EUROCHIP-III

European Cancer Health Indicator Project-III

Common Action

DELIVERABLE 02 – BULGARIA

Work-Package 4 activities in Bulgaria

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Introduction

Cervical cancer incidence in Bulgaria

In the past 20 years, cervical cancer incidence and mortality in Bulgaria have been constantly rising due to the slow and inconsistent health system reforms and the absence of organized preventive programs (Valerianova, Panayotova, Amati, Baili, & Group, 2010). Until the late 1980's mortality rates from cervical cancer in Bulgaria were comparable to those of many European Union (EU) countries. A dramatic increase in mortality rates started with the political and socio-economic reforms of the last two decades. In 2009, the standardized incidence of cervical cancer was 18.7/100 000 women, compared to 11.0/100 000women in Europe. However, during the past few years, overall incidents rates have been relatively constant, with a slight tendency toward decreasing. Absolute incidence rates are highest among women aged 40-49 (over 45.0 per 100 000). Looking at the age distribution for the years 1993, 2000 and 2009, it becomes clear that the increase in incidence rate reaches its maximum in 2009 for the group of women at age 50-59, in comparison to 1993 and 2000 (Figure 1).
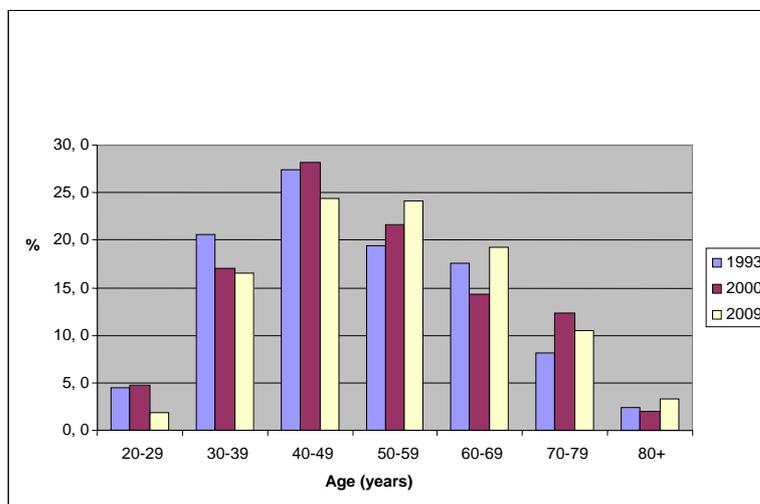

Figure 1: Distribution of new cervical cancer cases for 1993, 2000 and 2009 by age groups in Bulgaria

Table 1 shows that in 1993 about 60% of cases were diagnosed in stage 1 and 2. In the next years there was a gradual increase in the number of early diagnosed cases, with 65% of the newly registered cervical cancer cases in 2009 being in stage 1 or 2.

Year of diagnosis	Stage, in %					Total number
	I	II	III	IV	Unknown stage	
1993	28,5	39,3	18,9	4,3	9,0	797
1998	27,7	30,8	28,3	5,0	8,2	988
2003	31,3	30,7	30,8	4,4	2,7	1106
2009	41,6	24,0	24,6	4,9	4,9	1072

Table 1: *Stage distribution for new cervical cancer cases in 1993, 1998, 2003, 2009 in Bulgaria*

The data on the incidence rates of cervical cancer show significant regional variation in Bulgaria. In the period 1993 – 2008 the incidence rate reached 26/100000 women in some areas of the country (regions of Vratza, Pleven, Lovetch and Pernik), while in other regions it is much lower - 9/100000 women (Plovdiv, Smolyan, Kurdjali) (Bulgarian National Cancer Registry). These differences could be due to specific risk factors such as unequal access to health care for women in different regions, concentration of some ethnic groups in particular regions, and others.

In the period 1965-2009 mortality rates from cervical cancer have also increased. The rate of increase is approximately 0.5% per year. In 1965 the rate was 2.6 /100 000 women. In 2009 it doubled to 5.4/100 000 women.

In recent years in Bulgaria several studies focused on cervical cancer prevention in the context of healthcare reforms. A representative study conducted by our team also analyzed women's perspectives towards cervical cancer prevention(Avramova et al., 2005). Other publications regarding cervical cancer prevention in Bulgaria underscore the determinants of inequalities in cervical cancer screening (Todorova, Baban, Alexandrova, & Bradley, 2009)and the impact of providers' construction of women and their responsibility for prevention (Todorova, Baban, Balbanova, Panayotova, & Bradley, 2006). Research on health providers' assessment of the opportunity to implement an organized screening program in Bulgaria reveals the lack of instructions and serious organizational problems for establishing such a program (Panayotova, Todorova, & Valerianova, 2008).

Cytopathology practices in Bulgaria

Not much is known about the current state of cytopathology in the country. Several publications in the media alarm about the striking decrease in the number of pathologists[1], the insufficient equipment in laboratories[2], underpayment of this group of health professionals[3] and the absence of regulations and control over pathology laboratories[4].

The overview of the literature also shows a lack of information about management of pathology laboratories. Some papers focus on the educational requirements for screeners (Wiener et al., 2007). Another study tackles the issue of the changes in the system for incidence reporting in Bulgaria (Valkov, Zlatkov, & Kostova, 2004).

In Bulgaria the Papanicolaou numerical classification system for reporting cervical cytology is widely applied. In recent years some laboratories began to use descriptive Bethesda elements and started to report their results in accordance to the Bethesda system. Recently instructions for mandatory use of Bethesda system were included in the new standard of clinical pathology (Medical Standard of Clinical Pathology, 2002)[5]. According to Wiener at al. (2007), "completed grammar school" (secondary education) and additional study of biology are the minimal educational requirements for screeners working in gynecological cytology in Bulgaria. However, according to the national standard, biologists who perform screening should have a Master's degree in biology and should be supervised by a specialist in pathology.

Currently, there are no official data on the number of pathologists in the country. According to the information presented at the international conference *The Bulgarian Pathoanatomy and European Standards* in June of 2011 at the National Assembly, the number of pathologists in Bulgaria is 190. It is estimated that the number of pathologists per 100 000 population is very low - 2.58/100 000. For comparison, in the USA they are almost twice as many - 4.43/ 100 000. Pathologists are based in approximately 200 settings, such as pathology departments in hospitals (inpatient) and laboratories in diagnostic consultant centers (outpatient)[6]. Out of the 190 pathologists, 119 have a specialization in clinical pathology and part of them have a specialization in cytology. However, since there is no official registry of pathologists in Bulgaria, these numbers are approximate. One third of the pathologists are in retirement age.

