Clinical audit of patients with cervical cancer in slovenia - Data analysis for the year 2003

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Summary

Purpose of Investigation: The data gathered in 2003 on the patients with cervical cancer who regularly attended their gynecologist were analyzed with the purpose of clinical audit.

Methods: The data on newly detected patients with cervical cancer in 2003 who regularly attended their gynecologist were gathered simultaneously at three Advisory Boards for Gynecology in Slovenia.

Results: Of 149 patients in whom, according to our data, invasive cervical cancer had been diagnosed, 92 (61.7%) patients were examined by a gynecologist in the previous five years. In the majority of these patients, cervical cancer was diagnosed in early, localized disease stage. In the periods of 13-24 and of seven to 12 months before the diagnosis of cervical cancer, almost half the patients had Pap II, and three to six months before diagnosis, 67.6% of patients had Pap II.

Conclusion: These results encourage us to proceed with clinical audits to analyze individual cervical cancer cases, including another independent reevaluation of cervical smears in the five-year period before diagnosis. A suitable calendar of refresher training courses on colposcopy, which should be obligatory for all performing this examination method, also needs to be set up.

Key words: Clinical audit; Cervical cancer; State screening program; Premalignant cervical disease.

Introduction

Cervical smear test or Pap test is still considered to be the fundamental screening method for cervical cancer in opportune screening programs as well as in organized ones. In many countries where organized screening programs for cervical cancer were started the incidence of and death rate for this cancer have been considerably reduced. However, the cervical cancer incidence and death rate were not as favorable as were expected from the following scientific hypothetical assumptions that seemed more promising: (i) the collection of cervical smears is simple and painless; (ii) the Pap test is highly sensitive and specific; (iii) the progress of premalignant changes into invasive cervical cancer may go on for several years, whereas (iv) the treatment of premalignant changes is often fairly simple.

The incidence of and death rate for cervical cancer is even now one of the crucial health problems in the world. With early detection of cervical cancer, this disease is now considered as rare; however, it still affects too many women in reproductive age. Due to ignorance of some factors influencing the detection of cervical cancer, its incidence is relatively high in some countries, though cervical cancer is so far the only cancer that can be successfully prevented by early detection of premalignant changes [1].

In Slovenia, an organized screening program for cervical cancer was launched in 1998, at first as a pilot study, and in 2002 as a state program named "ZORA". The main reason for proceeding from an opportunistic program to an organized one was a continually growing incidence of cervical cancer that was first observed in Slovenia in the years following 1994. In 1997, the incidence was the highest (23.6/100,000), and in the following years it was about 20/100,000 [2]. The latest preliminary data for the years 2002 and 2003 may indicate to a decrease, but the incidence will most probably remain rather high in the coming years because the data gathered will also include the percentage of patients in whom cervical cancer will be detected by active screening programs. In 2004, the number of detected cervical cancer cases in our study was higher than in the same period of 2003.

In addition to a sufficient percentage of women included in the screening program, the measures that need to be fulfilled in order to assure the efficiency of the organized screening are successful detection of premalignant changes on the uterine cervix by smear or Pap test and their immediate and appropriate treatment. On the other hand, the factors that may reduce the efficiency are: (i) a too long time-interval between smear tests, (ii) improper sampling of cervical smear and reading of test results (false-negative cervical smear test results), (iii) and improperly interpreted premalignant changes in the smears [3]. Moreover, not much success could be hoped for if quality assurance indicators of each individual procedure of the multidisciplinary screening process are not rigorously followed-up, and if critical analysis, control, and appropriate measures to make up the deficiencies are not provided. The perfection of each individual procedure, were it the highest possible, cannot outweigh the inefficiency of any other procedure involved in the same

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process [4]. Data gathering in cancer and screening program registries, high-quality performance of information systems and of cytology laboratories are of paramount importance. Likewise, in view of the efficiency of screening, high-quality sampling of cervical smears carried out by a gynecologist and taking appropriate steps in case of pathologic smear test results cannot be disregarded either. Moreover, continual training of all involved in the screening program is also required, in particular of the specialists who perform cervical smear tests and evaluate colposcopy findings, *i.e.* two tasks that are very likely to be tainted by personal bias.

