner recruited 21.265 women for such a phase. In addition we completed recruitment for phase I, during which women in the experimental arm are tested for both liquid-based cytology (LBC) and HPV, that was started in 2002 and performed diagnostic work-up and test repeats concerning such a phase. Some 10.500 women were recruited for such a phase.

Results of both phases are presented here. Overall, data show a substantial increase in sensitivity but a reduced PPV when compared to conventional cytology. LBC caused a reduction in unsatisfactory smears. However, when compared to conventional cytology, increase in sensitivity for histologically confirmed high-grade lesions was lower than that observed with HPV testing while PPV was reduced similarly as with HPV testing. Adding cytology to HPV testing increased sensitivity only marginally. For women in phase II and those of age <35 years in phase I a substantial amount of diagnostic assessment is still running. In addition review of histology is on going. Therefore the present data are to be considered as preliminary

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 11 of 23 pages.

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

This partner has contributed to the Chapter 6 of the Guidelines.

The statistical evaluation was performed as planned. Coverage of the Screening Programme in 2003 throughout the region of Castilla y León was 32,03%, not including the screening cytologies performed in this specialisation in the public or private systems.

Analysing the 58.485 women with smear test in this period, 52.344 are women between 25 and 65 years old (89,50%), and 10,50% are younger than 25 or older than 65: of these, 6,75% (3.951) are women younger than 25 and 3,74% (2.190) belong to women older than 65. The percentage of women with more than one smear test, 0,1%, is lower than the percentage of women with an abnormal smear test, 14,18%. The number of smear tests per woman in the age group 25-65 is 1,03.

Of the 58.485 women who took part in the Programme, 49.710 (85,00%) did not have any pathology; 13,15%, 7.689 women had infections and only in 585 cases morphological disorders were found in the smear test.

Follow up of 98,98% of the anomalous cases including viruses and CIN has been performed; 265 (44,92%) with final results and 319 (54,07%) were not available in February 2004. 118 of the 265 cases with final results after the follow up are positive (44,53%) and 147 cases (55,47%) are negative. Distribution of the positive cases: 2 invasive carcinomas, 1 endocervical adenocarcinoma, 1 microinvasive carcinoma, 8 carcinomas in situ, 92 dysplasias and 14 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:** 11,76% of the women with morphological disorders in the screening smear tests are HPV +., and 41,17% of the women with morphological disorders have not done the HPV test in this province.



**Valladolid:** 38,55 % of the women with morphological disorders in the screening smear tests are HPV + and 34,08% are waiting for the test results. Only 4,47% of the women with morphological disorders have not done the HPV test in this province.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 13 of 31 pages.

**SWEDEN:** Lund University at Malmö

This partner has produced the subchapter "3.4 HPV" of the Chapter 3 of the Guidelines

Records of all cases of invasive cervical cancer and uterus UNS for the last 3 years (1998-2000) were obtained from the National Swedish Cancer Registry. For all cases, histological specimens have been obtained and forwarded for expert re-review of the histopathological diagnosis by a single expert reviewer (Dr. Walter Ryd, Gothenburg, Sweden).

Five control women have been matched to each case from the National Swedish Population Register. As the Mass Screening Registry is still not quite complete, the full screening history of the cases and controls has not yet been determined.

Dr. Dillner also co-ordinates nation-wide efforts to modernise cervical screening in Sweden using Human Papilloma Virus (HPV) testing within organised screening programs. Evaluation of the implementation of new screening technologies is not possible without a registry to monitor usage and effects.

These HPV testing efforts have been supported by a series of 1-year contracts from Europe against Cancer. Typically, the bulk of the work has been performed during the contract period, but finalisation of scientific papers has taken more time and publications have typically not appeared in print until some time later. This report therefore also contains the report of work finalised in this reporting period, also when most of the field work was performed in previous reporting periods. Work was performed during the reporting period in accordance with the planning:

Finalisation of a document with the policies, statutes and administrative structures of the new mass screening registry. The managers of regional screening programs in Sweden as well as the National Board of Health and Welfare were asked to comment on this document before the statutes of the new national registry was finalised on 13<sup>th</sup> of February 2002. The Statutes are enclosed as Annex 1 to the Swedish report (in Swedish, an official EU language).

A decision was reached on which data items are necessary to be kept in the Mass Screening Register and the format for supplying files. The format for supplying files and which data they should contain is supplied as Annex 2 to the Swedish report (in Swedish, an official EU language)

Permissions were requested from the Ethical Committees and the Data Inspection Board was asked to comment on the registry. Ethical permission for research use of the registry was obtained. The Data Inspection Board issued a formal letter stating that based on the data provided there were no objections to the registry (April to June 2003).

Retrieving the screening files from regional laboratories and screening organisations in Sweden. Data collection is ongoing and a majority of Sweden is now included in the registry.

The personal identities of 1500 cases of invasive cervical cancer and uterus UNS have been obtained from the National Swedish Cancer Register, which will form the basis for the calculation of effect and quality indices, as specified in the contract.

The specimen tissues for all the 1500 cases of invasive cervical cancer and uterus UNS from the pathological laboratories in Sweden have been requested. The histopathological re-examination of the specimens is ongoing, but not yet completed.

Selection of random control women from the National Swedish Population Register which will form the basis for the calculation of effect and quality indices, as specified in the contract, has been performed.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 14 of 100 pages.

### 3.3 New Technologies in Cervical Screening 2003

This cluster has produced the Chapter 3 of the "European Guidelines for Quality Assurance in Cervical Cancer Screening. The Guidelines documents are available at the WebForum via the Internet ([www.cancer-network.de](http://www.cancer-network.de))

Work was performed as planned during the reporting period 16. December 2002 to 15. December 2003. New technologies in the Cervical Cancer Screening were investigated and evaluated. Continuous incorporation of technical innovation allows to improve continuously the quality of the European cervical screening. The work was concentrated on following topics:

1. To continue the randomised trials comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions and follow-up (Belgium).
2. Randomisation of 2 x 1.500 women in group A & B. All women in group A have received liquid based cytology and Hybrid Capture II HPV testing; women in group B have received LBC (all) and HC II only in case of ASCUS or LSIL is found in the thin layer smear. Follow-up, diagnosis and treatment was carried out (Belgium).
3. To start a completely new and comprehensive quality assurance and feed-back system for the cervical cancer screening programme, which includes follow-up of screening coverage (Finland).
4. To conduct a study utilising IR spectrometry as a cervical cancer diagnostic tool, and to evaluate the obtained results (Greece)
5. To determine the diagnostic value (detection rate ratio, gain in sensitivity, specificity, positive predictive value, ROC-curves) of the ThinPrep method as compared to conventional. To determine the cost-effectiveness of the ThinPrep method as compared to conventional To determine the qualitative advantages of the ThinPrep Method as compared to conventional screening (Portugal).
6. The High Risk HPV type identify the risk to progression but cannot predict the outcome of each individual lesion (Sweden).
7. To conduct a combined study (Pap smear by ThinPrep Method and HPV testing) 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 (Portugal).
8. All regional health care organisers in Sweden were asked if they are willing to introduce HPV screening (Sweden).

This cluster includes 7 thematic projects from 7 Member States:

- BELGIUM: Scientific Institute of Public Health
- FINLAND: Finnish Cancer Registry, Helsinki
- GREECE: (Ormylia/Chalkidike): Our Lady Who Loves Mankind
- HOLLAND: University of Nijmegen
- ITALY: Unit of Cancer Epidemiology, Turin
- PORTUGAL: Centro Regional de Oncologia Coimbra
- SWEDEN: Lund University at Malmö

**BELGIUM:** Scientific Institute of Public Health

This partner has produced the Chapter 3 of the Guidelines.

Work was performed with following objectives:

- To continue the randomised trials comparing liquid based cytology (LBC)+ HPV screening versus LBC and HPV for triage of borderline/low-grade lesions.
- Follow-up of 100 women treated for HSIL with repeat cytology, HPV testing with HC II and PCR, colposcopy and biopsy if necessary.
- Triage of 400 cases if ASCUS/LSIL with concomitant repeat cytology and HPV testing (HC II and PCR using consensus primers for the L1 gene).
- Development of a cervical cancer screening programme for the whole of Belgium.
- Statistical analyses and reporting of the Belgian cervical screening data.
- Cost-effectiveness modelling of alternative screening strategies.
- Collect data from structural databases available at sickness funds (health insurance agencies) containing detailed information on smear taking and smear reading .

The ongoing randomised trial comparing liquid based cytology + HPV screening versus LBC and HPV for triage of borderline/low-grade lesions was continued.

The meta-analysis on liquid-based cytology compared with conventional cytology (2-cohort and split-sample) was continued. A new meta-analysis on visual inspection of the uterine cervix, P16 immunostaining, HPV mRNA detection, spectrometry was started.

In co-operation with the University of Liège studies were performed as follows.

#### Thin-layer liquid-based cervical cytology and PCR for detecting and typing human Papillomavirus DNA in Flemish women:

The objective of this study was to document the occurrence and to correlate the prevalence of different human papillomavirus (HPV) types with the cytological results on simultaneously performed thin-layer preparations in a large population of Flemish women. During one year, 69.290 thin-layer preparations were interpreted using the Bethesda classification system. Using an algorithm for HPV testing based on consensus primers and type specific PCR's in combination with liquid based cytology, we determined the occurrence and distribution of 14 different oncogenic HPV types (16,18,31,33,35,39,45,51,52,56,58,59,66,68). Reflex HPV testing was performed on cytologically abnormal samples and on an age matched randomly selected control group with normal cervical cytology (n=1.351). Correlation between cytology, age and prevalence for the 14 different high-risk HPV types is given. There is a significant increase in predominance of high-risk HPV types, with increasing abnormal cytology. Co-infection with multiple HPV-types also increased with cytological abnormalities, and was highest in HSIL (16.7%). In Flanders HSIL was most often associated with HPV types 16, 33, 35, 31, 18 and 51. Using thin-layer liquid-based cytology and PCR to detect HPV, it is feasible to screen large numbers of women.