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[1] Silvia Nikolova, Half of the hospitals without pathologists, Monitor, May 21, 2009, http://www.monitor.bg/article?id=199471; In Bulgaria there are 192 pathologists, 10 of them without a speciality, Hospital.bg, 02.06.2011, http://www.hospital.bg/news-2985-v-bulgariia-rabotiat-192-patolozi-ot-koito-10-sa-bez-spetsialnost.html

[2] Pathology in our country is in the Medieval age!, interview with S. Alexov, Blitz.bg, June 22, 2011, http://www.blitz.bg/article/25386;

[3] Boyko Bonev, Pathologists demanded new standards and adequate financing, Zdrave.net,02.06.2011, http://www.zdrave.net/Portal/News/Default.aspx?evntid=53371

[4] Silviya Nikolova. Laboratories are giving wrong cancer diagnosis. No institution to control them, Monitor, 20.10.2010, http://www.monitor.bg/article?id=265195

[5] Medical Standard in Clinical Pathology, 2002, 2007, http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=397

[6] HeliaBojilova, "State of pathology – finance and legal aspects, recourse provision. Presentation during the international conference The Bulgarian pathoanatomy and the European standards, 02.06.2011, National assembly

Some estimates show also that 75% of laboratories are concentrated in 5 cities with medical universities.[7]

In the second part of the EUROCHIP-2 report, the situation in two pathology laboratories in regard to their equipment and performance of cytology testing was analyzed (Kostova, Zlatkov, & Danon, 2007). Examining quality control (re-screening, comparability testing and external quality control) and comparing the standards in these two laboratories with the international standards, the authors concluded that even though the minimal requirements for cyto-diagnostics are available in these two laboratories, the lack of some additional conditions which are essential for effective screening is considerable. In particular, lack of cyto-technicians, problems with the staining system, lack of standardization of the terminology, problems with the storage system for the positive and the negative smears, poorly organized reporting system, incomplete laboratory registers, which are not or are weakly connected with the National Screening Registry are some of the problematic issues the researchers describe in the report (Kostova, et al., 2007).

TheEuropean Guidelines for Quality Assurance in Cervical Cancer Screening, including in cytology laboratories, focus on personnel and organization in laboratories, material resources (building, rooms, equipment, record system and teaching materials), handling and analysis of samples (sample assessment, workload and archiving), recording of results (information system, authorization of results and response time), internal and external quality management, and communication (Arbyn, Anttila, Jordan, & et, 2008).

Although there is some information on the situation in pathology laboratories in Bulgaria(Kostova, et al., 2007)the current practices in the laboratories and their level of adherence to the European standards have not been addressed. Taking into account the aggravated situation in the country in regard to the incidence of cervical cancer and mortality, and drawing on the existing research, we conducted a study on the current practices, resources and quality control in pathology laboratories in Bulgaria. The main issues addressed in the *European Guidelines for Quality Assurance* in cytology laboratories, as well as specific topics that we consider relevant to the Bulgarian situation, were addressed in the study.

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[7]Materials from the conference at the National Assembly
http://www.czpz.org/index.php?option=com_content&view=article&id=789%3A2011-06-01-14-53-43&catid=1%3A-&Itemid=2&lang=en

Factors, influencing late diagnosis of cervical cancer in Bulgaria

Although it is well known that cervical cancer has no symptoms in its precancerous and early phases, there is still little information on why Bulgarian women are diagnosed at late stages. Studies on screening history of newly-diagnosed cases of invasive cervical cancer could help the improvement of early diagnosis. This is why it is important to shed more light on the factors influencing the timely diagnosis of cervical cancer in its pre-invasive phase in countries with and without organized screening programs.

Drawing on the literature, we can hypothesize that some of the factors influencing late diagnosis are: 1) the inadequate screening that women had in the past (screening intervals longer than five years or never being screened); 2) thehigh level of false negative resultsfor women who do have Pap smearsand 3) the ineffective follow up of womenwith abnormal Pap smear results(Coldman et al., 2005; Janerich, Hadjimichael, Schwartz, & et al, 1995; Neminen, Kallio, Anttila, & Hakama, 1999; Nygård, Nygård, Skare, & Thoresen, 2005).

Studies in different countries reveal a relationship between screening history and stage of diagnosis.For example a study conducted in Norway in 2000-2002, one of the countries with most effective screening programs worldwide, compares the screening history for women with cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (ACIS) to that of women with different stages and subtypes of cervical carcinoma(Nygård, et al., 2005).The results reveal that 45.1% of patientswith invasive cancer FIGO[8] stage I and 10.5% of women with FIGO stage IV were screened according to the national screening program standard. However, women with invasive cervical cancer stage II-IV usually had an inadequate screening history. A meta-analysis of 42 studies demonstratesthat 53.8% of patients with invasive cervical cancer from Canada, United States, Australia, United Kingdom, Nordic countries, and other European countries were either not screened at all, or inadequately screened. More strikingly, 41.5% of all women identified by the analysis were never screened (Spence, Goggin, & Franco, 2007).A Finnish study shows that the strongest risk factors for development of invasive cervical cancer are age and smoking.Interestingly, the effect of socio-economic status and birth history of woman was moderate (Neminen, et al., 1999).

False negative Pap smear tests are another important reason for women who have been regularly screened in the past and especially those screened at longer time intervals to reach the invasive phase of the disease (Coldman, et al., 2005). Inadequate follow-up care received for any abnormal cytological smears could lead to advanced stages of cancer, as well. All these factors are closely associated with quality control and management of cervicalcancer screening programs.

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[8]FIGO - International Federation of Gynecology and Obstetrics

AIMS and METHODS

Taking into account the situation in the country regarding cervical cancer burden and prevention, and the already existing scientific research, including previous study within the EUROCHIP II, following actions were proposed for EUROCHIP III:

1. Develop and carry out a survey among the cytological laboratories throughout the country regarding their resources and quality control.

The aim of the study was to understand the current practices in pathology laboratories in Bulgaria and to assess to what extend these laboratories meet the European criteria for quality management. In addition, a specific aim of the study was to assess the capacity of laboratories to process an additional number of screening tests in order to ensure effective screening in the future. The requirements for quality control in the pathology laboratories, described in the *European Guidelinesfor Quality Assurance* were the main points of reference in designing the study. The study was conducted between February and December 2011.

