THE PAP TEST AND THE VALUE OF SCREENING IN THE PREVENTION OF CERVICAL CANCER

Roxana - Elena Bârcă, Diana – Elena Maftei

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INTRODUCTION

Cervical cancer is a major death cause in Europe, mainly in Romania. The first countries that joined EU test more than 45 million women each year, though the death rate is significantly lower. Women are assessed every 3 years by means of the Pap test, revealing the benefits of the screening programs [5, 6, 7, 10]. The main cause that induces this type of cancer is the HPV infection in 95% of the pacients. Cervical cancer, along with melanoma and breast cancer, may be prevented by early diagnosis and treatment. Early diagnosis for this disease is a key factor in order to achieve therapeutical success, considering the outburst of pacients [8].

The Pap test serves for diagnosis purposes, recommended by the gynecologist or for the early depict of precancerous lesions. The cervix cancer is a major death cause for women aged 15 to 44 years old. The most affected are the premenopause women belonging to the age segment of 45 to 54 years old. Since 2016, six women died each day as a consequence of undiagnosed cervix cancer.

MATERIAL AND METHODS

There is a high percentage of women that perish due to cervix cancer, as the prevention and early diagnosis programs are poorly enforced.

This study relies on the statistics provided by the Emergency Hospital from Roman town (Neamț county). It aims the enforcement of screening by means of the Pap test, for early diagnosis of cervix cancer. The Health Department introduced the free testing for women since 2012. The program is meant to depict the precancerous and cancerous cervix lesions. This screening is beneficial to all the tested women, improving the healing chances.

The target was a pacient group that had previously contacted the hospital or the family doctor for a gynecological examination of the cervix. The study was conducted between 2018 and 2020 and included women aged between 25 and 64 years old.

They were examined by means of the Pap test. The biological material was the vaginal fluid provided by the standard procedure [4, 5, 7, 11].
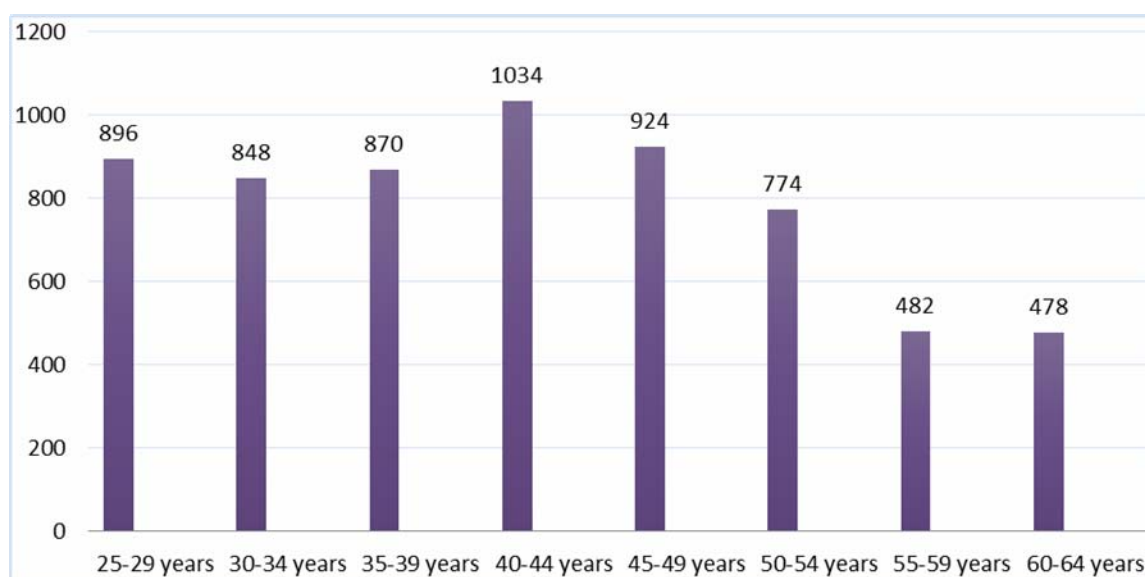
The lab staff (the anatomo-pathologist, the biologist specialized in Citology, the lab assistants) uses the following equipment: optic microscope, manual coloring stand, laminar air chamber, PC, printer, refrigerator, centrifuge, recipients for the used mixtures, protection equipment, lab reagents. The specimens are standard tested in the Cytology laboratory, the smears are already fixed, and submitted to colouring and microscopic examination. The registered slides are arranged on steel stands, in batches of 20, in order to be stained in the staining kit. The only accepted smear is the PAP one, that helps the cytologist depict various types of cells and their structure. The pacient's medical file is read before the microscopic examination of the slides.