Data gathering on patients with detected premalignant changes and with cervical cancer, and on the performed diagnostic procedures, treatment and follow-up is of vital importance for quality assurance of screening program. For continual improvement of the state-screening program, all technical problems in the areas related to the management of patients with premalignant changes and with cancer, e.g. information system, cytology, pathology and gynecology, should be investigated in detail. The results of such analyses may often be most helpful in cutting down eventual deficiencies. The control over the performance of all involved is an inalienable part of any screening program and can be carried out only if the program is well organized [4]. The data gathered in 2003 on the patients with cervical cancer who regularly attended their gynecologist had already been analyzed, thereby allowing further training of all involved personnel and improvement of their work efficiency.

In 2003, the data gathering of patients with cervical cancer detected in the same year was started. The data on newly detected patients were gathered simultaneously at three Advisory Boards for Gynecology in Slovenia, at the Institute of Oncology Ljubljana, Division of Obstetrics and Gynecology of the University Medical Center in Ljubljana, and at the Department of Gynecology and Perinatology of Maribor General Hospital. This approach to simultaneous data gathering at Advisory Boards has been chosen because the data are easily and instantaneously available at these Boards and also because, with this approach to data gathering, it is possible to keep under control the current circumstances and take immediate preventive measures; moreover, it also allows us to avoid the problem of gathering the data of deceased patients.

Of 149 patients, in whom, according to our data, invasive cervical cancer was diagnosed in 2003, 92 (61.7%) patients had been examined by a gynecologist in the last five years. The majority of patients who were not regularly visiting their gynecologist had had the last examination more than ten years before. Our data speak in favor of the assumption that women who are not regularly visiting a gynecologist, very rarely self-dependently decide on a gynecologic examination; almost half of them (41.6%) had not been examined in 15 years or more.

The data analysis results provide detailed information on cervical cancer of 56/92 women who were visiting their gynecologist in the previous five years before the diagnosis. Additional details about these patients were obtained from their medical records. The data were collected from questionnaires that were, with the consent of each patient involved, returned to us by the gynecologists who had been treating these patients.

In earlier analyses, it was often suspected that patients with cervical cancer do not always provide us with precise data about their gynecological examinations; this doubt, however, was not confirmed by the present analysis. No final conclusions could be drawn from the analysis of the data gathered in one year only. Yet, the collected data already point to some favorable conclusions as well as to critical ones. These latter ones will particularly require further detailed study by continual data gathering and analyzing.

Data Analysis Results and Observations

Data on cervical cancer

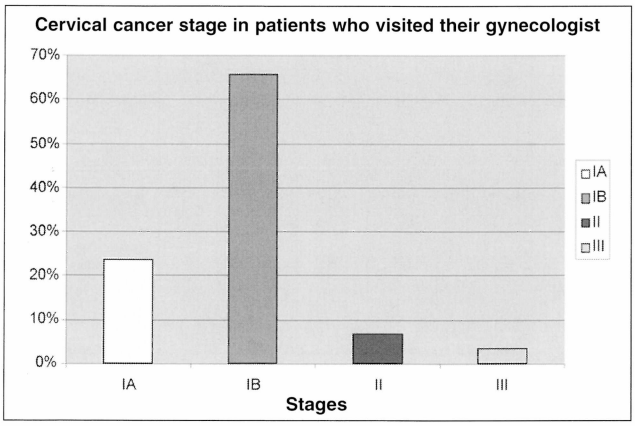
Comparison of the data on disease stage at the diagnosis of cervical cancer in patients who were visiting their gynecologists with the data for the whole of Slovenia shows a significantly positive difference. In the majority of patients who were visiting their gynecologist, cervical cancer was diagnosed in early, localized disease stage.

In nine of ten patients, cervical cancer was diagnosed as Stage I (89.8%), in 6.7% of patients as Stage II, in 3.3% as Stage III, whereas Stage IV was not detected in any of the above patients. In the percentage of the patients with Stage I disease, 23.7% of patients had Stage Ia (Ia1 in 71.4% and Ia2 in 28.6%) and 66.1% Stage Ib (Ib1 in 81.6 % and Ib2, 18.4%) (Figure 1). Disease stages of the patients who were not visiting their gynecologists are shown in Figure 2.

The higher percentage of cervical cancer cases detected in early stages is in perfect correlation with a higher percentage of surgically treated cervical cancer patients. Radical surgery was performed in 85.8% of patients, while the remaining 14.2% were treated with irradiation alone. In the majority of surgically treated patients (77%), no postoperative treatment was required; only 23% were postoperatively irradiated. The disease stages after surgery were as follows: Ia in 43.1%, Ib in 39.2%, II in 5.8% patients, and III in 11.7%. In most cases, postoperative histopathology findings confirmed poorly (36%) or mildly differentiated carcinoma (36%), and least frequently, well differentiated carcinoma (28%).