For the aim of the study, a detailed questionnaire was prepared by the research team, based on Chapter 4 of the *European Guidelines for Quality Assurance in Cervical Cancer Screening*: "Laboratory guidelines and quality assurance practices for cytology" (Arbyn, et al., 2008) (see Appendix 1).The questionnaire consisted of 92 open-ended and closed questions. It was available on hard copy and in electronic format for the participants. The questionnaire addressed several topics: material and human resources of the laboratories, workload, practices in cervical smears analysis, administration, management and quality, as well as readiness of the staff for participation in an organized screening program.

More than 50 laboratories were invited to participate in the study. The invitations were made in person during meetings, by phone and by e-mail. All cancer dispensaries were contacted through their managers and were asked for cooperation. The questionnaire was sent by email to the heads of the two professional organizations of pathologists in Bulgaria, and personal emails were also sent to pathologists. However, the response rate was low, even though the study received a formal approval from the Bulgarian Society of Pathologists.

The final sample included eighteen laboratories in the country: nine were state laboratories, five were municipal laboratories and four were private. Seven of the laboratories are located in Sofia, two in Varna, two in Burgas and seven in other cities. Pathologists who filled out the questionnaire were between the ages of 42 to 73, nine men and nine women, with length of service between 10 and 44 years.

In order to collect additional information on the current practices in pathology laboratories, we conducted an additional three in-depth interviews with pathologists. The interviews focus on similar topics as those in the questionnaire: human and material resources, practices related to screening activities, administration and management of the laboratories. The aim of the interviews was to acquire a deeper understanding of the issues that were identified as problematic from the other sources of information. The interviews were analyzed, using Thematic Analysis (Braun & Clarke, 2006). Additional information on the topic of research was gathered from different media materials (newspapers, magazines, and websites) published online.

2. Bulgarian meeting for pathologists

On January 20-21 2012 the Bulgarian team of EUROCHIP-3 has organized a meeting for pathologists, with about 60 participants throughout the country. The aim of the meeting was to give the pathologists in the country an opportunity to discuss their main problems in regard to participation in a future screening program (see agenda in Appendix 2). At the meeting there were representatives of The Ministry of Health and The National Health Insurance Fund. A memorandum was prepared and presented to the health authorities (see Appendix 3). In addition, for the aims of the meeting all pathologists received the Bulgarian translation of: *H. G. Wiener, P. Klinkhamer, U. Schenck, et al (2007). European guidelines for quality assurance in cervical cancer screening: recommendations for cytology laboratories. Cytopathology 18 (2), 67–78.*

3. Survey among women diagnosed with cervical cancer or precancerous lesions

In the case of Bulgaria there is a significant gap in knowledge about the reasons for the continued diagnosis of cervical cancer at late stages. Some issues, as lack of instructions, high number of not registered tests performed in the private sector, as well as the absence of screening registry in the country could give only partial explanation for the current situation. Additionally, there are no official requirements on re-reading of slides from past smear tests of women diagnosed with cancer. Although in the Bulgarian Standard of Obstetrics and Gynecology there are written instructions for follow-up of women with abnormal Pap smear results, in practice the control on follow up procedures and their accuracy is minimal[9].

Our study aims to shed more light on this issue by focusing on women's cervical screening history, their follow-up and their knowledge about the effectiveness of screening programs.

For this purpose, a survey among women diagnosed with cervical cancer or precancerous lesions was conducted by The Health Psychology Research Center in Bulgaria from June 2011 to January 2012. The aims of the study were to elucidate:

- The reasons for late diagnosis of cervical cancer in the country;
- Existing differences between screening histories of women with invasive cervical cancer and those with less advanced abnormalities;
- Age differences among women with invasive cervical cancer and those with less advanced abnormalities;
- Attitudes regarding screening programs among women with cervical abnormalities.

Results from the study will inform policy makers in the country on these important issues and contribute to the development of a population based screening program in accordance with European standards in the near future.

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[9]Based on personal communications with providers and key informants

Women with abnormal results or diagnosed with cervical cancer (Pap groups III and IV) were asked to respond to a short questionnaire (see Appendix 4). The questionnaire consisted of 11 questions regarding stage of diagnosis, Pap smear history, treatment and follow up. It also included questions about women's attitude towards screening programs – knowledge of their existence and effectiveness, as well as women's willingness for participation in such programs in the future.

Data were analyzed with SPSS software, version 20. We conducted univariate and bivariate statistical analysis. Frequency distributions of the main variables were analyzed. We applied bivariate statistical analysis (chi-square test for independence of two variables and correlation analysis based on Cramer's contingency coefficient) in order to study the link between various demographic characteristics of women and their screening history, attitudes towards screening programs and readiness for participation in them.

Several managers and gynecologists from oncological dispensaries throughout the country were asked to distribute the questionnaire among patients from inpatient and outpatient units. Together with the National Oncology Hospital in Sofia, oncology dispensaries form the most important part of the oncology network in the country. There are local cancer registries in every dispensary, providing information on newly diagnosed cancer cases, stage of diagnosis, etc. In all dispensaries there is a preventive unit for free check-ups, as well as inpatient units for cancer treatment.

Initially, in spite of the numerous invitations, reminders and additional contacts, there was a low response from the dispensary managers and gynecologists. The lack of collaboration made us restrict the scope of our research only to clinics and medical units in Sofia. At the second stage, the questionnaires were distributed among gynecologists in six settings - three oncology-gynecology departments for inpatient care and three settings for preventive outpatient care in Sofia. Most of the women with invasive cancer were recruited in the inpatient settings. In the preventive settings, gynecologists were asked to invite for participation only women who had already shown abnormal results. Although our team proposed to cooperate in the process of data collection, in all cases the doctors who agreed to collaborate with us preferred to administer the questionnaire themselves and to return the completed questionnaires to the research team.

The participants were informed in written form about the aims of the study and also about the anonymity of the information they provide.

> **4. Dissemination of the Bulgarian guidelines for good practice in cervical cancer screening, based on the European guidelines among the health specialists involved in the cervical cancer prevention.**

In 2011, the Ministry of Health has issued guidelines for good medical practice in screening for three localizations – cervix cancer, breast cancer and colorectal cancer. These documents are in accordance with the European standards. Dissemination of the Guideline for cervical cancer screening was an objective for the project team. Dissemination of guidelines for cervix were performed at Bulgarian meeting for pathologists (January 2012).