There were several acceptance criteria for the screening program: age between 25-64 years old; negative results in the beginning of this trial; pacients that were not previously diagnosed with cervical abnormalities; pacients undiagnosed with hysterectomy or cervical tumor. The smears are examined, the results interpreted, and registered to be statistically processed. The pacients are monitored on a longer time period.
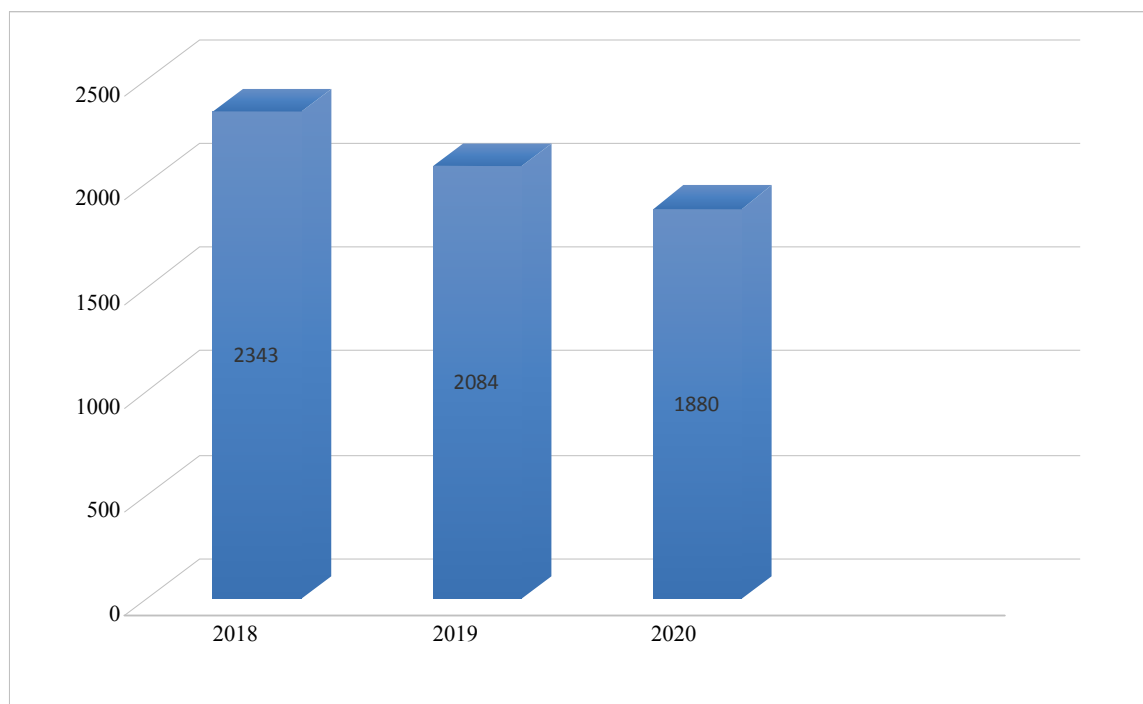
RESULTS AND DISCUSSIONS

During 2018-2020 there were examined 6306 cytological tests at the Roman Emergency Town Hospital (graph 1). For 192 pacients, there were depicted alterations of the cervical cytology.