#### The role of HPV DNA testing in follow-up period after treatment for CIN: a systematic review of the literature:

There is an emerging interest concerning the role HPV DNA testing in the follow-up period after conservative treatment for cervical intraepithelial neoplasia.

A MEDLINE and EMBASE search was done (1985 to March 2002), using the keywords HPV/HPV DNA, together with CIN, follow-up, recurrence and LLETZ. References of retrieved articles were also screened. Selection criteria were original published English-language reports of prospective or retrospective studies including women with an initial diagnosis of cervical

intraepithelial neoplasia, who received conservative surgical treatment and were followed with HPV DNA testing in addition to cytology, colposcopy and/or biopsy); the latter methods were used for verification of residual or recurrent disease.

There is a marked heterogeneity in the design, population, intervention and follow-up policy across different studies. The sensitivity of HPV DNA testing in detecting treatment failures was quite good in most studies, reaching 100% in four of them, whereas the specificity of the test differed across the studies, ranging from 44% to 95%. Among women in whom the treatment was considered to be successful, 85.1% had a negative postoperative HPV DNA test and 14.9% a positive one. The corresponding rates for cases with treatment failures were 17.1% and 82.8%, respectively.

It seems that a positive HPV test, even in the presence of normal cytology, can pick up quicker and more accurately a treatment failure. Cytology and colposcopy may still be needed in order to rule out false positive and false negative results.

A randomised trial comparing human papillomavirus screening with triage in combination with liquid-based cytology:

The goal was to evaluate two strategies of cervical cancer screening with high-risk human papillomavirus (HR-HPV) detection adjunct to liquid based cytology: HR-HPV screening of all women versus selective HR-HPV triage conditioned by minor cytological abnormalities in a randomised clinical trial.

Three thousand women, who had a liquid based cervical smear taken, were randomised in two arms. All samples from group A were used for ancillary HR-HPV detection using the Hybrid Capture II method (primary screening setting). HR-HPV testing in samples from group B was limited to those showing atypical or low-grade cytological changes (triage setting). Colposcopic assessment was performed in women either positive for HR-HPV or if cytology showed at least squamous high-grade (HSIL+) or glandular abnormalities. Detection of histological confirmed CIN2 or worse (CIN2+) was the main study outcome.

Cytological detection rates were comparable in both groups ( $p=0.92$ ). The prevalence of HSIL+ was 1.28% in the group A and 1.01% in group B. Nineteen CIN2+ lesions were histological confirmed in the screening arm: 10 were detected by HPV testing alone, one by cytology alone and eight by both methods. The sensitivity was 94.7% for the HPV test and 47.4% for 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 because of cytological HSIL+ or glandular abnormalities, five cases were detected only by subsequent HPV testing of ASCUS or LSIL. The relative sensitivity of liquid-based cytology to detect CIN2+ could be enhanced with 50% by HR-HPV triage of the ASCUS or LSIL cytological results. Screening all subjects for HR-HPV will detect 27% additional cases of CIN2+ compared to triage. This additional yield was not significant in this limited trial but required 22 times more HPV tests and doubled the call for colposcopy.

Management of women with minor cytological cervical lesions: repetition of the pap test versus HPV DNA-testing:

The objective was to document the occurrence and to correlate the prevalence of the human papillomavirus (HPV) 18 viral load with the cytological results on simultaneously performed thin-layer preparations.

The Belgian partner designed a multiplex real-time PCR that permits the simultaneous detection of a cellular target (β-globin) and HPV 18 E7. Viral loads were measured in 289 samples with normal cytology (NEG), in 590 samples classified as atypical squamous cells of undetermined significance (ASC-US) in 282 samples with low (LSIL) and in 180 samples with high-grade squamous intraepithelial lesions (HSIL). Viral loads were expressed as the number of HPV 18 copies /genome equivalent (cp/equi).

The amount of β-globin DNA raised with increasing abnormal cytology (NEG 38,85; ASC-US 44,26; L-SIL 44,43; H-SIL 47,46 ng / μl; p=0.05, ANOVA). The prevalence of HPV 18 positivity varied by cytological category: 5.8% in NEG, 5.8% in ASC-US, 15.6% in LSIL and 15.0% in HSIL ( $\chi^2 = 29.15$ , p<0.012). The HPV 18 viral load increased from NEG (2.5 cp/equi), to ASC-US (72.4 cp/equi), and LSIL (562.8 cp/equi) but then decreased to 394.1 cp/equi in HSIL (p=0.15, ANOVA).

Presence of HPV DNA was detected and viral load raised with increasing degree of cytological abnormality until LSIL, but no difference is observed between LSIL and HSIL. These data suggest that HPV 18 viral load might not be a good indicator for progression from low-grade to high-grade abnormality.

Manual screening of liquid based cytology versus assisted screening with the computerized scanning device FocalPoint slide profiler:

FocalPoint slide profiler is a computerized scanning system for the primary screening of cervicovaginal smears. The system provides maps, for smears indicated to require further review. The goal was to compare the number of abnormal slides detected by manual screening with the number detected by assisted screening using the FocalPoint slide profiler (TriPath, USA) over a six month period.

A consecutive series of manually screened liquid based cytology (Jan-Jul 2002) was compared with a consecutive series of liquid based cytology assisted screening using the FocalPoint (Jan-Jul 2003). Human papillomavirus (HPV) reflex testing using consensus and type specific PCR's was performed on all abnormal cytology.

In the 1<sup>st</sup> period, 33.432 preparations were screened manually. Ninety-eight percent (32.627) had normal cytology, 415 (1.2%) were classified as atypical squamous cells of undetermined significance (ASC-US), 300 (0.9%) as low-grade squamous intraepithelial lesions (LSIL) and 90 (0.3%) as high-grade or worse (HSIL+). From the 805 samples tested for HPV, 698 (86.7%) were positive. In the 2<sup>nd</sup> period, 38.635 liquid based cytology preparations from a similar population were screened using the FocalPoint. Only 37.140 (96.1%) had normal cytology, however, 797 (2.1%) ASC-US, 556 (1.4%) LSIL and 142 (0.4%) HSIL+ were detected. From these abnormal samples, 1.239 on 1495 tested positive for HPV (82.9%).

Screening using the FocalPoint slide profiler resulted in an increased detection of abnormal smears (ratio of 1.60, CI (95% confidence interval):1.48-1.74), accompanied by only a small but still significant decrease in HPV-positivity among cytologically abnormal cases (ratio 0.96, CI: 0.92-0.99).

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 3 of 268 pages.

**FINLAND:** Finnish Cancer Registry, Helsinki

This partner has produced the Chapters 2, and 9 of the Guidelines.

The Finnish partner has designed and launched already during the earlier years of activity a large-scale public-health study evaluating new technologies in the cervical cancer screening programme. The study is implementing a randomised multi-arm design on the various feasible and competing screening technologies within the framework of the Finnish cervical cancer screening programme and it has been going on since 1999, when the automation-assisted screening arm was implemented. During the current activity period from Dec 16, 2002 to Dec 15, 2003, the Finnish partner performed 31,285 tests in the automation-assisted screening arm. In addition some 1,200 quality control slides were scanned with the Papnet machinery. Altogether about 200,000 women have been recruited during the years 1999-2003. In addition 5,000 women were recruited in the primary HPV-DNA screening arm in seven municipalities (in these municipalities also the automation-assisted screening as well as manual screening serving as the control arm were in action). We randomised while drawing invitations for 2004 more than 35,000 women to be screened in the automation-assisted screening arm (for most of whom the second screening round started in the arm) and more than 20,000 women in the HPV-DNA-screening arm, respectively. We expect that during 2004 there'll be about 30,000 screenings in the automation-assisted screening and 17,000 in the HPV-DNA screening arm.

Biostatistical analyses were accomplished for the first three years' results for the automation-assisted screening. According to the results, the detection rates of the histologically confirmed CIN3 and invasive cervical cancer were not markedly higher in the automation-assisted screening arm as compared with the conventional screening -- unlike in some earlier studies where an increase sensitivity and detection of CIN3 lesions was suggested.

There were 157,346 invitations and 110,191 screening visits in the automation-assisted screening arm during 1999-2001; and 313,951 invitations and 220,254 visits in the control arm (conventional screening), respectively. The attendance rate was 70% in both of the arms. Cytological Papanicolaou group II results were obtained in 7.7% in the automation-assisted and in 7.4% in the control arm. Papanicolaou group III, IV and V results were obtained in 0.62%, 0.093% and 0.0045% in the automation-assisted screening arm and in 0.65%, 0.085% and 0.0042% in the conventional screening arm. Except for group II results (that were based on a very large number of observations, 8,500 cases in the automation-assisted screening and 24,850 cases in the conventional screening) the differences were not statistically significant.

Histologically confirmed CIN3 rates were 0.13% in both of the screening arms and the detection rate of the histologically confirmed cervical cancer was 0.013% in the automation-assisted screening and 0.012% in the conventional screening arm. There difference was not statistically significant.