RESULTS

Part One: Resources, quality management and readiness for implementation of cervical cancer screening - the case of Bulgarian pathology laboratories

Human Resources

Few laboratories provided information on the number of people who worked in the laboratories before 1989. Private laboratories were not able to provide data for the period 1970-1990, since they had not been established at that time. There is small variation in the reported number of personnel in these private laboratories in the last 10 years. A significant decrease of the personnel is reported in two of the state laboratories in the capital: from 30 people in 1980s to 5 people in 2010. In another laboratory the decrease was from 23 employed in the 1980s to 4 people currently working there.

The number of personnel in one laboratory varied from three to 29 people and the number of pathologists who analyze PAP smears ranged from one to nine. The specialties of the staff were pathologists, biologists, laboratory technicians, recorders (administrative personnel) and rarely other staff worked in the laboratories. In contrast to most European countries, in Bulgaria cyto-technicians are not present in all laboratories. In our study, biologists/cyto-technicians were employed in seven laboratories, but in all cases their number was less or equal to the number of pathologists. Only in one case- a big state laboratory that was specialized in screening in the past - nine biologists and two pathologists were employed. Laboratory biologists have different duties. In some laboratories they are involved only in registration and staining. In other laboratories they make the initial assessment and primary screening. In some cases, biologists are also responsible for re-screening and archiving.

Six laboratories, mainly the private ones, report that they also employ part-time personnel. During the interviews with pathologists it became clear that almost all pathologists in the country are combining duties in public and private laboratories for financial reasons. Moreover, due to the insufficient number of specialists in pathology in the country, there are laboratories with only one pathologist. In some regions, one pathologist is working in more than two laboratories sometimes located in different cities. European guidelines do not recommend laboratories with one pathologist because this could be an obstacle to an appropriate internal quality control.

Work Conditions

Five laboratories participating in the study were located in separate buildings, while the rest were placed within hospitals. The number of rooms varied from 1 to 15, but most often there were 2-3 laboratory rooms and several rooms used for offices. European guidelines for having at least three different rooms for registration, preparation and screening are not met in many laboratories. Very few laboratories had a separate secretarial room.

Regarding physical conditions (light, ventilation, space and silence) eight laboratories reported that the conditions are satisfactory. In one laboratory all physical conditions were reported as insufficient. Some insufficient conditions were reported in all municipal laboratories. Lack of space and high noise were the main problems. In state laboratories, problems were related to different conditions, while private laboratories reported the best conditions.

Twelve of the laboratories had adequate space for sample storage. Although the National Medical Standard requires 10 years of storage of all samples, laboratories reported different time of storage that varies from one to ten years.

Equipment and Staining

In all of the laboratories there were enough or more than enough microscopes for the screeners. Usually microscopes are used personally. Very often in one laboratory there are different microscopes in terms of characteristics and year of production. However, the respondents point out in the interviews that many of the microscopes used by their colleagues are too old. Usually, microscopes are serviced once a year but in some cases more often – every 3 or 6 months.

In eight laboratories an electronic system for storage and reporting of results is available. However, all the laboratories use paper journals for back-up of the results. Most laboratories (N=10) keep request forms for ten years or more, but there are cases when forms are stored for a shorter time – for one or for three years.

All but one laboratory use manual staining. The predominant way of staining is with Haematoxylin and Eosin. There are laboratories in which both types of staining are practiced. One state laboratory reportedGiemsa's Azure Eosin Methylene Bluestaining. Few of the laboratories follow the European guidelines for PAP stain.

Allocation of Duties and Workload

The workload reported by the laboratories ranged from 500 to 6000 smears per year. The daily workload per laboratory varies from 10 to 50 smears. The quoted numbers concern only PAP smears and do not take into account the other specimens that are analyzed in a given laboratory. The time reported for (primary) screening varies from 5 to 25 minutes per slide for both preventive and diagnostic smears. Although the European Guidelines recommend that continuous screening should not exceed 2 hours without a break, we found that in 16 out of 18 laboratories pathologists work more than two hours without a break. The reported working hours per day are 6 or 7, but these hours reflect the time spent by pathologists in the particular laboratory of study. They do not reflect the fact that virtually all pathologists work part time at other places.

The workload of pathologists was a topic in the in-depth interviews, as well. According to one of interviewed experts, the recommendations for workload given in the Guidelines are irrelevant for pathologists in Bulgaria. This is because guidelines are for screening laboratories and do not take into account the complexity of work performed by pathologists. Since all the specialists are involved in analysis of cytology and histology specimens and have enough experience to provide high quality analysis, workload standards in the European Guidelines are considered not applicable. The interviewee shared also that the work hours reported in the quantitative part of the study, might not be realistic because many pathologists are combining work hours in public and private laboratories and the questionnaire does not reflect their second and third contracts.

According to the data obtained from the study, allocation of duties differs from one laboratory to another. Only six laboratories reported to have any administrative personnel. In others registration is done by pathologists or laboratory technicians. Staining is the only activity which is reported as not being performed by pathologists. Usually it is done by laboratory technicians. Initial assessment is done by biologists or pathologists and only in one reported case - by a laboratory technician. In most of the cases, primary screening, re-screening and additional assessment are done by pathologists. In the laboratories that have biologists in the staff (N=7) they are also involved in the primary screening. In all other laboratories primary screening is performed by specialists (pathologists).Re-screening and additional assessment is always performed by pathologists.

The study found that all laboratories have a recording system, which is in accordance with the European Guidelines and includes patient identification data, name and address of the laboratory, date of arrival of the smear in the laboratory, indication for examination (screening, follow-up or clinical), type of examination (cytological, histological or virological), advice for repeat sample or referral, date of final report, and name of the person(s) who evaluated the sample. In spite of the fact that all the information mentioned is required to be filled-in, it is doubtful if it is done in practice. This raises also some doubts about the quality of documentation in the laboratories. Usually in Bulgaria the request form is also a reporting form.