As displayed in the graph 1, the most numerous pacient group is comprised by women aged 40-44, followed by 45 - 49 years old, then aged 25-29, 35-39, and the least numerous tests belong to the age segments 55-59, and 60-64 years old, respectively. There was a decrease of testing within the screening program for the time range 2018-2020, based on the changes induced by the coronavirus pandemic (graph 2).
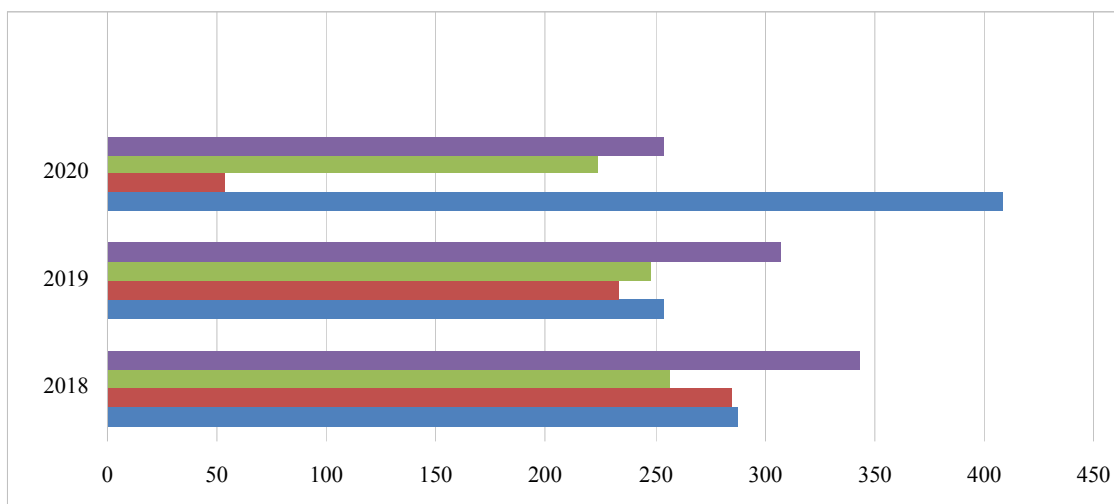
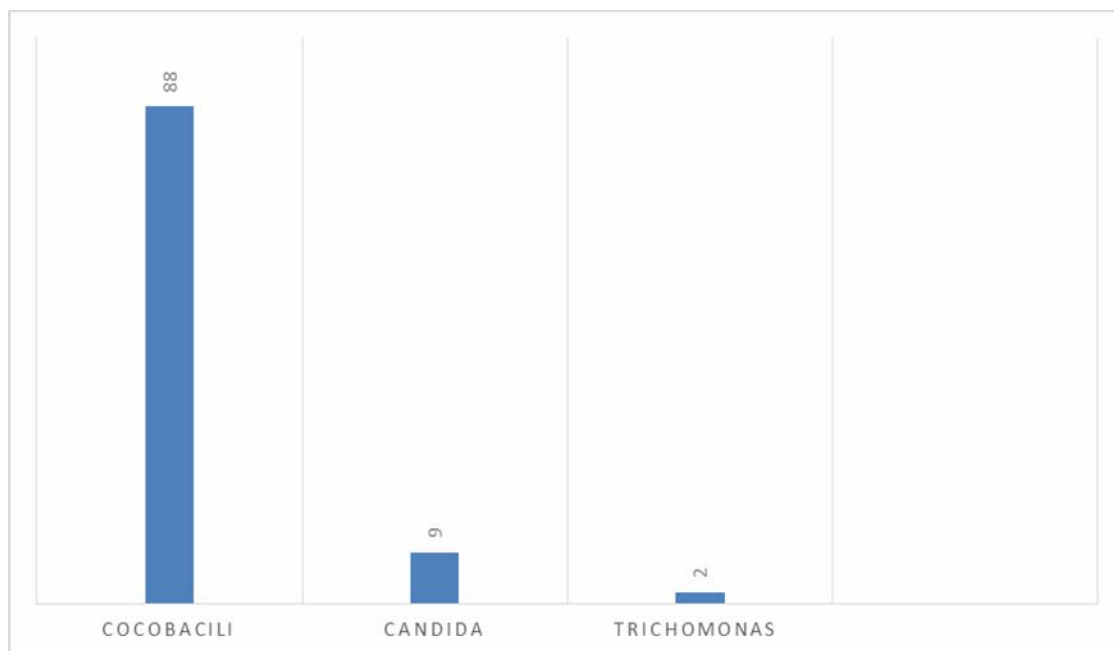Graph 1. Distribution of smears on age segments between 2018 and 2020