Histopathological evaluation of cervical cancer in our patients roughly agrees with the data for all Slovenia [3]. The most frequent was planocellular carcinoma (76.8%), followed by adenocarcinoma (14.2%) and adenosquamous carcinoma (7.1%); the least frequent was small cell carcinoma (1.8%).

The patients who had already been treated for premalignant changes of the uterine cervix are at greater risk of developing invasive cervical cancer. Of 56 patients with cervical cancer who provided us with reliable data and were also included in the study, 12.5% underwent coniza-



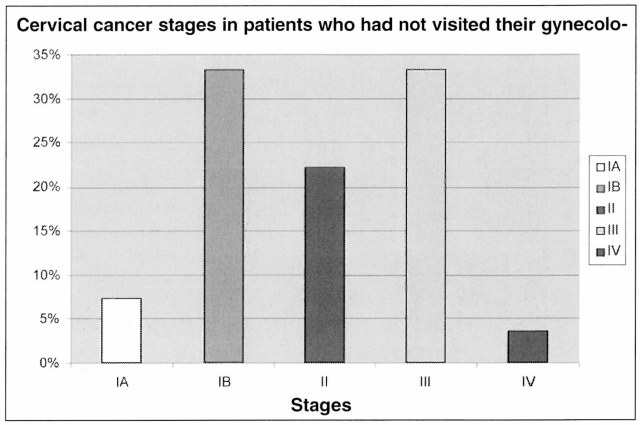


Figure 1. — Disease stage at diagnosis in patients who were regularly visiting their gynecologist.
Figure 2. — Disease stage at diagnosis in patients who were not regularly visiting their gynecologist.

tion. Their age at diagnosis of cervical cancer ranged from 35 to 39 years, which is less than the mean age of the whole group (43 years). Approximately half of the patients who underwent conization (57%) were then regularly, once a year or more, attending their gynecologist, whereas the other half, despite having been treated for cervical intraepithelial neoplasms (CIN) and despite strong recommendations to visit their gynecologist more often, came for follow-up checks every three years or casually, at times [5]. Considering these data and due to recurrent CIN, these patients are at higher risk for developing cervical cancer, and should be therefore referred to oncogene human papilloma virus (HPV) testing [6].

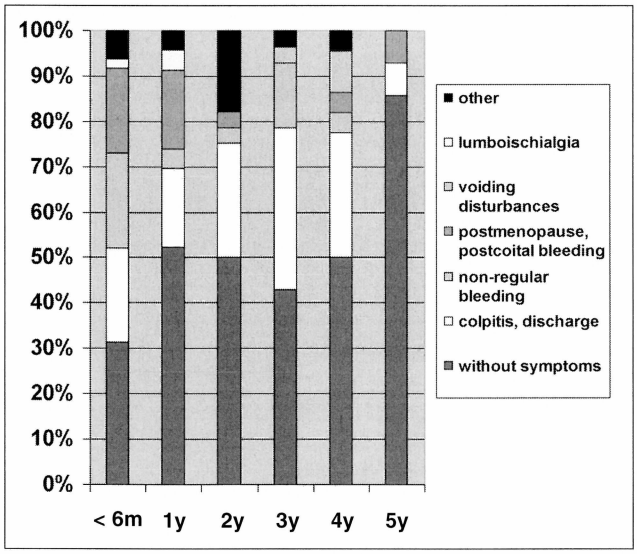
Frequency of gynecological examinations, symptoms and results of cervical smear tests

The patients who regularly attended their gynecologist were, on average, 13 years younger (43 years) than those who did not. The majority of patients (20.8%) fall into the age group of 40-44 years, followed by the age group of 35-39 years (19.7%), while the age group of 60 years and more comprised 11 patients (11.9%). As the state program "ZORA" covers only women aged 20-64 years; those exceeding this age limit are not actively invited to have cervical smear tests, but they are all welcome if they decide on their own initiative to be tested. We assume that, since the progress of premalignant changes of the uterine cervix into invasive cervical cancer takes several years, the percentage of patients who would be regularly taking smear tests and would nonetheless develop cancer, will be low. According to our data from 2003, invasive cervical cancer was diagnosed only in three (3.5%) women who were regularly attending their gynecologist and who were aged over 64. The oldest patient of the three was 74 years old.