The results from the survey reveal also that the test results are reported in different classification standards - most often PAP groups, Bethesda 2001 or 2008. There were various answers when pathologists were asked if there is a national classification system for results reporting. Some respondents believe that such a system does not exist. Other respondents do not know how this issue is regulated in the national standard of pathology. Only few of the participants in the survey were aware of the fact that they have to report their results in accordance to the Bethesda system or at least that the results have to be transferable to it. However, all laboratories included in the study, reported that their results can be transferred to Bethesda classification.

Time of results reporting varies from 1 to 14 days. However, in practice the results are very often available on the 3rd work day. Only one laboratory reported different times for preventive and for diagnostic smears - 5 and 3 days respectively.

All laboratories are able to provide information on previous test results for cervical cytology and histology of the patient (if the investigations are done in the same lab).Seven laboratories were able to provide information on clinical outcome after cytology tests, including colposcopy, biopsies, and others.

Quality Management

Looking at the recommendations for quality management, it becomes clear that since an organized screening program nonexistent, there were many details mentioned in the European Guidelines that were irrelevant for the Bulgarian case. Thus, only a few questions on the availability of methods for internal and external control and on management of documentation were included in the questionnaire.

From the main methodologies for internal quality control of cytology included in the European Guidelines, all laboratories reported control based on re-screening. Only seven of them reported to apply control based on correlation of cytology with clinical/histological results. Methods based on monitoring of screening detection and reporting rates were not available in any of them. Regarding re-screening procedures, almost all laboratories reported to perform at least one form of re-screening. The procedure of reviewing smears initially reported as negative or inadequate was not mentioned in any case, while all other methods of re-screening seem to be equally used among the laboratories.

In regard to the general management of the laboratories, in all settings the documents presenting an overview of the laboratory were reported to be available. This is also true for the description of personnel positions with their levels of competence and responsibilities.

Different forms of continuing education were mentioned in 16 of the 18 laboratories participating in the survey. Participation in regular meetings on review cases was reported by many participants. In twelve laboratories, attending workshops and symposia by the staff was a regular practice. In seven laboratories regional inter-laboratory slide review sessions were often performed. Eight laboratories trained pathology residents. In fourteen laboratories specialist from the staff were members of professional organizations. Proficiency testing is not practiced at any laboratory. Eight laboratories reported to have external certification. Only three laboratories have been re-certificated at least once.

Communication

The laboratories are not connected to each other. There is no screening registry in the country and communication with the cancer registry is not always effective. A national database for PAP-smears does not exist. Many PAP-smears are taken and analyzed in the private sector where physicians do not officially report either the number of smears, or the results. In these situations, the pathologists report results directly to the gynecologists. Pathologists do not communicate directly either with the General Practitioners, or with the women themselves. Some laboratories report cancer cases to the National Cancer Registry on a regular basis, i.e. once or twice a year.

The survey uncovered two types of attitudes of pathologists regarding participation in a future screening program. Some of them were willing to take part in such a program. Other respondents considered whether their laboratory would have the capacity to accept more smears. Although all laboratories expressed a positive attitude towards participation in a screening program, there were some that reported they had no capacity for increasing their workload under the current conditions. Those who could participate in a future program reported a capacity for 30 to 100 additional gynecology smears per day.

Conclusions

The main conclusion from our study is that in Bulgaria the *European Guidelines for Quality Assurance* for cyto-pathology are not strictly followed. The level of adherence to them is not satisfactory. There are no clear instructions on quality assurance and management of the pathological laboratories. Practices for internal and external quality control are insufficient. In many cases these practices do not follow the European Guidelines. Due to the lack of national standards for personal and laboratory workload, laboratories included in the study significantly differ from one another.

Another important finding from the study concerns the urgent need for developing education and training policies for cytopathology in the country. The availability of training programs in cytopathology for biologists could be a solution for overcoming the observed shortage of human resources, mainly in primary screening. Lectures and courses on quality assurance for pathologists from leading experts could help Bulgarian pathologists to follow more strictly the European recommendations and keep their expert knowledge up to date. Initiating recertification and proficiency testing according to the standards can be a solution for improvement of the quality of work. It can also improve the communication between different specialists.

The information gathered in this study presents some issues and problems that pathology specialists in Bulgaria face in their work. However, there is a need for additional information to assess the number of laboratories that would meet at least the minimal European recommendations for quality control in a future screening program.

Part Two: Bulgarian meeting for pathologists (January 20-21 2012)

At the end of January 2012, as a part of the project activities, a meeting for pathologists, doing cervical screening was organized. It was planned for 15-20 participants, mostly experts, but the unexpected interest led to a meeting of more than 60 participants working throughout the country. Health authorities were also presented at the meeting.

An information package was prepared and distributed during the meeting, including translation of materials in English (*H. G. Wiener, P. Klinkhamer, U. Schenck, M. Arbyn, J. Bulten, C. Bergeron, A. Herbert (2007) European guidelines for quality assurance in cervical cancer screening: recommendations for cytology laboratories,Cytopathology 18 (2), 67–78.*), and copies from the Bulgarian guidelines for good practice in cervical screening, based on the European guidelines, author   Nikola Vassilev, member of the EUROCHIP III national group of experts.

In the first part of the meeting there were plenary sessions and discussions, and the second part was devoted to a discussion on the preparedness of the laboratories for implementation of organized screening program and the readiness of their staff to participate in it. Many issues were discussed - financial, organizational and administrative. Although the aim of the meeting was to assess and give better understanding on the willingness and readiness for participation in organized screening program, participants focused their discussions to their current problems, and put down conditions for participation in the future screening program. The meeting was unique for the pathology society and was well covered by media.

Among the discussed issues were the recommendation for workload and the national practices. According to some experts, recommendations for workload in the Guidelines are irrelevant to the current situation in the country, because do not take into account the complexity of work performed by pathologists. Because all the specialists are involved in analysis of both cytology and histology specimens and have enough workload to maintain good quality, they considered workload standards in the Guidelines as unnecessary high. Moreover, pathology labs are not evenly distributed in the country, some of them could meet the requirements, and other could not.

Calling on the existing in Europe schemes for defining workload not just as function of number of the tested smears, but taking into account the complexity of their work and professional skills, pathologists insisted on applying these methodology for the Bulgarian pathologists as well.

The issue of cytotehnicians was also discussed during the meeting, showing different attitudes to the nessesity of education programs and to the need of cytotehnicians as lab staff. On one hand, pathologists admited that there is need for cytotechnicians, but in the current way of funding, the inclusion of cytotechnicians would cut from their insufficient payment. On the other hand, there were voices that investment in education of cytotechnicians would be useless and unnecessary, because they won't stay in the country and would go in Europe for better payment, because there is a need for these specialists. Some experts proposed at the beginning of the screening program no cytotechnicians to be required but to leave place for their education and involvement in the coming future.