Graph 2. The number of tests examined between 2018-2020

The chart in graph 3 displays a range of testing for each semester of every year in the target population of the Roman Hospital. An obvious decrease in the second semester of 2020 was registered, compared to the first semester, in which the screening came first within the Romanian health system. Precancerous conditions of the cervix are changes in cervical cells that make them more likely to develop into cancer. Of a total of 6303 tests, 5200 patients displayed either infections or inflammation, that, untreated as it should, may alter the epithelium and cause precancerous cervical lesions, therefore their diagnosis and treatment is extremely important. The majority of negative results smears included inflammatory altered cells, mainly caused by a pathogen. Fewer cells of 50-64 year old pacients were characterized by athrophy. The most common is the coccobacilli infection (88 %), followed by the *Candida albicans* infection (9%), than *Trichomonas vaginalis* (2%). *Actinomyces* and *Herpes Simplex* virus were not detected among the etiologic agents (graph 4).

Graph 3. The Pap test ratio for the investigated subjects during 2018-2020

Graph 4. The distribution of pathogens for the investigated subjects

Of all the tested pacients, 154 women displayed a normal cytology, 5200 had infections and characteristic inflammation, 757 presented cervico-vaginal atrophy. There were no cases of alterations caused by radiotherapy, intrauterine devices, or following a hysterectomy. The inflammatory processes may be triggered by bacteria - coccobacilli (fig.2), fungi - *Candida albicans* (fig.1), parasite-induced-*Trichomonas vaginalis* (fig.3), or viral - HPV or HSV (fig.4), or by a non-specific infection. The epithelium inflammation may evolve acutely or chronically, inducing cytologic atypia. The inflammation affects the entire cell, that may differ in size, shape, nucleus, or cytoplasm. These alterations may mislead the correct diagnosis, if it is either inflammation or dysplasia, especially nucleus hyperchromasia, anisokaryosis or pyknosis. The nucleolus is present in inflammation and absent in case of dysplasia.

Dysplasia (fig. 5) is a precancerous condition that may sometimes become cancer [7, 8]:

- 70% of pacients display an infection od basal and metaplsisc cells (non-keratinizing dysplasia or metaplasia);
- 20 % of pacients display a preexisting inflammation and skip the dysplasia phase, the inflammation causes basal cell hyperplasia and small cell CIS (carcinoma *in situ*) appears;
- 7% of all cases are characterized by keratinizing dysplasia;
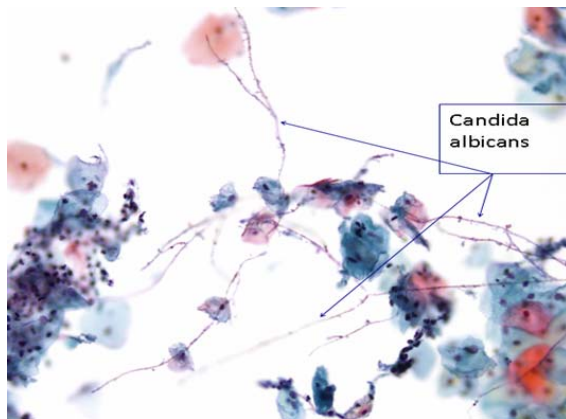- in 3% of patients, the storage cells are affected and cause glandular dysplasia.

