

Analysis of the results of national screening programs for early active diagnosis of cervical cancer and proposal of improvement strategy

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Abstract

In the case of all types of cancers, it is universally valid that early detection significantly improves the survival rate. In the case of cervical cancer, this statement extends to more advanced forms where the proper treatment is associated with significant disease control. The prevention and control of cervical cancer depend significantly on national policies and implemented guidelines. Also, informing targeted population is a key point of a successful prevention program. There are two key points of a screening program for directing it to success. First, educating health carriers and the general population on the importance of detecting preinvasive lesions and early stages of cancer and, secondly, increasing the accessibility and affordability of a proper medical approach. Our proposal includes a database notification program which identifies and highlights the patients suitable for HPV vaccination and those for cervical cancer screening through cytology. The idea of this program can be adapted and used for any existing database and for any other screening programs.

Keywords: cervical cancer, screening, strategy, database

Submission date:
16.07.2021
Acceptance date:
29.07.2021

Rezumat

În cazul tuturor tipurilor de cancer, este universal valabil faptul că detectarea precoce îmbunătățește semnificativ rata de supraviețuire. În cazul cancerului de col uterin, această afirmație se extinde la forme mai avansate pentru care tratamentul adecvat este asociat cu un prognostic semnificativ mai bun. Prevenția și managementul pacienților cu cancer de col uterin depind în mod semnificativ de politicile naționale și de liniile directoare implementate. De asemenea, informarea populației vizate este baza unui program de prevenție de succes. Există două puncte-cheie ale unui program de screening pentru ca acesta să fie de succes. În primul rând, educarea responsabililor din sănătate și a populației generale cu privire la importanța detectării leziunilor preinvazive și a diagnosticării stadiilor incipiente de boală și, în al doilea rând, creșterea accesibilității pentru investigațiile medicale adecvate. Propunerea noastră cuprinde un program de notificare ce include o bază de date care identifică și evidențiază pacienții potriviți pentru vaccinarea HPV și, respectiv, pentru screeningul cancerului de col uterin prin citologie. Ideea acestui program poate fi adaptată și utilizată pentru orice bază de date existentă și pentru orice alt program de screening.

Cuvinte-cheie: cancer de col uterin, screening, strategie, bază de date

Analiza rezultatelor programelor naționale de screening pentru depistarea activă precoce a cancerului de col uterin și propunere de strategie

Suggested citation for this article: Coravu V, Țurcan G, Țurcan N, Grădinaru-Fometescu D, Sajin M, Cirstoiu MM. Analysis of the results of national screening programs for early active diagnosis of cervical cancer and proposal of improvement strategy. *Ginecologia.ro*. 2021;33(3):30-35.

Introduction

Cervical cancer is one of the few types of cancer for which primary prevention, vaccination and secondary prevention, respectively, screening and treatment of precancerous lesions, are known and possible⁽¹⁾. In the case of all types of cancers, it is universally valid that early detection significantly improves the survival rate. In the case of cervical cancer, this statement extends to more advanced forms where proper treatment is associated with significant disease control. Diagnosed in early stages, cervical cancer associates a five-year survival rate

of 92%; in contrary, the diagnosis in the final stages is associated with a five-year survival rate of only 17%⁽²⁾. With the clear establishment of the etiological agent, namely the infection with high-risk HPV genotypes, the development of the vaccine and the implementation of large-scale screening programs, the expected result was the elimination of cervical cancer from public health problems over generations.

According to World Health Organization (WHO), in 2018 cervical cancer was the fourth most common cancer in women; at that point, an estimated number

of 570,000 new cases per year were declared and, in the same year, 311,000 women died due to cervical cancer⁽³⁾. In the aforementioned context, these are huge numbers. For 2020, The American Cancer Society offers the following estimated numbers: a total of 13,800 new diagnosed cases of invasive cervical cancer and 4290 deaths⁽⁴⁾.