The most discussed issue during the meeting was funding. A lot of problems connected with the organization of funding came up. Experts said that the pathology specialty is underrated and payment is less than in other medical specialties. In the last years, the National Health Insurance Fund has defined a payment for smear reading, equal to 5.40 leva, less than 3 Euro. From 2012, this sum became about 4 Euro. With this money, the smear should be registered, analysed and reported. Moreover, if the laboratory is public, the hospital or out-patient setting is taking substantial part of the sum, according to the contract. And, when the pathologists are working on a contract, in most cases their payment is constant and does not depend on the number of smears/specimens analyzed. In this situation, pathologists are dissatisfied of their job, there are no young specialists and the prestige of the specialty is extremely low.

During the meeting discussion, pathologists were trying to persuade organizers, the presenting health authorities and the media that radical changes have to be made in the organization of pathology in the country in terms of funding and organization of their work. Regarding screening program, they insisted on development of new regulations that would consider the realities and would ensure enough capacity and funding. According to the participated specialists, in a situation of lack of cytotechnicians and insufficient number specialists, screening tests might be analyzed in few but reliable laboratories, with quality management meeting European criteria.

Discussion included also issues of laboratories registration and eligibility for the participation in the future screening program. Specialists raised the question on how would "cytology laboratory" be defined within the program. Currently, some pathology or clinical laboratories have defined cytology sector, other do not. They worried that the requirements in the Bulgarian guidelines for good medical practice would not be feasible for many of the currently existing laboratories. Some pathologists worried that if an organized program starts soon, they won't be paid enough for smear testing, and the same time would lose the income that could have now in the opportunistic screening, where women are paying out of pocket. Pathologists worry also about the selection of specialists that would participate in the screening program and if there would be selection criteria. However, looking back to the last 20 years, specialists were not optimistic about the implementation of an organized program. Even though there is a political will, several consensus documents among the health professionals, there is still no program.

Through all the meeting, many of the participated pathologists were showing negative attitude to questions regarding adherence to the European recommendations, insisting on the need of adapting them to the Bulgarian situation and practices. Another issue was communication with other participants in the screening process - obstetricians, Ministry of Health and NHIF. It was pointed out that quality of pathologists' work depends to a great degree on the quality of smear taking and often they get pap smears with unsatisfactory quality. Pathologists proposed organization of another meeting, where all health professionals, involved in cervical screening could discuss their problems and find decisions.

At the end of the meeting a memorandum was voted and it was presented to the Health Minister together with a document on the results of the meeting (see Appendix 3).

Part three: Pap smears history of women diagnosed with cervical cancer or precancerous lesions

The total number of women who took part in the survey was 98. The mean age was 43.9 (S.D. – 13.3). Of the sample, 47% had university education; 45% secondary education and 8% primary education (Table 1).

Table 1. Sample characteristics

	Frequency	Percent
N	**98**	
Mean age	43.9 (S.D. 13.3)	
Distribution of the respondents by hospital		
- Hospital 1	33	33.7
- Hospital 2	18	18.4
- Hospital 3	16	16.3
- Hospital 4	10	10.2
- Hospital 5	12	12.2
- Hospital 6	9	9.2
Total	98	100.0
Diagnosis		
- Pap III	34	41.0
- Pap IV (Ca in situ)	8	9.6
- Cervical cancer	41	49.4
Total	83	100.0
Age		
- under 30	18	18.6
- 31-60	69	71.1
- 61+	10	10.3
Total	97	100.0
Education		
- University/ college	46	46.9
- Secondary/ High School	44	44.9
- Lower than secondary	8	8.2
Total	98	100.0

There were 41 women diagnosed with cancer: 8 with cancer in situ (Pap IV) and 34 with precancerous lesions (Pap III). Of those, 62% of the women were diagnosed in the last year and 75% reported that they were diagnosed with abnormal results in the last 3 years.

Screening history

Screening history was assessed based on women's past experiences with the Pap test. Frequency of Pap tests in the past is presented in Table 2. Frequency of Pap tests in the past was additionally recoded into two categories – adequate and inadequate testing. Women who had their Pap-smears regularly (up to three years screening intervals) were considered as having adequate testing. Women who had their Pap testing five years ago, as well as those who reported that they had been tested rarely, never, or who did not know/remember the time of their last test, were considered as inadequately tested. Although there are countries where a five years screening interval is practiced, in Bulgaria such an interval is not recommended. Therefore, women who were tested more than three years ago were classified as inadequately tested[10]. As a result, from all the women participating in the survey 53.1% had adequate screening in the past and 45.9% had inadequate screening in the past (Table 3).

Table 2. Frequency of Pap-testing in the past

How often have you been tested in the past?		Frequency	Percent
Valid	Two times a year	14	14.3
	Every year	29	29.6
	Every 3 years	9	9.2
	Every five years	3	3.1
	Less than once in every 5 years	31	31.6
	I don't know	4	4.1
	I don't remember	1	1.0
	Never	5	5.1
	Just once	1	1.0
Missing		1	1.0
Total		98	100.0

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[10] There are two proposals for national screening program and guidelines for good medical practice in screening and all of them propose three-year screening interval after two negative pap smears.

Table 3. Adequacy of screening intervals in the past

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	adequate	52	53,1	53,6	53,6
	inadequate	45	45,9	46,4	100,0
Total		98	100,0		

Screening history according to stage of diagnosis

One of the main questions of the study was if women who were diagnosed with invasive cancer had different screening history than those at less advanced forms of the disease. The results from Table 4, which classifies women in two groups of in/adequately screened in the past show that 80.0% of women diagnosed with cervical cancer received inadequate testing in the past. The picture in the group of women with precancerous lesions is completely different. Most of them reported adequate screening and only 9.5% of them had inadequate screening intervals in the past. Of all 34 women with Pap III, 9 were going twice a year for smears, 17– once a year and 5 (14.7%) every three years (Table 4).