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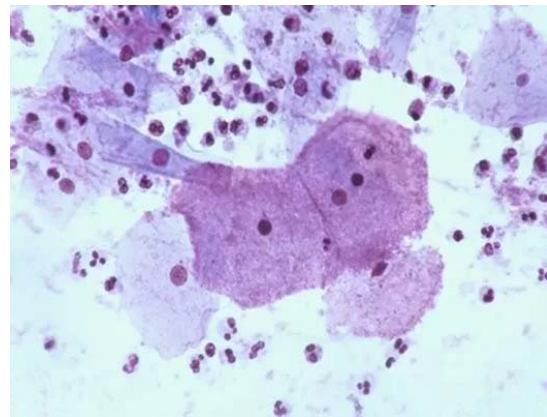Fig. 1. Cytologic slide - display of *Candida albicans*
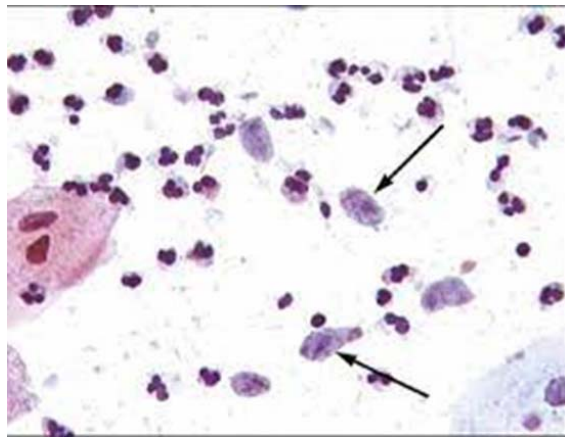

Fig.2. Cytologic slide - display of cocci

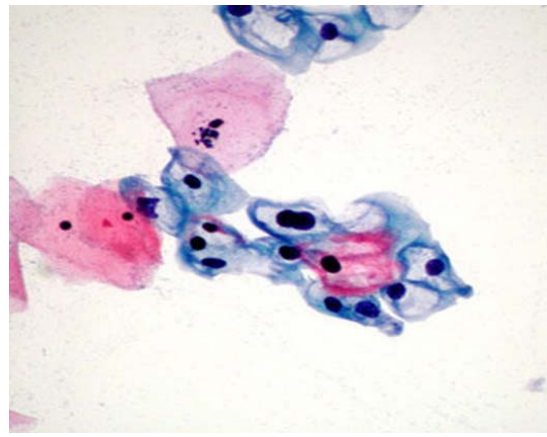Fig. 3 Stained slide - *Trichomonas vaginalis*
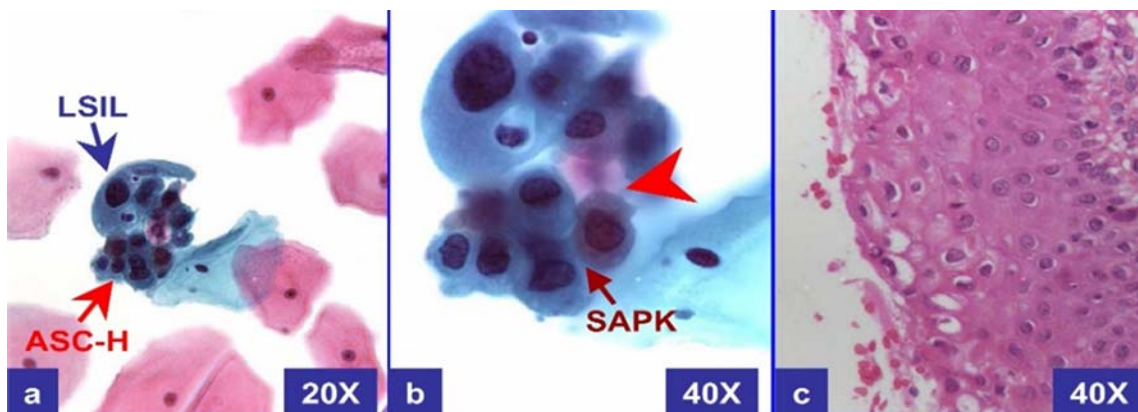