During 2002 (fourth year) the attendance rates were 70.5% in both of the screening arms. The detection rate of histologically confirmed CIN3 was 0.13% and that of cervical cancer 0.01% in both of the arms. Difference in the detection of suspicious cytological findings (Papanicolaou group II) had apparently disappeared between the two screening arms.

The study demonstrates that the evaluation programme is feasible. As the routine use of the test methods may appear different from specific scientific laboratory studies, the particularistic aspects in the routine programmes as to the test methods in large-scale use needs to be directly considered. The results also suggest that the automation-assisted method is usable in the population-based screening programmes; even though for this latter conclusion follow-up of cancer rates after the screening visits still to be done to confirm efficacy.

Piloting with HPV-DNA testing proved out to work well and thereafter the HPV-DNA screening arm has also been started. In the feasibility and piloting studies on liquid-based cytology the results were not affirmative but the detection appeared somewhat lower than with the other methods and therefore we do not plan currently to introduce such an arm in the Finnish programme. In Finland the sample quality is excellent already with the conventional method. More research on the liquid-based cytology is required in Finland before any potential larger-scale implementation.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 4 of 14 pages.

#### **GREECE (Ormylia/Chalkidike): Our Lady Who Loves Mankind**

This partner has contributed to Chapters 8 and 10 of the Guidelines.

Work was continued in order to determine the prevalence of HPV infection in a sub sample of the screened population. The results obtained by a preliminary study in December 2002 were compared with the preliminary results of this project. However, additional evaluation work is requested, and the final results will be available in 2004.

The detailed study utilising IR spectrometry as a cervical cancer diagnostic tool was started. This involves a random sample of 30 pap smears that have already been diagnosed utilising conventional cytology practices and AIC quality control being analysed by the IR spectrometer of the Greek lab. This occurs in co-ordination with leading centres in the USA who have pioneered this methodology and have demonstrated to some degree its accuracy and usefulness. The final results will be available in 2004.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 9 of 22 pages.

#### **HOLLAND: University of Nijmegen**

This partner has produced the Chapter 4 of the Guidelines. Work was performed during the reporting period 16.12.03-15.12.03 with following objectives:

- To determine the diagnostic value (detection rate ratio, gain in sensitivity, specificity, positive predictive value, ROC-curves) of the ThinPrep method as compared to conventional screening.
- To determine the cost-effectiveness of the ThinPrep method as compared to conventional screening.
- To determine the additional qualitative advantages of the ThinPrep Method as compared to conventional screening.

The work was performed as planned. The research project was carried out in GP and gynaecology practices and at pathology departments in the Eindhoven and Nijmegen areas, the Netherlands. The research population consisted of a two year screening population in the adjoining regions of Eindhoven and Nijmegen (N=60,000 smears/women). This number is sufficient (power = 0.8, alpha = 0.05) to indicate an increase in sensitivity of 24% (ASCUS+) and 27% (HSIL+). In several studies an increase has been indicated of 10-25% (LSIL+) (Ferenczy, Sheets, Carpenter, Bolick).



The GP practices were randomly distributed between ThinPrep and conventional smears. All smears were taken with the Cervex Brush by participating general practitioners (GPs). There will be a two year follow-up period (2004 and 2005). The final results will be available in 2005.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 10 of 11 pages.

**ITALY:** Unit of Cancer Epidemiology, Turin  
in co-operation with the University of Ferrara

This partner has performed the review of Chapters 2, and 9, and produced Chapter 11.

The work was performed in co-operation with the University of Ferrara.

Aim of the study was to evaluate the biological intermediate markers predictive of progression in normal samples, in HPV related lesion, dysplasia and infiltrating carcinoma of uterine cervix. The study will develop in two steps.

1. analysis of the most informative progression marker(s) in archival histological samples.
2. application of the results to screening-collected cytologic liquid phase cervical samples, showing evidence of HPV infection.

The Italian partner selected 94 consecutive cases from patients seen in 2001 with diagnosis of squamous dysplasia, in situ and microinvasive squamous carcinoma. The selected samples included normally more than one grade of squamous dysplasia. Referring to the highest grade of dysplasia presented in every sample, we studied 3 condilomas (CIN 1), 32 moderate and 38 severe squamous dysplasias and 19 in situ squamous carcinomas. The Italian partner also included 2 cases with foci of microinvasive carcinoma. Section of 3-4 micron were cut from archival paraffin tissue blocks and submitted to in situ hybridization for HPV-HR and to immunohistochemical reaction for p53 and p16. For p16 we tested two antibodies for strongest reactivity. The specimens were negative for HPV-HR in 35 and positive in 59 cases (62,76%). The positivity was detected as large circular/ovoid dark to light blue nuclei or as small dots. A semiquantitative scale (percentage of positive nuclei) was performed for p53. 51 percent of the lesions belonged to class 1 positivity (<5%), 29% to class 2 (6-25%) and the remaining 19% presented >25% of positive nuclei.

No differences were found between severe dysplasia and carcinoma in situ. Moderate dysplasia belonged preferably to class 2 compared to severe dysplasia/carcinoma in situ. The small foci of microinvasive carcinomas presented a strong abrupt positivity for p53. We evaluated also the intensity of staining (high versus low) and the distribution of positivity in the three compartment of the squamous epithelium (basal, intermediate, superficial).

The intensity was generally high and the distribution of positive nuclei was basal in condilomas, also if present as contextual adjacent lesion. The intensity was variable and the positive nuclei distributed among the different levels of the epithelium in high grade dysplasias. There was no association between the presence or absence of HPV-HR and p53 positivity. For better evaluating the reactivity to p53, we intend re-evaluate the staining with the Image Analyzer recently acquired. P16 yielded a cytoplasmic and nuclear staining. The evaluation are in progress using the Image Analyzer.

The low expression of p53 in high grade dysplasia could indicate the attenuation/degradation of the protein by E6 of HPV-HR. The higher percentage of class 2 moderate dysplasia compared to severe dysplasia/carcinoma in situ could be perhaps explained by the different progression probability of moderate dysplasia. The strong positivity for p53 in

microinvasive carcinoma could be on account of the higher synthesis of the p53 protein as a result of excessive DNA damage or accumulation of the E6-p53 complex.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 11 of 23 pages.

**PORTUGAL:** Centro Regional de Oncologia Coimbra

This partner has performed the review of Chapters 4, 5 and 8 of the Guidelines.

The aim of the performed work was to continue the previous work on a combined study (Pap smear by ThinPrep Method and HPV testing) on women whose first cytological test was 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 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 was conducted 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 were 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 were women who have had hysterectomies and those with previous diagnoses of intra-epithelial lesions or cervical carcinoma.
- The smears were 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 were prepared with the ThinPrep 2000 device, and screened and classified according to the Bethesda System.
- All the smears classified as ASCUS or AGUS were reviewed by two cytopathologists, submitted to a HPV test with Hybrid Capture II (HCH) and referred for colposcopy. The colposcopies are 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, the Portuguese partner has screened 10.085 women by the ThinPrep Method, for 1.825 of the women it was not the first cytological test in the screening programme.

## Cytological results ThinPrep Method

Total smears 10.085

Unsatisfactory	37	0,37%
Negative	9 576	94,9%
ASCUS/AGUS	268	2,66%
LGSIL	164	1,63%
HGSIL	34	0,34%
Invasive carcinoma	6	0.06%

## HPV TEST by HYBRID CAPTURE II

In 161 negative smears that have previous minimal abnormal findings, 289 women with a smear classified as ASCUS/AGUS, 63 with persistent LGSIL and 31 cases with HGSIL, Carcinoma and Recidive, a HPV TEST by HYBRID CAPTURE II was realised, with the following results:

Negative -- 161	AR+ 34	21,11%
ASCUS -- 289	AR+ 116	40,13%
LGSIL -- 63	AR+ 40	63,49%
HGSIL, Carcinoma and Recidive -- 31	AR+ 30	96,77%

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 12 of 4 pages.

**SWEDEN:** Lund University at Malmö

This partner has produced the Subchapter 3.4 HPV of the Guidelines Chapter 3.

Work was performed with following objectives:

- To explore the possibility of establishing a sentinel system within the organised cervical screening programme for measuring population-based trends over time of the major cervical cancer risk factors in Sweden.
- To explore the possibility to implement primary HPV screening as a randomised health care policy in Sweden.

Work on the establishment of a sentinel system within the organised cervical screening programme for measuring population-based trends over time of the major cervical cancer risk factors in Sweden has been started. However, an exploratory study determined that a more rapid ascertainment of the population-based trends over time of the spread of HPV and other cervical cancer risk factors was possible to perform using the population-based serum banks associated with the Maternity Care system (Laukkanen et al, 2003). The data show a marked increase of HPV type 16 infection over time in some age groups.

Work was also started on exploring the possibility to implement HPV screening as a randomised health care policy in Sweden.

Several regional health care organisers were asked if they are willing to introduce HPV screening as a randomised health care policy. This has materialised in the greater Stockholm county where all 12 health care providers agreed to be randomized to “old” or “new” policy for follow-up of patients with CIN 1 or ASCUS. “Old” policy is colposcopy and biopsy, new policy is HPV testing with colposcopy and biopsy only if the woman is HPV positive. If the woman is HPV-negative in the “new” policy, a Pap-smear will be taken about 1 year after the HPV test.

The randomised health care policy was approved by the Ethical Committee of the Karolinska Institute. All 60.000 women resident in the Stockholm area and due for screening during 2003 were informed by letter about the randomised policy for follow-up of patients with CIN1 or ASCUS.