Table 4. Adequacy of screening, according to stage of diseases, age and education

			Adequate	Inadequate	Total
Results /Diagnosis	Cervical cancer	N	8	33	41
		%	19,5%	80,5%	100,0%
	III & IV Pap group	N	38	4	42
		%	90,5%	9,5%	100,0%
	Total	N	46	37	83
Age	Under 30	N	15	3	18
		%	83.3%	16.7%	100.0%
	30 -59	N	34	34	68
		%	50.0%	50.0%	100.0%
	60+	N	2	8	10
		%	20.0%	80.0%	100.0%
	Total	N	51	45	96
Education	Higher education	N	34	12	46

		%	73,9%	26,1%	100,0%
Secondary and lower	N	18	33	51
		%	35,3%	64,7%	100,0%
Total	N	52	45	97

Screening history according to age and education

The results reveal a strong link between cervical screening history and the severity of diagnosis. Taking into account that treatment of the disease could be influenced by various socio-demographic characteristics of women, as a next step we take a closer look at the differences by age and education between women with and without adequate screening history.

The mean age of women diagnosed with cancer was 52.6, while for the ones with less advanced disease the mean age was 35.1. Within the age range of 30 to 59 (the age recommended for organized screening programs) - an equal number of women (N=34) had adequate and inadequate screening history (Table 4).

Table4also reveals that there are significant differences between women with different levels of education in terms of frequency of Pap testing in the past: 73% of women with higher education had adequate screening history, while 35.3% of women with secondary education or lower had adequate screening history. This striking difference suggests that women with low education, who usually are of lower socio-economic status, are one of the most vulnerable groups in the population. Among them the risk of cervical cancer is significantly elevated. Lack of information about the disease and its prevention, limited financial resources, hampered access to health care system are some of the potential reasons(Avramova, et al., 2005) for the reported strong educational differences in the screening history of Bulgarian women.

Thus, our analysis confirms that frequency and timeliness of screening is an important factor influencing the risk of cervical cancer. The study also illustrates the strong age and educational differences between women who have adequate and inadequate screening history. This result suggests that larger social inequalities in Bulgaria contribute to the differences in women's stage of diagnosis.

When asked about recommendations given by health professionals for treatment and follow up, women's responses show that they were followed according to different schemes and no unified protocols were used. Half of the women with Pap III group were referred to colposcopy and half were not. This result is not in agreement with the European guidelines that required every woman with abnormal results to be referred to colposcopy after a positive smear.

Women's attitudes to screening programs

Our study addressedthe attitudes of the participants towards the screening programs in the country. Most of the women (63%) reported that they had information about the existenceof screening programs and 84% of them evaluated these programs as effective. Interestingly, the women with invasive cancerwere better informed about the existence of screening programs (68.3 %), than the women with Pap III and Pap IV. Over 90% of women, regardless of their health status(diagnosed with cancer or having precancerous lesions) reported that they would participate in a screening programme, if invited. Over 90% of women stated also that they would recommend screening to their relatives or friends.

Discussion

This small study presents results on Pap smear history for women diagnosed with cervical cancer and women with less advanced phases of cervical neoplasms. There were an almost equal number of women in both groups – 41 cancer patients and 42 women with less advanced stages of cervical abnormalities. Our results show significant differences in the screening history of these two groups. The women with invasive cervical cancer report that they have been rarely screened in the past compared to women with less advanced abnormalities of the cervix. Women with invasive cervical cancer were older and had lower education in comparison to those with abnormal results. The mean age for women with cancer (52.6)is similar to the one reported for example in Malta(Busuttil, Dalmas, & Vincenti, 2006), but lower than reported for other countries with developed screening programs such as Finland (Neminen, et al., 1999). The reported age and educational differences suggest that broader socio-economic inequalities among women in Bulgaria have a strong differential effect on the risk of cervical cancer.

Our previous study shows that women of lower social status and living in smaller citiesin Bulgaria usually have insufficient information on the availability of preventive programmes and opportunities(Avramova, et al., 2005).Programs need to address the needs of vulnerable groups of women. Epidemiological data reveal that even though in the public sphere there is plenty of information on cervical cancer prevention, screening and HPV vaccination, cervical cancer related mortality continues to rise in the last decades (Cancer Incidence in Bulgaria 2009, 2011). Similar to the situation in other countries without organised opportunistic screening programmes,currently in Bulgariaa large part of the female population is not being screened (Busuttil, et al., 2006).

These results are in concordance with our previous studies and show that women of higher age, lower educational status and inadequate smear history are at ahigher risk for development of invasive cervical cancer. Results also show that in the absence of organized cervical screening program and clear policies for cervical cancer prevention, the disease is often diagnosed at later stages that requiredifficultand expensive treatment.

The results on the willingness of women toparticipant in screening programs in the future are very optimistic. However, these women represent a specific group which has already been diagnosed with cervical abnormalities. In order to complete the picture it is necessary also to take into account the opinions of healthy women and their level of awareness and readiness to participate in an organized screening programme. This could be a topic for future research.

Conclusions

This study gives the opportunity to compare screening history of women diagnosed with cervical cancer and women who have abnormal smear results. The results show that most of the women diagnosed with cancer have not been screened for more than five years, while those with minor abnormalities have had an adequate screening history. Women diagnosed with invasive cancer were of higher age and had lower educational status. Women with less advanced abnormalities were younger and had more years of education. Age and educational differences between these two groups of women suggest of the relevance of broader social inequalities differentiating the risk of cervical cancer among Bulgarian women.

Currently, in Bulgaria there is no procedure for re-reading of past smear test slides and thus no information on false negative results could be obtained and analysed.

Women receive different type of treatment and follow up. It seems that there are no routine algorithms and standards followed among the medical units in the country.

As a whole, women evaluate positively the development and implementation of a screening programme in the country. Women with abnormal results from Pap smears are less informed about the existence of such programs.

Recommendations

1. In order to better understand the screening history of women diagnosed with invasive cancer, their treatment and follow up, a qualitative study could be designed and carried out. It can provide more detailed information on women's experiences prior the diagnosis, the main barriers, both personal and structural, they meet in they access to screening. The results from such a study can inform an expanded quantitative study focused on the factors influencing the late diagnostics of women. Policy-makers, politicians and public health specialists would benefit from such mixed-method analysis. The results can be used for the development of population based screening programme that takes a differential approach to the different groups of women. In order to delineate the factors influencing Pap history, an expanded study should take into account additional risk factors such as socio-economic status, place of living, smoking, number of pregnancies/children and others.