Fig. 4 Stained slide - HPV
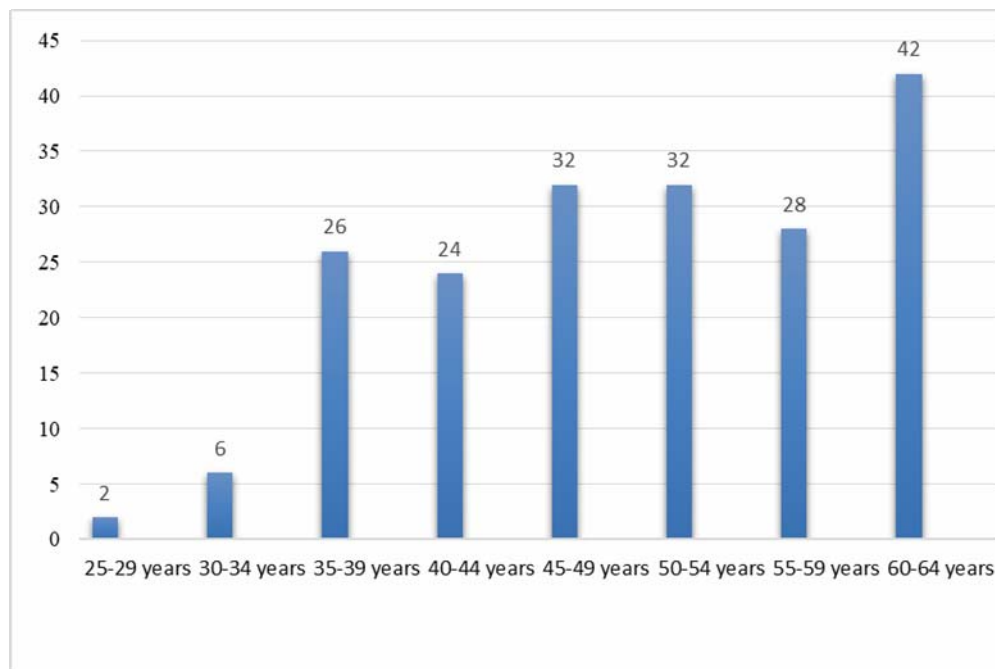

Fig. 5. Cervical dysplasia

Out of all the tests examined during the three years, 192 were positive. The array on age groups is shown in graph 5; the pacients aged 60-64 was the least tested, and it displayed alterations of cervical epithelium more frequently. A significant number of lesions were depicted in the pacients of the following age segments: 45-49, and 50-54 years old, respectively (start average age for cervical cancer).

The young women (25-29, and 30-34 years old) were least affected. The average age for diagnosis is about 52, nevertheless lately it occurred earlier (35-39 years old).
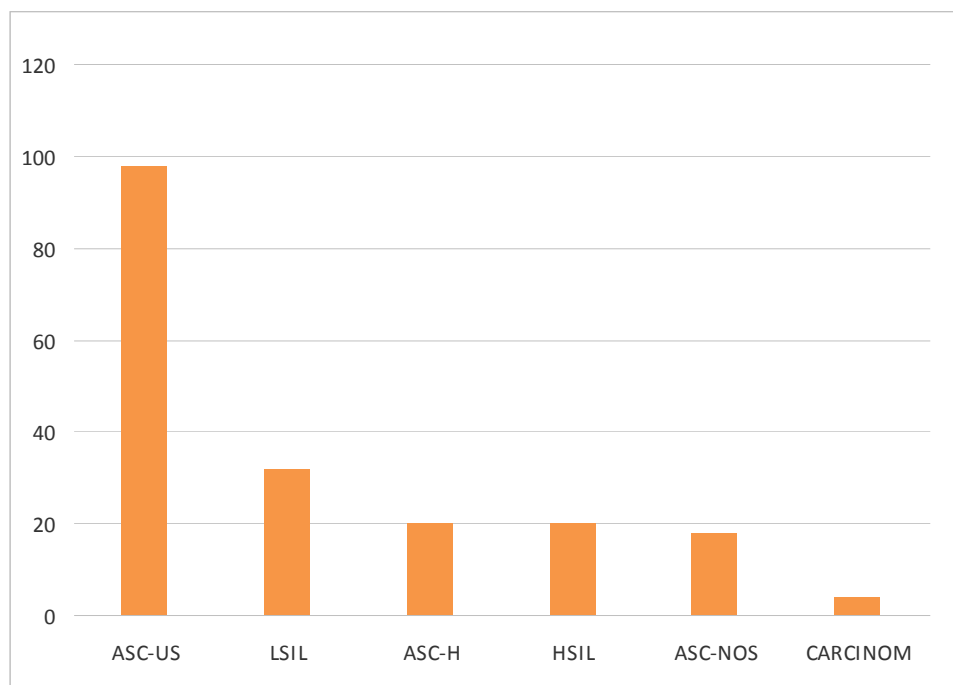
Regarding the distribution of positive cases, the majority are represented by atypical squamous cells undetermined significance (ASC-US) - 98 cases (51%) of the total 192 positive ones, followed by