The health care providers randomised to new policy switched policy on 1<sup>st</sup> April 2003. As of 15<sup>th</sup> of December 2003, 399 patients with diagnosis of CIN 1 or ASCUS have been referred to the health care providers where HPV testing is implemented as a new health care policy. Out of those 315 women have been HPV tested and 208 patients were HPV positive (66%).

Concerning the possibility to implement primary HPV screening as a randomised health care policy in Sweden, several health care providers requested data from cost-effectiveness modelling studies applicable to the Swedish situation. To reply to these requests, a senior gynaecologist (Dr. Peter Bistoletti) was hired to perform such a study in collaboration with the Health Technology Assessment institute of Linköping University. The report is in Swedish (an official EU language) with English summary and has been submitted for publication as an HTA (Health Technology Assessment) report.

The detailed description of the performed work and the obtained results are provided in the attached Final Report No. 14 of 100 pages.

### 3.4 Web Forum for Info Dissemination 2003

- Objective: Development and use of WebForum, the communication platform for teamwork, discussions and dissemination of the network results in Internet
- Development of Multimedia Interactive User Interface
  - Development of Document Management Facilities
- Leader: Prof. Schenck (Co-ordination Centre)

#### 3.4.1 Document management and Internet access

The software development work the Co-ordination Centre was continued (December 2002 - December 2003) for improving the WebForum as follows:

1. Development of Document Management Facilities for supporting large size documents on the WEB. These facilities are requested for the presentation of the "European Guidelines for Cervical Cancer Screening" on the WEB.  
(January -June 2003)
2. Development of Multimedia Interactive User Interface in order to allow the direct access of medical staff to multimedia data (text, tables, images, electronic patient data, laboratory patient results, microscope images, etc) for research and training reasons (May - October 2003)
  - Continuous presentation of the changing version of the "European Guidelines for Cervical Cancer Screening" and immediate access of all Network participants to information about Network activities
  - Free access (read and download) for all experts outside of the Network

#### 3.4.2 Users of WebForum

All individual projects have access to WebForum. Discussions within the project team improved the team work. Dissemination of the obtained project results was performed world wide via Internet, and have facilitated the feedback from a large number of specialists in cervical cancer screening.

The WebForum 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:

1. AUSTRIA: University of Vienna
2. BELGIUM: Scientific Institute of Public Health
3. FINLAND: Finnish Cancer Registry, Helsinki
4. FRANCE: WHO – IARC, Lyon
5. FRANCE: Association EVE, Strasbourg
6. GERMANY: Cytological Institute of the Bavarian Cancer Society
7. GERMANY: SWS Tumorcentre Zwickau
8. GREECE: Hellenic Foundation of Oncology, Athens
9. GREECE: (Ormylia-Chalkidike): Our Lady Who Loves Mankind
10. HOLLAND: University of Nijmegen
11. ITALY: Unit of Cancer Epidemiology, Turin
12. PORTUGAL: Centro Regional de Oncologia Coimbra

13. SPAIN: Health and Social Welfare Council, Junta de Castilla y León, Valladolid
14. SWEDEN: Lund University at Malmö
15. UNITED KINGDOM: Birmingham Women's Hospital

Co-operation with one project from SWITZERLAND and 5 projects from 4 Candidate States was continued:

- HUNGARY: St. John's Hospital, Budapest
- POLAND: Pomeranian Medical University, Szczecin
- ROMANIA: Institute of Oncology Bucharest
- ROMANIA: Timisoara University Clinic, Foundation "Bega"
- SLOVENIA: Institute of Oncology Ljubljana

### 3.4.3 Guideline presentation in Internet

The Guidelines are structured in 12 Chapters and Appendices. Each chapter contains subchapters and annexes. The Guidelines components are continuously improved by the Network partners, and many versions are produced. The management of all Guidelines components is illustrated below, together with the implemented "easy access" to the multimedia data (text, tables, images, electronic patient data, laboratory patient results, microscope images, etc) for research and training reasons.

The Multimedia Interactive User Interface allows a comfortable access to all Guidelines documents and to the information about the "Guidelines Workshops" held in the reporting period.

#### Access to Guidelines

The "read and download" access paths to Guidelines Chapters, Subchapters, Annexes and the Appendices is as follows:

1. access Internet
2. [www.cancer-network.de](http://www.cancer-network.de)
3. click on "European Cervical Cancer Screening Network"
4. click on "English" for selecting the English language
5. click on the green button "Guidelines"
6. click on the displayed Chapters, Subchapters, Annexes and Appendices.
7. read and download the documents.

Below is illustrated (on 12 pages) the access path via Internet to the produced guidelines documents during the reporting period (16.12.02 – 15.12.03)

Below is also illustrated the multimedia presentation of the Guidelines Workshops held in Munich on 5.-7. March 2003, Helsinki on 29.-30. June 2003, and Ormylia on 21-24. September 2003 (on 3 pages), and the 15 Network partners in 2003 (on 1 page).

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## Multilingual user interface:



# Guidelines Presentation in the Internet



A screenshot of a web browser window. The title bar reads "Welcome to the ...". The address bar shows "http://www...". The main content area features the logo for the "EUROPEAN CERVICAL CANCER SCREENING NETWORK" and a navigation menu with items: "Welcome", "Web Forum", "Project", "Partners", "Documents", "Guidelines", "Activities", "Congresses", and "Bavarian Cancer Society". A red arrow points to the "Guidelines" item. Other visible text includes "Photos Netw conference '17th Trai", "Bayerische Kre", "Contact: Medical Technical", "Search", and "No. of visitors: 5.457". The browser status bar at the bottom shows "Done" and "Internet".




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Network conference "17th Training Conference on Clinical Cytology" in Munich/Germany

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### European Guidelines for Quality Assurance in Cervical Cancer Screening

**List of Guidelines Activities (of 30. June 2003)**

1. July - 31. August 2003	Chapter integration
1. September 2003	Integrated chapters available on Internet
21-24. September 2003	Guidelines workshop in Ormylia Discussions of integrated chapters
1. Oct. - 20. Nov. 2003	Guidelines integration by Co-ordination Centre + UK
1. November 2003	Review of integrated Guidelines by selected external experts
20. November 2003	Release of 1st Draft of Guidelines
26. November 2003	Presentation of Guidelines at 17th International Seminar and Training Conference on Clinical Cytology in Munich
18-19. December 2003	Network Meeting in Valladolid / Spain Network continuation in 2004-2006 (if accepted by European Commission)

Table of Contents		Release date
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 6 of 22. Sept. 2003 of Network)</a>		18.9.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 5 of 24. June 2003 of Network)</a>		24.6.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 4 of 7. Mar. 2003 of Network, following Munich workshop)</a>		7.3.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening'</a>		6.3.2003

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EUROPEAN CERVICAL CANCER SCREENING NETWORK

Photos Network conference '17th Training Conference on Clinical Cytology' in Munich/Germany on 26. November - 1. December 2003

Table of Contents		Release date
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 6 of 22. Sept. 2003 of Network)</a>		18.9.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 5 of 24. June 2003 of Network)</a>		24.6.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 4 of 7. Mar. 2003 of Network, following Munich workshop)</a>		7.3.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 3 of 6. Mar. 2003 of Network, integrating changes to Chaps. 2, 3, 6, 7, 9, 11)</a>		6.3.2003
<a href="#">Table of Contents of new 'European guidelines for quality assurance in cervical screening' (draft 2 of 17. Dec. 2002 of Network, following Luxembourg workshop)</a>		17.12.2002

For storing the document: (1) click on the document with the left mouse button, (2) wait to get the text on screen, (3) press F12 button on keyboard and (4) store the document.

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Chapter 2: Epidemiological guidelines for quality assurance in cervical screening Chapter 9: Data collection on treatment of screen-detected lesions Chapter 11: Summary table of key performance indicators Chapter responsible: Ahti Anttila (ahti.anttila@cancer.fi)		Release date
<a href="#">Chap 2 of 2.9.03 for Ormylia meeting</a>		2.9.2003
<a href="#">Chap 9 of 2.9.03 for Ormylia meeting</a>		2.9.2003
<a href="#">Chap 11 of 2.9.03</a>		2.9.2003

Network conference "17th Training Conference on Clinical Cytology" in Munich/Germany


		Release date
<a href="#">Chap 2 of 2.9.03</a> for Ornylia meeting		2.9.2003
<a href="#">Chap 9 of 2.9.03</a> for Ornylia meeting		2.9.2003
<a href="#">Chap 11 of 2.9.03</a> for Ornylia meeting		2.9.2003
<a href="#">Chap 2 of 24.6.03</a> by Chap. 2 working group		24.6.2003
<a href="#">Chapter 2, 9 drafts for Copenhagen meeting 24-25.3.03</a> Chap. 2.1, 2.2, 2.3, 2.4, 2.5, 9		24.3.2003
<a href="#">Agenda Copenhagen Workshop 24-25. March 2003</a> by Ahti Anttila, Elsebeth Lynge		31.1.2003
<a href="#">Chap 2.2.3, 2.2.4, 2.2.5 Contribution of France-Strasbourg</a> by M. Fender, J.-J. Baldauf		27.2.2003
Comments: <a href="#">1. March 2003 by A. Müller (DKFZ, Heidelberg, Germany)</a>		
<a href="#">Chap 2 Contribution of Ornylia</a> by C. Anthony		10.2.03
<a href="#">Chaps. 2, 9, 11 Table of Contents (in detail)</a> by Ahti Anttila		31.1.2003