The preponderantly involved ages are 35-44 years old, only 20% of cases occurring in women over the age of 65. The development of cancer before 20 years old is exceptional⁽⁵⁾.

The great majority – about 80% – of HPV infections are autolimited. The recommended European strategy for an efficient screening implies the cytology testing for 25-35-year-old women and, in the context of a positive result, the HPV testing is recommended. For the 35-64-years-old age group, the primary testing focuses on evidencing the signs of persistent HPV infection⁽⁶⁾.

The prevention and control of cervical cancer depend significantly on national policies and implemented guidelines. Also, informing the targeted population is a key point of a successful prevention program. The screening tools, cytology and/or HPV testing should be generally affordable. The primary prevention, respectively vaccination, should be promoted correctly by highlighting the benefits and focused on teenagers (9-14 years old).

In order to stimulate the population to participate, for maintaining a positive functional program, real and positive results should be declared, at regular time

intervals, in order to increase the public confidence in the effectiveness of prevention and the screening programs.

The aim of this article is to analyze the results of national screening programs implemented for early detection of preneoplastic lesions and cervical cancer, as in 2020, according to World Health Organization, in Romania cervical cancer had an estimated number of new cases of 3380, representing 7.5% of all diagnosed types of cancer in females of all ages (Figure 1).

According to the last reported data, Romania ranks first among European countries in terms of incidence (34.9 new cases/100,000 women) and mortality (14.2 deaths/100,000) of cervical cancer, this rate being four times higher than the European mean incidence⁽⁷⁾.

Results

The National Screening Program for Cervical Cancer in Romania begun in 2012 and was aimed for a period of five years. The targeted population were the women aged 25-64 years old, including a total of 5.4 million women, Romanian citizens, with or without health insurance, who respected the following criteria:

1. The absence of a confirmed diagnosis of cervical cancer.
2. Asymptomatic.
3. The lack of pathologies in personal medical history suggestive for cervical cancer.
4. Cases with congenital or postsurgical absence of cervix uteri were excluded.