LSIL (17% - 32 cases), then by ASC-H and HSIL, 20 cases each; the scarce were AGC-NOS (18 cases (9%)), and squamous carcinoma with only 4 cases (2%), (graph 6).
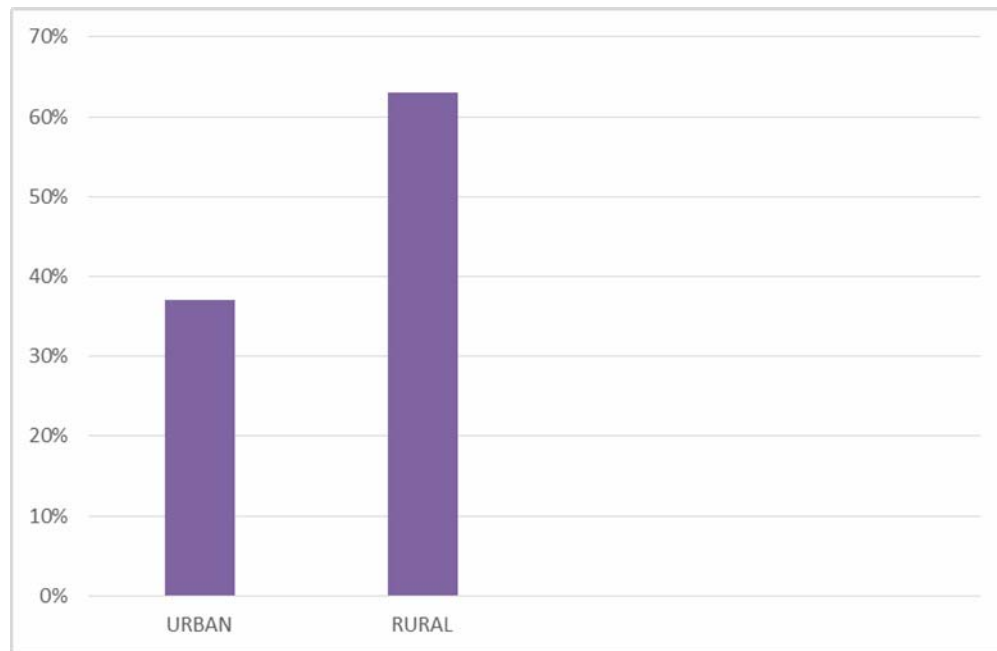
The malignity ratio rural: urban is 1.7:1. The genital cancers start around the age of 60-64. The statistics show higher occurrence of cervical cancer for women in the rural area. (graph 7).