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Chapter 3: Methods and techniques of cervical screening Chapter responsible: Marc Arbyn (m.arbyn@ihe.be)		Release date
<a href="#">Chap 3.2 HPV of 12.9.03</a> for Ornylia meeting		12.9.2003
<a href="#">Chap 3 of 10.9.03</a> for Ornylia meeting		10.9.2003
<a href="#">Chap. 3.2 HPV of France of 24.3.03</a> by J.-J. Baldauf		24.3.2003
<a href="#">Chap. 3.2 HPV of France of 24.3.03</a> by J.-J. Baldauf		24.3.2003
<a href="#">Chap. 3.3 Pap of Germany of 23.4.03</a> by J.-J. Baldauf		23.4.2003
<a href="#">Chap. 3.4 Thin-Layer</a> by O. Real		4.3.2003
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<a href="#">Chap. 3.6 UK Colposcopy Guidelines</a> by J. Jordan, J. Patrick		4.4.2003
<a href="#">Chap. 3.6 Colposcopy of France of 31.3.03</a> by J.-J. Baldauf		31.3.2003
<a href="#">Chap. 3.6 Colposcopy of Portugal of 30.3.03</a> by J.-J. Baldauf		30.3.2003


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<a href="#">Chap. 3.6 Colposcopy of Portugal of 30.3.03</a> by D. Da Silva		30.3.2003
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<a href="#">Chap. 3.6 Draft 1 Colposcopy Standards</a> by D. Luesley, J. Jordan, C. Redman, M. Maresh		3.3.2003
<a href="#">Chap 3, App. 3: Collection of adequate Pap smears</a> by M. Arbyn, E. McGoogan, J. Patrick		25.6.2003
<a href="#">Chap 3, App. 5: Reporting form Strasbourg, France</a> by M. Fender, J.-J. Baldauf		31.3.03
<a href="#">Chap 3, App. 5: Reporting form Spain</a> by M. Blasco, V. Herreros, E. Zozaya, G. Domenech, A. Hernández		31.3.03
<a href="#">Chap 3, App. 5: Reporting form Belgium</a> by Marc Arbyn		5.3.03
<a href="#">Chap 3, App. 5: Discussion on Terminology</a> by Odete Real		4.3.03
<a href="#">Chap 3, App. 5: Cytological reporting system</a> by Ulrich Scheack		26.2.2003
<a href="#">Time schedule and content Chap. 3</a> by Marc Arbyn		20.1.2003
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Chapter 4: Laboratory guidelines for cervical screening Chapter responsible: Paul Klinkhamer (p.klinkhamer@pamm.nl)		Release date
<a href="#">Chap. 4 of 17.9.03</a> by Paul Klinkhamer		18.9.03
<a href="#">Chap. 4 of Holland of 23.4.03</a> by Paul Klinkhamer		24.4.03
<a href="#">Chap. 4 of Spain of 31.3.03</a> by A. Hernandez, G. Domenech, E. Zozaya		3.4.2003
<a href="#">Chap. 4.2 Software in Portugal for QA in the lab</a> by Odete Real		3.3.2003
<a href="#">Chaps. 4, 5 Draft 1 of 3.3.03</a> by Paul Klinkhamer		3.3.2003
<a href="#">Chap 4.5-4.11 Contribution of Ormvia</a> by C. Anthony		10.2.03
<a href="#">Time schedule and content Chaps. 4, 5</a> by Paul Klinkhamer		15.1.2003

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Chapter 5: Quality assurance practices in screening laboratory Chapter responsible: Ulrich Schenck (ulrich@schenck.de)		Release date

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Chapter 5: Quality assurance practices in screening laboratory Chapter responsible: Ulrich Schenck (ulrich@schenck.de)		Release date
<a href="#">Chap. 5 of 25.6.03</a> by Ulrich Schenck		25.6.03
<a href="#">Chap. 5 Portuguese contribution</a> by Odete Real		3.3.2003

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Chapter 6: Certification of the screening process and staff skills Chapter responsible: Helene Wiener (helene.wiener@akh-wien.ac.at)		Release date
<a href="#">Chap. 6 of 18.8.03</a> for Ormylia meeting		18.8.03
<a href="#">Chap. 6 Draft 3 of 30.3.03</a> by Helene Wiener, Reinhard Horvat		3.4.2003
<a href="#">Chap. 6 Draft 2 of 3.3.03</a> by Helene Wiener, Reinhard Horvat		3.3.2003
<a href="#">Chap. 6 Draft 1 of 19.2.03</a> by Helene Wiener, Reinhard Horvat		19.2.2003
<a href="#">Time schedule and content Chap. 6</a> by Helene Wiener, Reinhard Horvat		14.1.2003

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Chapter 7: Quality assurance guidelines for pathology in cervical screening Chapter responsible: Reinhard Horvat (reinhard.horvat@akh-wien.ac.at)		Release date
<a href="#">Chap. 7 of 12.9.03</a> for Ormylia meeting		12.9.2003
<a href="#">Chap. 7 Spanish Contribution based on Draft 1</a> by Juan Aragón, Enrique Zozaya, Amaya Hernández, Silvia Tejero		4.3.2003
<a href="#">Chap. 7 Draft 1 of 19.2.03</a> by Reinhard Horvat, Helene Wiener		19.2.2003
<a href="#">Chap. 7 Spanish Contribution</a> by Juan Aragón, Enrique Zozaya, Amaya Hernández, Silvia Tejero		7.2.2003
<a href="#">Time schedule and content Chap. 7</a> by Reinhard Horvat, Helene Wiener		14.1.2003

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Chapter 8: Guidelines for management of women with cervical cytological abnormalities Chapter responsible: Ulrich Schenck (ulrich@schenck.de)		Release date
<a href="#">Chap. 8 of 9.9.03</a> for Ormylia meeting		9.9.03
<a href="#">UK Colposcopy Guidelines</a> by J. Jordan, J. Patrick		4.4.03

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by Juan Aragón, Amaya Hernández		3.4.03
<a href="#">Chap. 8 of Spain (including flow charts, reporting form) of 2.4.03</a>		
by Juan Aragón, Amaya Hernández		30.3.03
<a href="#">Chap. 8 Management in Spain of 30.3.03</a>		
by Ulrich Schenck		24.2.03
<a href="#">Chap. 8 Draft 24.2.03</a>		
by C. Anthony		10.2.03
<a href="#">Chap. 8 Contribution of Ornylia</a>		
by Ulrich Schenck		25.2.03
<a href="#">Chap. 8 Flowcharts</a>		

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<b>Chapter 10: Guidelines for training</b> Chapter responsible: Ulrich Schenck (ulrich@schenck.de)		<b>Release date</b>
<a href="#">Chap. 10 Draft 23.6.03</a> by Ulrich Schenck		23.6.03
<a href="#">Chap. 10 Slovenia of 9.5.03</a> by Ana Pogacnik, Maja Zakelj		9.5.03
<a href="#">Chap. 10 Draft 3.3.03</a> by Ulrich Schenck		3.3.03

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General Documents		Release date
<a href="#">European Guidelines for Quality Assurance in Cervical Cancer Screening (old)</a>		6.4.1992
This version is also available online, at: <a href="http://crsg.abc.kun.nl/quate/guidelines/entire.html">http://crsg.abc.kun.nl/quate/guidelines/entire.html</a>		
<a href="#">AGREE Instrument - Standard recommendations for guideline update</a> URL: <a href="http://www.agreecollaboration.org/">http://www.agreecollaboration.org/</a>		1.9.2001
<a href="#">Improvement suggestions from Strasbourg, France</a> by <a href="#">Dr. Muriel Fender</a>		19.12.2001
<a href="#">Improvement suggestions from Ormylia, Greece</a> by <a href="#">Dr. Charles Anthony</a>		10.9.2002

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Discussion		Release date
<a href="#">Discussion on Cytopathology in Germany</a> by <a href="#">Prof. Ulrich Schenck</a>		28.4.2002
<a href="#">Discussions of ECCSN Terminology Group</a> by <a href="#">Prof. Ulrich Schenck</a>		5.5.2002
<a href="#">Towards a common European classification and coding system for Pap-smears</a> by <a href="#">Dr. Antonius Hanselaar</a>		25.9.2002

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from left to right: Dr. C. Zarogianni (Greece), Br. C. Anthony (Greece), Prof. R. Horvat (Austria), Dr. Laura Kotaniemi (Finland), Prof. Matti Hakama (Finland), Prof. Ulrich Schenck (Co-ordinator, Germany)