Two-thirds of the patients were regularly visiting their gynecologist: 37.5% more than once per year, 5.3% once a year, 14.2% once every two years and one tenth (7.1%) of patients once every three years. One-third (35.7%) of patients were only occasionally visiting their gynecologist. In the last three years before the diagnosis of carcinoma, 87.5% of diagnosed patients had had at least one test performed, which is more than in earlier three-year data analyses [8]. On average, each patient with diagnosed cervical cancer had had seven gynecological examinations in the last five years before the diagnosis. One-third (33.9%) of the patients had undergone three or less gynecological examinations in the last five years before the diagnosis and the rest (two-thirds) of the patients had had four or more examinations. More than one-fifth (17.8%) of patients had had ten or more examinations. The average number of collected smear samples per patient was 3.7. In half (48.2%) of the patients, three or less smear samples had been taken, and in 33.9%, four to five smear samples had been taken. In nearly one-fifth (17.8%) of patients, six smear samples or more had been taken.

Cervical diseases, such as premalignant changes or cancer, are associated with considerable health problems. Patients in whom cervical cancer was diagnosed had been frequently visiting their gynecologist and complaining about their health problems. This was already proven by earlier analyses. Gradual occurrence of the symptoms typical of cervical cancer before the diagnosis may be well seen from the data gathered for the year 2003. The symptoms reported by the patients were, in view of the time interval from occurrence to development into cancer, very diverse. Five years before diagnoses, the patients had no gynecological disorders. Three years before diagnosis, the patients complained of vaginal discharge and colpitis, and in the last year, the disorders that they complained of were typical symptoms of premalignant changes or cancer itself (Figure 3). A more detailed analysis shows that five years before diagnosis 85% of patients had had no gynecological disorders, four years before diagnosis 50% of patients had, while 10% or more of patients had already complained of vaginal discharge and colpitis. Three years before diagnosis, 42% of patients were without gynecological problems, whereas the percentage of those with vaginal discharge and colpitis was gradually increasing (36%), accompanied also by

Fig. 3



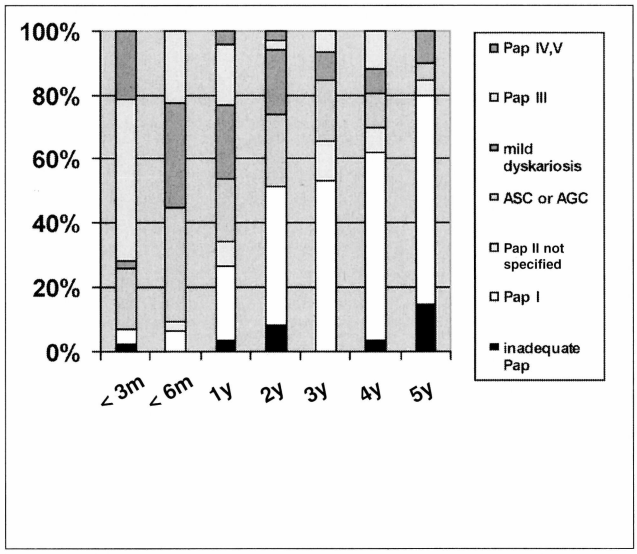


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Figure 3. — Clinical symptoms of cervical cancer in patients who were regularly visiting their gynecologist.
Figure 4. — Cervical smear test results distribution by time-intervals before the diagnosis of cervical cancer.

bleeding between menstrual cycles (7%) or prolonged menstrual bleeding (7%). Two years before diagnosis, the relation was much the same as the previous year. Six to 12 months before diagnosis, 52% of patients did not have any gynecological disorders, more than 10% reported postcoital bleeding, about 10% had vaginal discharge or colpitis, postmenopausal bleeding or bleeding between menstrual cycles, and pain in the lumboischiadic region. Six months before diagnosis, 32% of patients did not have any gynecological problems, while the rest of the patients most frequently mentioned bleeding between cycles, blood in the discharge, and postcoital bleeding as well as colpitis, postmenopausal bleeding, prolonged menstrual bleeding, and pain in the lumboischiadic region.