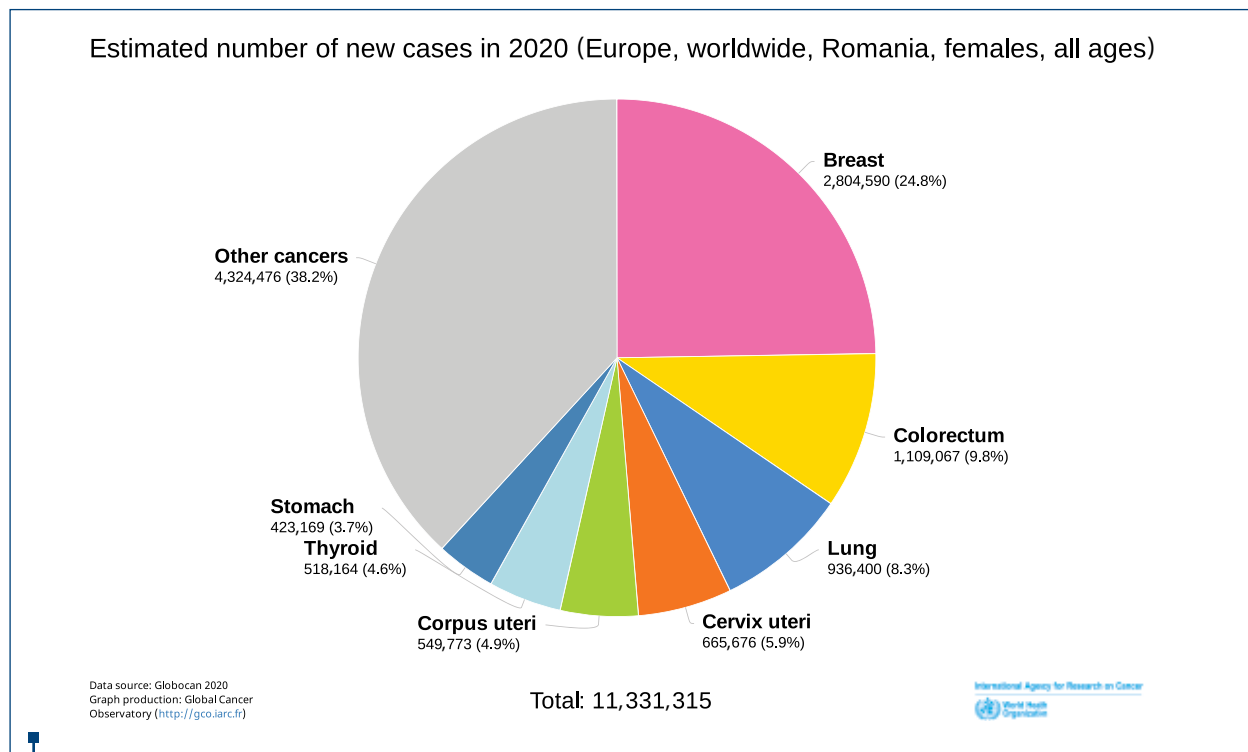


Figure 1. Proportion of cervix uteri cancer among all ages, in females, in Romania, in 2020 (WHO)