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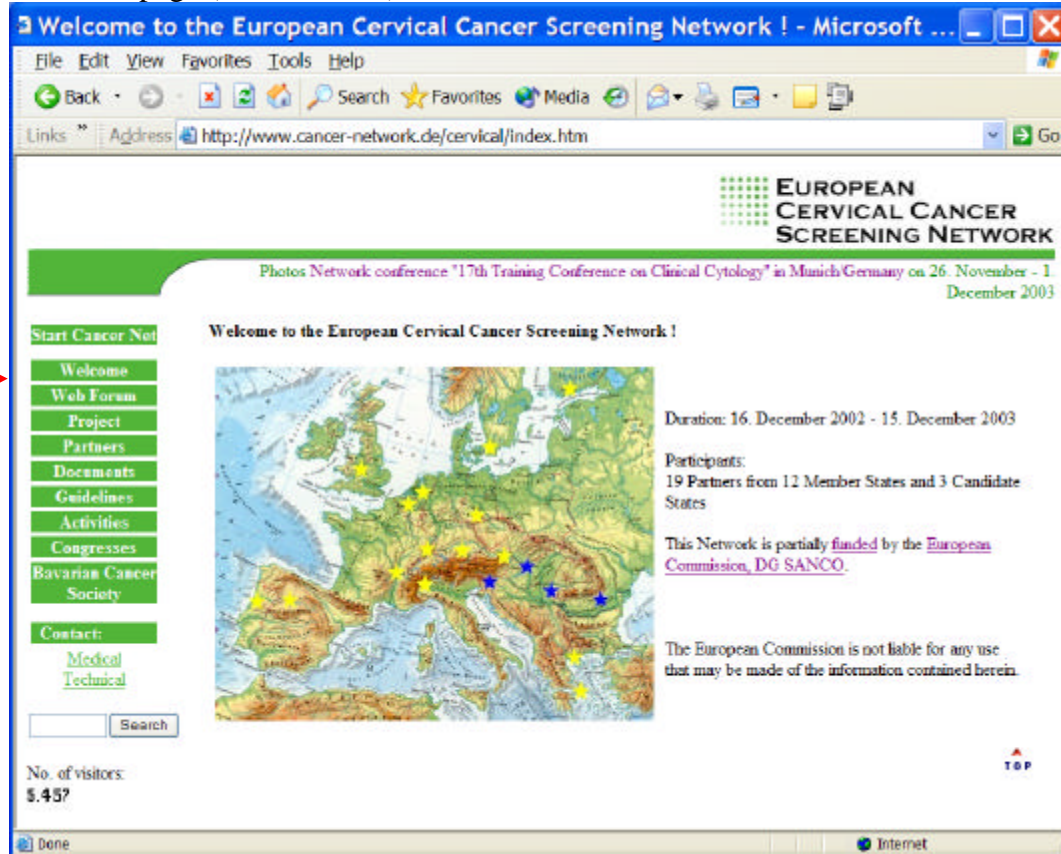


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2. Horvat R.  
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4. Horvat R.  
Target and organ contouring in MRI based treatment planning of cervix cancer brachytherapy – pathologist's point of view. Vienna University, General Hospital, July 4th, 2003
5. Wiener HG, Bock E, Greiner D, Kwasniewski D, Glück G, Eser B, Stani J, Horvat R.  
ISO-certification in cytology: motivation or demotivation? 29<sup>th</sup> European Congress of Cytology, Praha, 5-8 Oct 2003
6. Horvat R.  
Aufarbeitung von Konisationspräparaten und Qualitätssicherung in der Zytologie. 17. Fortbildungstagung für klinische Zytologische. München, 26.November-01.Dezember, 2003
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10. Arbyn M, Crott R, Bourgain C, De Sutter P, Van Ranst M, Buntinx F.  
Cost-effectiveness of HPV DNA detection in addition to or as alternative for cytological screening for cervical cancer.  
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22. De Boeck G.  
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31. J.-J. Baldauf, J. Ritter  
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## 5. Previous work

### 5.1 Previous results 2000

#### 5.1.1 Quality Assurance and Quality Control 2000

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.

### 5.1.2 Monitoring, Epidemiology and Evaluation 2000

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 (Cytoc 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.

### 5.1.3 New Technologies in Cervical Cancer Screening 2000

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.

#### **5.1.4 Dissemination of the Network results 2000**

The project WEB was developed at the Co-ordination Centre in Germany, and a WebForum 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 2001

### 5.2.1 Quality Assurance and Quality Control 2001

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 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 WebForum was developed, and supports an open discussion between the network partners, and also integrates the feedback from a large number of specialists outside of the Network. The first draft of the "Updated European Guidelines for Quality Assurance in Cervical Cancer Screening" was released as an internal document, and collection of the contributions of the network partners about Guidelines improvements was started in December 2001.

In Belgium the work was concentrated on studying the gain in diagnostic performance of thin layer liquid based cytology coupled with ancillary HPV DNA.

A randomised trial called "Primary versus triage based HPV detection in combination with Thin layer cytology" was conducted in co-operation with the Free University of Brussels with the aim of improving the quality of screening. Work was performed in evaluating the diagnostic properties of rapid screening, and collaborating with the Cytological Institute in Munich in improving the quality control in cervical screening.

In Greece (Hellenic Society of Oncology, Athens) the project work was performed by using own funds, with no request of financial support from the European Commission.

The 4th Round of the Screening Programme to the county of Messinia has been completed. Screening was performed on vaginal, ectocervical, and endocervical smears. The 5th round of the Cervical Cancer Screening program was prepared and started in the county of Ilia. Invitation letters were sent to the target population in this region, inviting them to participate to the program.

The Cervical Assessment Steady Unit was founded in Athens by the Hellenic Society of Oncology and the Hellenic Anticancer Institute and continues with great success to carry out its activities, as a permanent cytological laboratory. High standards of

laboratory practices are ensured by advanced quality assurance procedures. The staff/workload ration is satisfactory, one cytopathologist screens 15-20 cervical smears daily.

In Greece (Our Lady Who Loves Mankind, Chalkidike) work was continued to closely follow-up all women tested positive and regularly update their screening files with all available data on further assessment and treatment. Data on 6.408 patients and their smears was recorded, 1.293 tests were classified as abnormal, and a reliability study of smear reading on a random sample of Pap-smear test was performed. Co-operation work was performed with the Cytology Laboratory of the General Hospital of University of Athens, which is the Greek national centre of excellence in cytopathology and epidemiological research.

In Holland work was continued in implementing optimally integrated screening (evidence based) of cervical cancer in general practice and to transfer experiences from one country to another. This can be achieved in a phased manner. In previous projects, as a member of the EC Network for Cervical Cancer Screening, the group has developed and tested a general practice-based call system in a population-based screening programme for cervical cancer. In addition, at a local level, the evaluation of two different communication systems between smear-taking general practices and the cytological laboratories took place (based on the European Guidelines for Quality Assurance in Cervical Cancer Screening, the national guidelines of the Dutch College for General Practitioners, and the guidelines for Pathology laboratories concerning cervical smears) to maximise follow-up of abnormal and unsatisfactory smears.

In Italy the work performed is concentrated in another area, in "Monitoring, Epidemiology and Evaluation". However, the addressed topic "Improving methods for data collection and analysis for cervical cancer screening evaluation" is an important feedback information for the area "Quality Assurance and Control". In particular, the collection of data about the "women screened for the first time" and "women participating to following rounds" is of great importance. Here separate evaluation tables are needed, because the expected detection rate of histologically confirmed intraepithelial lesions (and measures depending on disease prevalence as the Positive Predictive Value) changes if the "prevalence" screen, or following rounds are considered.

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

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

Smears from 38.901 women were screened independently of the phase of the programme. The obtained cytological results show that the number of unsatisfactory smears seems lower but they don't reflect the unsatisfactory smears obscured by inflammation. These cases are included in the inflammatory category that need to repeat the smear after treatment.

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

In Spain work was performed as planned. The computer-based data acquisition of information about cervical cancer occurrence in the target group of women aged 25-65 living in Spanish regions Castilla and León was continued. Data collection of 58.383 smears was performed and the smear analysed, and this data was stored together with diagnosis data. Appropriate evaluation parameters were used for the Quality Control of the tests, and the results were made available to the GPs of these regions.

## 5.2.2 Monitoring, Epidemiology and Evaluation 2001

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 smearer in general and, in the case of moderate severe abnormalities, a reminder by the laboratory.

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

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

In Italy work was performed in order to monitor the value of process indicators for cervical cancer screening in 73 different organised screening programmes in Italy. The target population includes 8.372.646 women aged 25 to 64 years (about 52% of women).

We have continued to identify problem areas in Italian screening programmes and have started actions to improve them. Quality indicators need to be quite stable in time and relevant variations should be observed only if real changes of the situation arise. The project has analysed data on process indicators, obtained from 52 organised programmes active in 2000. In the year 2000 a number of 1.325.663 women were invited, and 502.884 were screened. The obtained results include:

- Distribution of cytological diagnosis
- Percentage of women referred for colposcopy by each Italian centre
- Positive Predictive Value (PPV) of a AGUS or more severe cytology in predicting a CIN II or more severe histology. In 7 of 42 programmes PPV was

significantly lower than expected, suggesting that criteria for cytology classification were too broad.

- The detection rate of histologically confirmed CIN II or more severe lesions was analysed by a Poisson regression model.

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

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

In Spain work was continued in the computer-based data acquisition, data monitoring and evaluation of information about patients with cervical cancer for the target group of women aged 25-65 living in Castilla and León regions. All women of these regions were invited to smears tests, and a set of sound epidemiological results were provided. Data collection of 58.383 smears was performed together with smear analysis, and the information was stored together with diagnosis data. Appropriate evaluation parameter were used, and statistical information was worked out.

In Sweden the experimental work on the HPV treatment methods was continued. The evaluation of the treatment methods is also relevant to Part 3 "NewTechnologies".

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

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

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

- Cohort 1 enrolled 37 women who were referred for treatment of CIN. Previous data had shown that treatment with carbon dioxide laser conization was effective for treating HPV infection. As a pilot study, the HPV clearance rate after treatment with LEEP was determined. The results showed a 96% clearance rate after 3 months, which was better than previously reported for carbon dioxide conization.
- Cohort 2 had during the time of the contract enrolled 84 women who were referred for treatment with CIN. The women were randomised to treatment with either loop electrosurgical excision procedure or to conisation. During the time of the contract HPV testing and analyses of the data was completed for the pre-treatment samples of the first 64 women. Although all women enrolled into the study had had CIN as a reason for referral, on the date of treatment 19 of 68 women had a normal smear. Spontaneous regression and/or removal of the lesion by the diagnostic biopsy are

possible reasons for this finding. As expected, 86% of women who still had a dysplastic smear were HPV-positive. As expected, HPV-positivity correlated strongly with presence of a dysplastic smear (OR: 19.5 (CI: 4.8-86.9)). The enrolment and the testing performed so far has been satisfactory.