Key factors that can assure high quality of test results are proper smear sampling, immediate fixation in 95% ethanol, cytologically appropriate examination of smear samples and accurate reading of test results by qualified experts. The percentage of negative test results (Pap I) was the highest (65%) five years before the diagnosis of cervical cancer and was, in the following years, gradually decreasing: four, three, and two years before the diagnosis of cervical cancer, the percentage of negative Pap I results was 57%, 53%, and 42%, respectively; seven to 12 months before diagnosis it was still relatively high (23%) and in the last three to six months it dropped to 6.4% (Figure 4).

In contrast, the percentage of pathologic test results and normal test results were related in inverse proportion. The percentage of pathologic results gradually increased as the date of the diagnosis approached. Five years before the diagnosis no test results had been evaluated as Pap III, Pap IV, or Pap V. Four years before the diagnosis no test results had been evaluated as Pap IV or V, and 11.5% of test results had been evaluated as Pap II; three years before the diagnosis no test results had been evaluated as Pap IV or V, while 6.2% were Pap III; two years before diagnosis no test results were Pap V and 5.6% had been evaluated as Pap III or IV; seven to 12 months before diagnosis 23.0% of test results were Pap III or IV, and no results had been evaluated as Pap V; three to six months before diagnosis no test results were evaluated as Pap IV or V but 22.5% were Pap III, and in the three-month period immediately before the diagnosis of cervical cancer, the test results of 71.3% cases were evaluated as Pap III, IV or V. In 21% of cases mildly dyskariotic, atypically squamous or glandular cells were found, in 2.3% of cases smear samples were inadequate, and the results of two patients had been evaluated as Pap I.

From numerous earlier analyses made in Slovenia, it can be concluded that a few years before the diagnosis of cervical cancer, the test results of pathologic smears of the patients with cervical cancer were most frequently evaluated as Pap II, i.e. containing atypical squamous or glandular cells or mildly dyskariotic cells. From the data analysis of the patients with cervical cancer performed in 2003 for a five-year period before the development of malignancy, similar conclusions could be drawn. The sensitivity of Pap smear testing for detecting CIN is considered to be average, ranging from 50-70%, which means that the test results may be false in 20-25% of cases despite frequently repeated smear sample taking. To detect the most important pathologic premalignant changes, such as CIN 2 and 3, classic techniques, e.g. colposcopy with biopsy, are applied. In recent years, the European guidelines for quality assurance of cervical cancer screening recommend, particularly after the detection of most early pathologic changes, more frequent use of oncogenic HPV testing as an additional diagnostic method [8].

Five, four, and three years before diagnosis, Pap II

(atypical squamous or glandular cells or mildly dyskariotic cells) had been diagnosed in 15.0%, 19.0%, and 28.2% (almost one-third) of patients, respectively. In the periods of 13-24 and of seven to 12 months before the diagnosis of cervical cancer, almost half (42.7% and 42.4%, respectively) of the patients had Pap II, and three to seven months before diagnosis, the test results had been evaluated as Pap II in 67.6% of patients. Of these 67.6% of patients, 32.2% had mildly dsykaryotic cells, 19.3% had atypical squamous cells, and 16.1% atypical glandular cells. Due to the percentage of mildly dyskaryotic cells vs atypical squamous or glandular cells three years before the diagnosis of cervical cancer, Pap II was detected in the largest percentage in this period. Earlier, more than three years before the diagnosis, the percentage of atypical squamous cells was equal to or higher than that of dyskaryotic cells.

Throughout all these periods, a relevant percentage (3.8%-15.0%) of inadequate or limited smears was present, which could have had an unfavorable effect on the detection of premalignant changes of the uterine cervix. The percentage of inadequate or limited smears was the highest five years (15%) and two years (8.5%) before the diagnosis of cervical cancer.

Diagnostic procedures

The basic diagnostic method applied in the detection of recurrent primary pathologic changes in cervical smears (2 x Pap II without inflammation) and in Pap III-V is colposcopy. Colposcopy not only detects pathologic changes of the uterine cervix, it can also assess the size of the lesion and determine one or two locations that would be the most appropriate for biopsy. If pathologic changes are observed on the uterine cervix while the colposcopy is negative, it is generally recommended to perform diagnostic conization using one of the conservative excision methods, such as LLETZ [9]. The data collected in 2003 on the patients with cervical cancer who were regularly visiting their gynecologist show that the number of performed colposcopies increased in line with a higher percentage of diagnosed primary pathologic changes of the uterine cervix. Biopsies or curettage of the cervical canal were also on the increase, but the percentage did not rise in proportion to the number of performed colposcopies, which became particularly evident in the three-year period before the diagnosis. The question as to why biopsies or curettage were performed less frequently than presumed needs an urgent answer. Only in the last year before the diagnosis were all diagnostic procedures performed following the recommendations [5].