Graph 5. The range of positive tests by age segments

Graph 6. The array of pacients that tested positive as reported to diagnosis groups

Graph 7. The range of positive cases (rural versus urban areas)

Considering each type of dignosed lesion, the graphs displayed a high incidence of positive pacients for women in the rural areas, and the squamous carcinoma was only detected for this environment. The explanation resides in their way of living, diet, smoking, sex life early debut, multiple partners, young age births. 63% of the positive cases belong to rural environment, and 37% to the urban one.

The occurrence of cervical cancer by age is: 30-59 years old – intraepithelial lesions with squamous atypia - 91%, glandular atypia 9%, as opposed to the 60-64 age group characterized by squamous lesions in 90% of all the positive cases. The only neoplasia found in women past 70 is only vaginal or vulvar. The incidence of cervical cancer between 45-49 years old is higher than for women younger than 40, peaking at 60-64 (less tested). The detected lesions are more advanced for the latter age group, unlikely in young women, mainly displaying early stages lesions. These results prove the necessity of enhancing the screening programs for mature women aged 40-50 years old, in view of an early diagnosis of intraepithelial cervical lesions.

There are three paths in the evolution of these lesions: regresion, persistence, and turning to neoplasms:
CIN I--- CIN II--- CIN III---CIS ---INVASIVE CARCINOMA
The time span is very large to to CIS stage (10 years), and other 10 years of cell evolution to invasive cancer. CIN I may turn into CIS, though it disappears spontaneously in 50% of cases. Considering this process, the tests should be ran starting with the age of 25-30 years old, in order to cure the illness properly, and avoid the occurrence of cervical neoplasm.

The early treatment in case of ASC-US consists of topic anti-inflammatory medication. If persistant lesions, there are some recommended medical procedures: electrocauterization, cryotherapy, laser vaporization, check ups every 6 years. If the colposcopy is not relevant, the excision will be surgically performed, as well as conization after histopathological examination, or cervical amputation.

CONCLUSIONS

The cervical cancer is a severe condition, although treated in early stages may prevent death of pacients. All the above may be accomplished by means of a proper screening program.

The lesions of the cervical epithelium may be identified using the Pap test, that is a screening method to detect the precancerous alterations and the early stages of invasive cancer.

Women should be aware of the benefits of the testing method in cervical cancer.

The present study displays the results of the Pap screening in Roman and its neighbouring villages.

Of all the tested pacients, 154 women displayed a normal cytology, 5200 had infections and characteristic inflammation, 757 presented cervico-vaginal atrophy.

The inflammatory processes may be triggered by bacteria - coccobacilli, fungi - *Candida albicans*, parasite-induced - *Trichomonas vaginalis*, viral - HPV or HSV, or a non-specific infection.

Of a total number of 6303 tests, 192 were positive, the majority of patients with early lesions (ASC-US), and living in rural regions.

51% of the positive pacients displayed ASC-US, 17% LSIL, 11% ASC-H, 10% HSIL, 9% pacients AGC-NOS, and 2% were diagnosed with carcinoma in situ.

The malignity ratio rural: urban is 1.7:1.

There was registered a decrease of the cervical cancer occurrence in Romania, due to the screening programs, and the informing of women on the testing benefits.

ABSTRACT

The Pap test serves for diagnosis purposes, recommended by the gynecologist or for the early depict of precancerous lesions. Women are assessed every 3 years by means of the Pap test, revealing the benefits of the screening programs. The main cause that induces this type of cancer is the HPV infection 95%. Cervix cancer, along with melanoma and breast cancer, may be prevented by early diagnosis and treatment. Early diagnosis for this disease is a key factor to achieve therapeutical success, considering the outburst of pacients.

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AUTHORS' ADDRESS

BÂRCĂ ROXANA – ELENA - Roman Emergency Hospital, Anatomo-Pathology Department, Roman, Romania,
e-mail: roxanikrom@gmail.com;

MAFTEI DIANA – ELENA - 'Vasile Alecsandri' University of Bacău, Faculty of Sciences, no 157 Mărăşeşti Street, Bacău, Romania, e-mail: diana.maftei@ub.ro.