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

In Slovenia (Cancinate State) 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.

### 5.2.3 New Technologies in Cervical Cancer Screening 2001

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, 38,300 smears were scanned. The results of these screenings will be available in late 2002. A summary of the first and second year results suggest that automation-assisted screening may be at least as sensitive and specific as the conventional screening practice in Finland - in a country with highly effective and well documented screening programme. The overall rate of detecting a pre-cancerous lesions is materially the same in both of the arms (4.2 per one thousand in the Papnet vs. 4.4 in the conventional screening arm).

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

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

Planning on a large-scale human papillomavirus (HPV) based screening trial within the Finnish programme has proceeded along with the pilot results. We arranged a

Nordic meeting to finalise the planning aspects. This means that we need to recruit some 40,000 women per year for five years duration of the randomisation period to obtain 80% statistical power to detect a hypothetical 50% decrease in the cancer risk after the screening visits (comparison to manual pap smear screening).

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

- a historical comparison for each of the laboratories of the distribution of smear tests according to the cytological result during two 12-month periods before and after the introduction of the new technique. The training period of the thin layer technique of 6 months was excluded. A control group of laboratories still using conventional Pap was also included.
  - a study of the positive predictive value of the thin layer method relative to conventional Pap smear for high-grade smears where the systematic taking of a histological sample is compulsory.
  - the comparison of the degree of cytological-histological correlation for the two methods for low grade smears followed by histological examination. For those followed by cytology only, results of subsequent smears have also allowed a comparison of the two methods.
- *Feasibility of thin layer technique:* The analysis of diagnostic performances of the methods was done regarding quality of the smear taker (medical speciality gynaecologist or GP and relative rate of inadequate smears).
- *Obtained results:* Comparison of the distribution of smears tests according to the cytological results was done for the two laboratories (A and B). The work of the Control Group has also been performed as planned
- In laboratory A a number of 37.440 smears from the first period (i.e. 12 months before introducing the new technique) and a number of 38.222 smears from the second period (i.e. 12 months after introducing the new technique) were included in the study.
  - In laboratory B a number of 8.759 smears from the first period and a number of 10.699 smears from the second period were included in the study.
  - The Control Group has addressed a number of 39.442 smears from the first period, and 43.376 from the second period.

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

In Greece (Chalkidiki) experimental investigation of new screening technologies was performed in the reporting period in accordance with the planned activities.

Estimations of the false-negative rate of Pap smears at the Center of Panagia Philanthropini cancer center vary according to the laboratory used, and a previous estimate of the false-negative rate ranged from zero to 29.7 percent. A 1999 technology assessment on the evaluation of cervical cytology screening was prepared for the Agency for Health Care Policy and Research (now known as the Agency for Healthcare Research and Quality). The study involved an exhaustive review of the accuracy of cervical cytology and new technologies. Unfortunately, the reviewers could not meet their objectives because of the lack of high-quality research. Sufficient precautions were



taken to avoid bias in only three of 84 studies on cervical cytology. The sensitivity of the Pap smear in these three studies was relatively low (56, 53 and 29 percent), the test performed best in the detection of high-grade dysplasia, which is more likely to progress to cancer if left untreated.

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

→ *HPV Testing* was initiated to the degree that was economically feasible within the stringent budget and very limited resources of the Center.

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

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

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

→ *Study for women with ASCUS:* Research conducted by Center staff regarding the 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* 0.69% unsatisfactory, 85.35% normal, 9.9% inflammatory, 3.1% ASCUS/AGUS, 1.7% LGSIL, 0.32% HGSIL, 0,05% invasive carcinoma

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.

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)).

#### 5.2.4 Internet Dissemination 2001

- Performed work: Development and use of WebForum, 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
- Obtained Results: All network partners have access to WebForum. The 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 WebForum prototype was installed (<http://www.cancer-network.de>)

The integration of the web sites of the European Breast Cancer Network and of the European project VIDEOCOM (Video-communication workplace) was performed with the aim of promoting the co-operation with these European projects, and for providing a direct access world-wide of the medical staff via Internet to the project results.

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

##### Development work in reporting period

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

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

Services of WebForum 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).

## 5.3 Previous results 2002

### 5.3.1 Quality Assurance and Quality Control 2002

In Germany Munich the work in this reporting period had two main objectives:

- to improve the quality control and quality assurance, and to evaluate their impact on cervical cancer screening process.
- to update the European Guidelines for Quality Assurance in Cervical Cancer Screening.

The 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 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 WebForum 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 16<sup>th</sup> 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 WebForum.

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.

In France Strasbourg the obtained results in evaluating the thin layer techniques were similar to the results obtained in 2001. The study has 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.

A number of 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. About 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.

In Greece Chalkidike 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.

In Holland 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.

*Study 1: 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  $\geq$ low-grade lesions and 85.7% (CI: 77.8-93.6%) for  $\geq$ 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.

*Study 2: 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.

*Study 3: 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 by GP assistants (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).

*Study 4: "Virtual slide" technology in electronic 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.

*Study 5: 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.

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 11<sup>th</sup> 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 11<sup>th</sup> 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.

### **5.3.2 Monitoring, Epidemiology and Evaluation 2002**

Work was performed for the 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 are Belgium, Finland, Germany-Zwickau, Greece-Athens, Holland, Italy, Spain, and Sweden

In Belgium work was performed as follows.

*Statistical analyses* of data from Flemish Cervical Screening Register. The obtained results were published in the "International Journal of Cancer 2002" (Paper: "Trend of cervical cancer mortality in Belgium (1954-1994): tentative solution for the certification problem of not specified uterine cancer")

*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.

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.

In Finland a planning meeting was held 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. This activity was continued in co-operation with ENCR. This analysis includes 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).

In Germany 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.

Support was provided to cytological laboratories in the south-west Saxony region for uniform registration of cytological and histological data on cervical lesions. The obtained results were presented to the network participants to the meeting in Munich on 5-6. September 2002: (i) statistical analyses of incidence and mortality trend concerning cervical and other uterine cancer, and (ii) temporal and spatial variation in relation with influencing factors (screening, age-period-cohort effects, treatment, survival).

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.

In Greece during this round (Phase VI) of the programme was performed as follows:

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

*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

*Maximise* the participation rate of the target population (women aged 25 to 64 years), and optimise cervical cancer early diagnosis.

*Ensure* that all staff of the programme receive proper training.

*Optimise* cervical cancer early diagnosis.

*Dissemination* of the results obtained on the WebForum, discussions with the project partners, participation to congresses and scientific meetings.

In Holland 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 specific aim 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.

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.

In Spain work was performed on the Cervical Cancer Screening in the most extensive region in Europe, the Autonomous Community of Castilla y León, with an area of 94.147 square kilometres, and 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 smear tests.

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:

- *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:

In Sweden the performed work was as follows.

*Implementation* of a randomised health care policy of secondary HPV testing in Sweden.

*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

### 5.3.3 New Technologies in Cervical Screening 2002

Work was performed with the aim of continuously incorporation of technical innovation for continuously improvement of the quality of the European cervical screening.

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

In Belgium work was continued for evaluating the 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 work 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.

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 Finnish work was concentrated on implementating and evaluating 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

automated-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.

Work was performed on the evaluation of new technologies in cervical cancer screening, as follows.

(i) *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.

A number of 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 feed-back 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).

(ii) *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 enlargen 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.

In France work was continued on the evaluation of thin layer techniques, as common practices within the framework of the campaign for cervical cancer screening in the Bas-Rhin region, and the long term survey of ASCUS and AGUS in our organized screening programme was continued.

This study has shows 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.

A number 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.

In Greece Ormylia work was performed on evaluating the suitability of the FT-IR spectroscopy for detecting cervical cancer. 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.

In Portugal work was performed on 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 analysed 33.277 smears. We found the following results: 2,24% ASCUS/AGUS, 1,57% LGSIL, 0,41 HGSIL, 0,03% Invasive carcinoma.

*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. We found the following results: 1,69% ASCUS/AGUS, 1,41% LGSIL, 0,14% HGSIL, 0,05% Invasive carcinoma.

*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. We found from 114 cases 41,26% ASCUS.

In Sweden ork was performed on HPV-screening technique as follows:

Implementation of a randomised health care policy of secondary HPV testing in Sweden. 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.

### 5.3.4 Internet Dissemination 2002

Performed work: Development and use of WebForum, the communication platform for teamwork, discussions and dissemination of the network results in Internet.  
Display non-stop all Network information to all partners.

Users all 12 partners: Belgium, Finland, France, Germany (Munich, Zwickau), Greece (Athens, Chalkidiki), Holland, Italy, Portugal, Spain, Sweden

#### Previous work in 2000

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 WebForum 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).

#### Previous work in 2001

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.

#### Performed work in 2002

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 WebForum in 2002:

- 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.