Five years before the diagnosis of cervical cancer 30% of the patients had undergone colposcopy during gynecological examination, whereas in 20% of the patients biopsy with or without curettage of the cervical canal had been performed. Four years before diagnosis colposcopy had been performed in 35% of patients and biopsy in 15%; three years before diagnosis 54% of patients had undergone colposcopy and 18.1% biopsy; two years before diagnosis 47.8% of patients had had colposcopy and 17.4% biopsy. The last year before diagnosis 52.4% of patients had undergone colposcopy. Three to six months before diagnosis the percentage of women in whom conization had already been performed was gradually increasing, while the percentages of colposcopies and biopsies were 26.0% and 13.0%, respectively. In the last six months before diagnosis methods using ablation (LLETZ, conization with scalpel, reconization) were more frequently applied in 18.3% of patients. Cryotherapy (destructive method) was performed only in one patient two years before diagnosis, and reconization in one patient a year before diagnosis. The correlation between the performed diagnostic procedures and ablation-based or destructive methods throughout each separate period is presented in Figure 5.

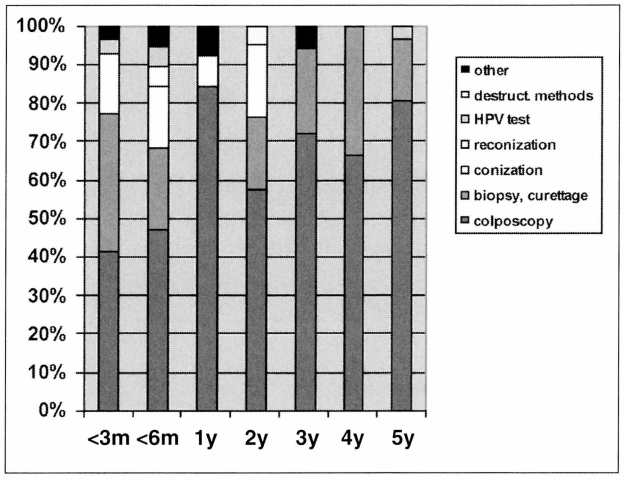

Figure 5. — Diagnostic procedure distribution by time-intervals before the diagnosis of cervical cancer.

Conclusion

Analysis of the data collected in one calendar year on gynecological examinations and diagnostic procedures performed before the diagnosis of cervical cancer may not serve as a reliable starting point to draw definitive conclusions. The results however indicate an urgent need to continue with clinical audits of patients with cervical cancer, or rather gathering and analyzing the data on all procedures performed in patients with cervical cancer who had been visiting their gynecologist before diagnoses. It is also imperative to analyze individual cervical cancer cases, including another independent reevaluation of cervical smears and of eventual histopathologic biopsies collected in the five-year period before the diagnosis of cervical cancer. A suitable calendar for refresher training courses on colposcopy, which should be obligatory for all performing this examination method, also needs to be set up, similarly as has already been done in screening programs for cervical cancer organized abroad. These courses are intended to improve the quality of colposcopy and smear sample taking, and to pay more attention to the deficiencies identified during monitoring patients with

cervical cancer. Furthermore, it must always be remembered to conscientiously follow the recommendations for detection, treatment and follow-up of women with premalignant changes of the uterine cervix [5]. In view of the gathered and analyzed data, it appears to be sensible to introduce systematic HPV testing as an additional diagnostic method to be applied in Slovenian women with primary pathologic cervical smear test results and in those who have been treated for CIN. In Slovenia this step should necessarily be made because of the high incidence of cervical cancer and high percentage of Pap II in many Slovenian cytology laboratories – according to the data gathered by the registry ZORA the mean percentage is 14.2% (range 5.5%-25.8%). At the departments of gynecology and obstetrics of Slovenian hospitals, more effort should be made to establish effective operative centers or outpatient departments for the detection and treatment of cervical diseases which would be specialized in diagnostics, thus assuring also high-quality diagnoses as well as immediate and effective treatment of premalignant changes of the uterine cervix according to national guidelines that also require monitoring of the quality assurance indicators. Finally, women should be more aware of the inevitable inclination for regular gynecological examinations in case of pathologic smear test results or gynecological disorders indicating premalignant changes, especially after having already been already treated for CIN.

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