2. Improvement of smear history documentation at a national level, and especially that of patients once registered with abnormal results, cervical-related symptoms and pathology would substantially contribute to the accurate evaluation of the effect of screening in the future.

3. It should be guaranteed that women diagnosed with cervical cancer could ask for a re-reading of their previous slides. This would help to clarify whether there was a false negative result or other reason for the cancer development. Health professionals who are involved in cancer diagnosis should have access to the records of previous smear tests and be given the opportunity to ask for re-reading of previous slides, if necessary.

4. The follow-up for women with Pap test abnormal results should be standardized, practiced and controlled according to the national and European guidelines.

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Appendix 1 - Questionnaire for pathology laboratories (English version)
NOTE: Original Bulgarian version of the questionnaire is available at:
www.tumori.net\eurochip\material\WP4\Bulgaria_questionnaire_BUL.pdf

Appendix 2 - Agenda of the meeting for pathologists

Organization, current situation and perspectives of cytology cervical screening in Bulgaria

20-21 January 2012, Central Forum Hotel, Sofia

AGENDA

20 January

Moderator :   *Anna Mihova*

13.30 - 13.40	Z.Valerianova	Welcome
13.40 - 14.00	Y. Panayotova	EUROCHIP-3 - Project Presentation -
14.00 - 14.20	M. Kamenova	European Guidelines for Cervical Cancer Screening
14.20 - 14.40	D. Dimova	European experience in Cervical Cancer Screening
14.40 - 15.00	H. Bojilova	Cervical Screening - management, problems, goals and perspectives for the pathologist
15.00 -15.30	Discussion	
15.30 - 16.00	Coffee break	

Moderator: Helia Bojilova

16.00 - 16.20	G. Petrova	Economic perspectives of primary prevention (vaccination), secondary prevention (screening) and current cervical cancer prevention
16.20 - 16.40	K. Ivkova, E. Lambreva	"STOP and GO for a check-up project" and the participation of cyto-patholgists
16.40 - 17.00	G. Gantchev	HPV distribution in intraepithelial neoplasm
17.00 - 17.20	S. Alexov	Introduction of p16 +Ki67 /HR-HPVs / for early diagnostic of CIN 1 and CIN 2
17.20 - 18.00	Discussion	
19.00	Dinner	

21 January

Moderators: Daniela Dimova and Stoyan Alexov

9.00 - 10.30	Discussion -	Readiness of the cyto-pathology laboratories in Bulgaria to participate in organized population-based screening program - defining the problems
10.30 - 11.00	Coffee break	
11.00 - 12.30		Memorandum
12.30	Z. Valerianova	Final words

Appendix 3 – Meeting MEMORANDUM

From a workshop with pathologists, organized by the Bulgarian team of EUROCHIP-3 in regard to the cervical screening program, January 20-21 2012

1. The existing pathology laboratories could be engaged in the screening program. All laboratories should have equal opportunity for participation if meet the requirements for laboratories in the outpatient care.
2. Cytology diagnostic would be performed by pathologists with a specialty in cyto-pathology.
3. Pathologists should contract screening program directly and not as subcontractors.
4. Screening program should provide laboratories with unified forms and software for reporting and archiving the diagnostic results.
5. Laboratory procedures should follow national clinic and pathology standard and results should be reported in Bethesda and PAP system.
6. Forms and slides might be stored in the laboratories for five years.
7. Soon after the program starts (six months), a meeting should be organized to discuss the experience and results and to propose ideas for improvement.
8. The proposed cost for a cytology testing of one woman (one or two slides), based on cost analysis for consumables, personnel costs (including pathologist, laboratory technician, administrator) and other costs is 16.80 leva, 8.4 Euro. If the organizer of the screening program does not cover this cost, pathologists in Bulgaria won't participate in the program.
9. Screening program should be worked out with the participation of pathologists.
10. According to the majority of participated in the meeting pathologists, the existing within the National Health Insurance Fund program for preventive cervical check-ups is effective and could be used as a foundation for future initiatives.

Bulgarian pathologists, list of signatures

Appendix 4 - Questionnaire for women's PAP history

Dear Mrs/Ms,

You are invited to participate in a study on cervical cancer in Bulgaria. This study is part of the EUROCHIP-3 project, funded by the EC. EUROCHIP is focused on the main elements of cancer control: primary prevention; early detection (screening), treatment, follow up and registration of cancer cases. The EUROCHIP aim is to cooperate for improvement of the cancer control organization in individual countries and to propose steps for better prevention and control. More information on the project and its aims could be find at the project website: http://www.tumori.net/eurochip.

Within the Eurochip project every participating country has a local group of experts, working in cooperation with the Ministry of Health and other institutions. In Bulgaria, the main partner is the Bulgarian National Cancer Registry.

The aim of the study in which you are invited to participate, is to evaluate the history of Pap-smear of women recently diagnosed with cervical cancer. You would be asked to answer few questions on your experience with Pap smears in the previous years, and subsequent treatment, if any. Your physician would ask you to complete a short self-administered anonymous questionnaire, provided by our research team. Your experience and opinions are very valuable and they can help us learn more about the research topic.

Your contribution to this research is voluntary and you can choose not to participate if you don't want to. There are no direct benefits to you for participating in the study. Your participation in the study is anonymous. Data would be presented in a summarized form, without mentioning names of participants. You must be at least 18 years old to be in this research project.

1. When were you diagnosed with cervical cancer?

2. At what stage was the cancer at diagnosis?

3. Have you ever been tested for cervical cancer using PAP-smears?

   YES

   NO

4. How often do you used to go for a preventive PAP-smear in the past?

5. When was your last preventive PAP-smear prior the diagnosis?

6. Have you ever had abnormal results from your Pap-smear tests?

   NO -> Go to Q7

   YES -> How many times?

7. When was the last time you had abnormal results from your Pap-smear test?

   What were the recommendations of your physician?

   - No treatment + another PAP-test in 3/6 months
   - Prescribed treatment and new PAP-test in 3/6 months
   - Colposcopy
   - Biopsy
   - Surgical treatment and follow-up

8. Have you ever heard of screening programs for preventing cervical cancer?

   YES

   NO

9. Do you think they are effective?

10. Would you participate in such program, if available?

11. Would you recommend regular PAP-smears or participation in screening programs to your relatives and friends?

    YES

    NO

Demographic data:

Age:

Education:

Place of residence:

Current occupation:

Thank you for cooperation! We highly appreciate your participation!