The URL of the WebForum is: <http://www.cancer-network.de>

## 5.4 Publications 1999 - 2002

### 5.4.1 Publications 1999 - 2000

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GERMANY: Cytological Institute of the Bavarian Cancer Society

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FRANCE: Association EVE, Strasbourg

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ITALY: Unit of Cancer Epidemiology, Turin

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SWEDEN: Karolinska Institute, Stockholm

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127. Ph. De Sutter, C. Bourgain, M. Arbyn A randomised trial comparing HPV screening with triage in combination with liquid-based cytology.
128. M. Arbyn, C. Bourgain, P. De Sutter, J. Debehogne, F. Willocx, C. Van Phan, J. Timmermans, M. Abarca Triage HPV versus primary HPV screening in combination with liquid-based cytology: The Brussels trial Report, Brussels, Scientific Institute of Public Health
129. M. Arbyn, F. Buntinx, M. Van Ranst. Triage of women with atypical or low-grade abnormalities of the cervix by HPV testing. Systematic review and meta-analysis. EPI-REPORT 2001-019. Brussels, Scientific Institute of Public Health. Registered as systematic review study by the Cochrane Gynecological Cancer Collaborative Review Group.
130. C. Davister. Attitudes et représentations face au virus HPV dans le cadre du dépistage du cancer du col. (Phase exploratoire novembre-décembre 2002.)
131. M. Arbyn. Evaluation of the diagnostic properties of rapid screening of Pap smears: literature review and meta-analysis. Update 2002. IPH/EPI-REPORT 2002-004. Brussels, Scientific Institute of Public Health.
132. M. Arbyn. Meta-analysis of the diagnostic properties of HPV testing in the triage of borderline and low grade cytological lesions. 1st European Conference on Cervical Cancer Screening in Europe, organised by the Cervical Cancer Consortium Europe and the European Consortium for Cervical Cancer Education, Tübingen (Germany), Institute of Medical Virology, 7-8 June 2002.
133. M. Arbyn, F. Buntinx, M. Van Ranst. Meta-analysis of the performance of HPV triage versus repeat cytology in women with an atypical Pap smear. 20th International Papillomavirus Conference, organised by the International Papillomavirus Society, Paris (France), 4-9 October 2002.
134. M. Arbyn, U. Schenck, E. Ellison, A. Hanselaar 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.
135. M. Arbyn. 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.
136. M. Arbyn. 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.
137. M. Arbyn HPV testing and its role in cervical cancer screening. Institute of Oncology, Ljubljana (Slovenia), 14 October 2002.
138. M. Arbyn HPV et cancer du col de l'utérus. Seminary organised by the Centre Anti-Cancéreux de l'Université catholique de Louvain. (lecture) Clinique Universitaire Saint-Luc, Brussels (Belgium), 16 may 2002.

139. 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
140. Statistical analyses and reporting of data from the Flemish Cervical screening register (meetings) Advanced statistical analysis of incidence and mortality trend concerning cervical and other uterine cancer (meetings)
141. M. Arbyn, H. Geys. Trend of cervical cancer mortality in Belgium (1954-1994): tentative solution for the certification problem of not specified uterine cancer. *Int J Cancer* 2002; 102: 649-654.
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147. Training Course in SPSS, an informatics programme to realise statistics. Place: Leuven, Belgium Date: 17-18/6/02. Participant: Ginette Marchant
148. M. Arbyn, C. Bourgain, P. De Sutter, J. Debehogne, F. Willocx, C. Van Phan, J. Timmermans, M. Abarca *Triage HPV versus primary HPV screening in combination with liquid-based cytology: The Brussels trial Report*, Brussels, Scientific Institute of Public Health
149. M. Arbyn Potential clinical use of molecular markers predicting progression of cervical cancer precursors. HPV/Genetic Risk Factors for Cervical Cancer, organised by the International Agency for Research on Cancer, Lyon (France), 18-19 December 2002.
150. 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.
151. Nieminen P., Viikki M., Hakama M., Tarkkanen, Anttila A. The effect of automation assisted screening on cervical cancer screening. First year results. *Int J Cancer* 2003; 103: 422-426.
152. 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).
153. Nieminen P, Anttila A. Kohdunkaulan syövän epidemiologiaa. *Suomen Lääkärilehti* 21. 2309-2310. 2002. [Epidemiology of cervical cancer. A review published in the Finnish Medical Journal.]



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155. J-J. Baldauf *Conduite à tenir face aux CIN1.12<sup>ème</sup> Salon de Gynécologie Obstétrique Pratique.* Paris 21-23 mars 2002.
156. J-J. BALDAUF, J. RITTER, D. HAMID, A. MINETTI, P. WALTER. The outcome of conservative management of CIN during pregnancy. 11<sup>th</sup> Congress of Cervical Pathology. Barcelona 9-13 june 2002.
157. J-J. BALDAUF. Systematic treatment of low grade intraepithelial lesions of the cervix. HPV 2002 Congress, Paris 4-9 october 2002.
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160. J-J. BALDAUF. Recherche de l'ADN viral dans le dépistage primaire. XXVIème Congrès National de la Société Française de Colposcopie et de Pathologie Cervico-Vaginale. Paris 24-25 janvier 2003.
161. J-J. BALDAUF. Management of CIN during pregnancy. 5th International Congress of Papillomavirus in Human Pathology. Paris 13-16 april 2002.
162. J-J. BALDAUF. Management of normal colposcopy after abnormal smear. 5th International Congress of Papillomavirus in Human Pathology. Paris 13-16 april 2002.
163. J-J. BALDAUF. Reliability of colposcopy during pregnancy. 17th World Congress of FIGO. Santiago de Chile 2-7 november 2002.
164. M. FENDER, J. SCHOTT, J-J. BALDAUF, J. MULLER, E. SCHLUND, P. DELLENBACH. Eve, une campagne régionale de dépistage du cancer du col de l'utérus : organisation, résultats à 7 ans et perspectives. *La Presse Médicale* (submitted in December 2002).
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## 6. Overview of Annexes

Following annexes are attached:

- Final Report 1 of Cytological Institute of the Bavarian Cancer Society  
Munich, Germany (37 pages)
- Final Report 2 of University of Vienna  
Vienna, Austria (48 pages)
- Final Report 3 of Scientific Institute of Public Health  
Brussels, Belgium (268 pages)
- Final Report 4 of Finnish Cancer Registry  
Helsinki, Finland (14 pages)
- Final Report 5 of WHO – International Agency for Research on Cancer,  
Lyon, France (19 pages)
- Final Report 6 of Association EVE,  
Strasbourg, France (32 pages)
- Final Report 7 Germany: South-west Saxony Tumorcentre  
Zwickau, Germany (19 pages)
- Final Report 8 of Hellenic Foundation of Oncology  
Athens, Greece (4 pages)
- Final Report 9 of Our Lady Who Loves Mankind  
Chalkidike, Greece (22 pages)
- Final Report 10 of University of Nijmegen  
Nijmegen, Holland (11 pages)
- Final Report 11 of Unit of Cancer Epidemiology  
Turin, Italy (23 pages)
- Final Report 12 of Centro Regional De Oncologia de Coimbra  
Coimbra, Portugal (4 pages)
- Final Report 13 of Junta de Castilla y León Valladolid, Spain (31 pages)
- Final Report 14 of Lund University Malmö, Sweden (100 pages)
- Final Report 15 of Birmingham Women's Hospital, Birmingham, UK (55 pages)

# Final Report 1

of Cytological Institute of the Bavarian Cancer Society  
Munich, Germany (37 pages)

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of University of Vienna  
Vienna, Austria (48 pages)

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**Final Report 3 (part 1)**  
of Scientific Institute of Public Health  
Brussels, Belgium (268 pages)

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**Final Report 3** (part 2)  
of Scientific Institute of Public Health  
Brussels, Belgium (268 pages)

Attached 29 Annexes (17 annexes in Part 2)

13. Hierarchical Bayesian Models
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15. Questionnaire on existing systems for cervical cancer screening
16. Attitudes et représentations des gynécologues et des femmes face au virus HPV dans le cadre du dépistage du cancer du col
17. Thin-layer liquid-based cervical cytology and PCR for detecting and typing human Papillomavirus DNA in Flemish women.
18. Conventional cervical smears were better than monolayer cytology or human papillomavirus testing for detecting cervical neoplasia
19. The role of HPV DNA testing in follow-up period after treatment for CIN
20. A randomised trial comparing human papillomavirus screening with triage in combination with liquid-based cytology, Submitted for publication
21. Potential clinical use of molecular markers predicting progression of cervical cancer precursors
22. Management of women with minor cytological cervical lesions: repetition of the pap test versus HPV DNA-testing (presentation Barcelona)
23. Management of women with minor cytological cervical lesions: repetition of the pap test versus HPV DNA-testing (presentation Mexico)
24. Human papillomavirus 18 DNA viral load in normal and abnormal liquid-based cervical cytology
25. Manual screening of liquid based cytology versus assisted screening with the computerized scanning device FocalPoint slide profiler.
26. Meta-analyse liquid-based cytology: liquid-based cytology compared with conventional cytology (2-cohort and split-sample):
27. Follow-up of women after treatment for cervical intra-epithelial neoplasia using HPV DNA testing methods
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  - Prediction of high-grade cervical intra-epithelial neoplasia by detection of markers indicating HPV DNA integration in the human genome
29. Thesis: First evaluation of p16<sup>INK4a</sup> as a new biomarker to demonstrate oncogene transformation in cytologic smears caused by HPV

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## **Final Report 4**

of Finnish Cancer Registry  
Helsinki, Finland (14 pages)

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## **Final Report 5**

of WHO – International Agency for Research on Cancer  
Lyon, France (19 pages)

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Strasbourg, France (32 pages)

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Turin, Italy (23 pages)

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## **Final Report 12**

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of Birmingham Women's Hospital, Birmingham, UK  
(55 pages)

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