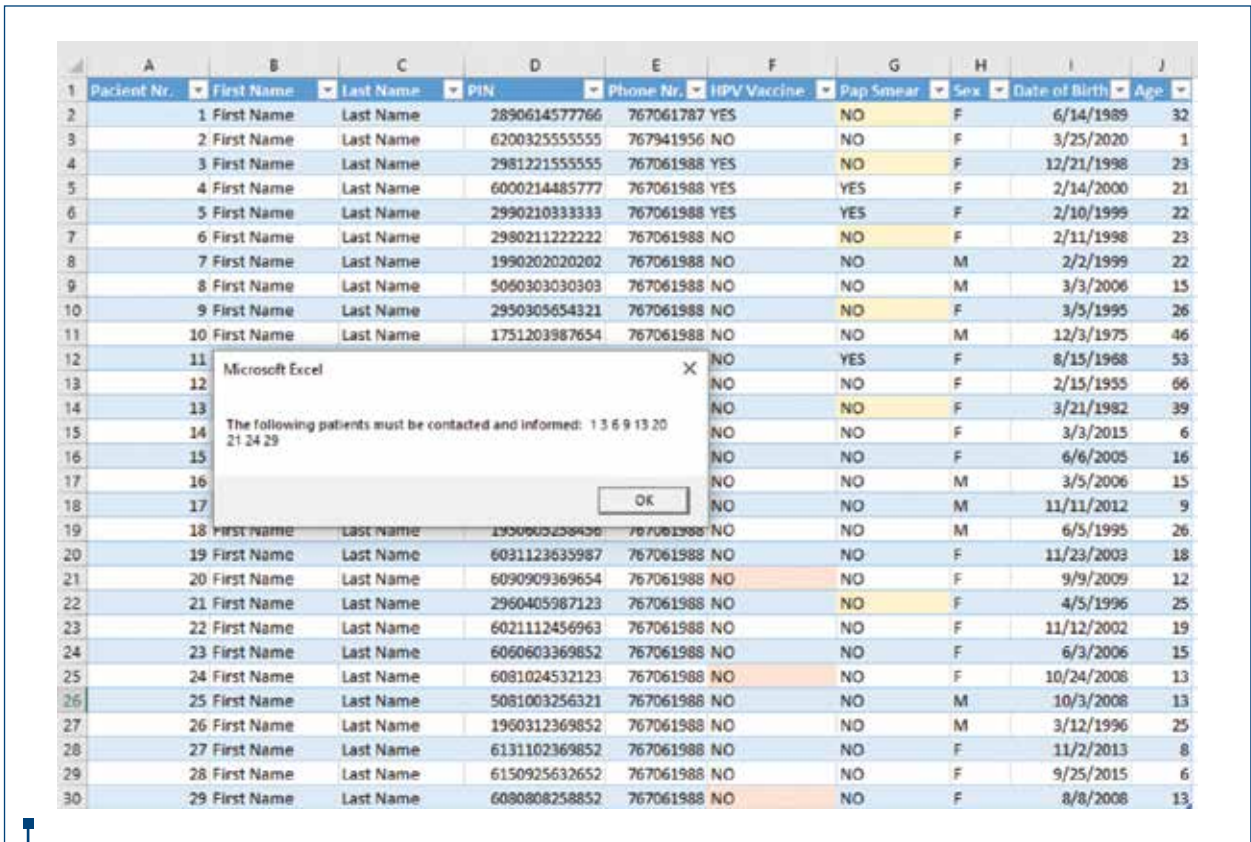


Figure 2. Screenshot of the database notification program for HPV vaccination and cytology testing. In light pink there are marked the patients suitable for vaccination and in light orange those suitable for Pap smear testing. After changing the status in "YES", the software cell becomes unlighted

At the national level, the unit responsible for conducting the program was the National Institute of Public Health, along with other nine regional units. The evaluation of the program was performed by the cancer experts from the World Health Organization and the International Agency for Research on Cancer in 2017. The conclusions of the evaluation were that during the program only 10% (611,630 tests) of the targeted population was assessed, and the program did not include a proper follow-up of the patients with positive results, implicitly with the lack of a well-defined process for

diagnosis and treatment. From the managerial point of view, the program was characterized by inappropriate monitoring and evaluation⁽⁸⁾.

Having these conclusions, the experts made some key recommendations regarding the reintroduction of HPV vaccination in the immunization program and the inclusion of the adequate management of patients with abnormal cytology as a part of the screening program.

There are two key points of a screening program for leading to success: first, educating health carriers and

Table 1 Precancerous cervical lesions (Bethesda system)

Atypical squamous cells	of undetermined significance (ASC-US) cannot exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL)	HPV/mild dysplasia Cervical intraepithelial neoplasia (CIN 1)
Hig-grade squamous intraepithelial lesion (HSIL)	Moderate and severe dysplasia ■ Carcinoma <i>in situ</i> (CIS) ■ CIN 2 ■ CIN 3

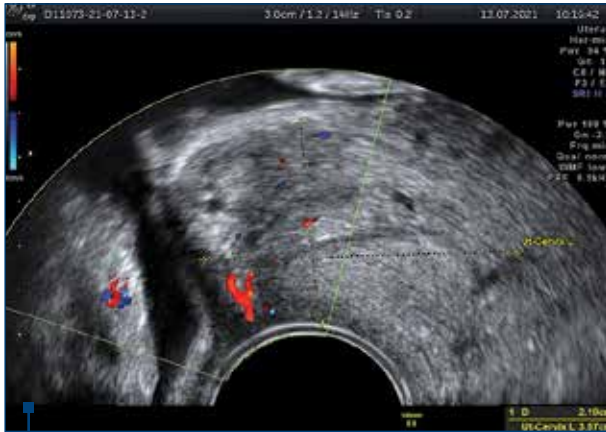


Figure 3. Sonographic aspect of the cervix in a 26-year-old patient with the cytology diagnosis of uterine cervix carcinoma

the general population on the importance of detecting preinvasive lesions and early stages of cancer and, secondly, increasing accessibility and affordability of a proper medical approach⁽⁹⁾.

Having these data, we propose a strategy for facilitating the selection of patients aged and clinically suitable for primary and secondary screening, respectively vaccination and cytology. Our proposal includes a database notification program which identifies and highlights the patients suitable for HPV vaccination and those for cervical cancer screening through cytology. The idea began from one important deficit of the national screening programs for the early active diagnosis of cervical cancer, which was the lack of information. It is a well-known fact that in Romania the medical staff is insufficient to cover the requirements of a perfectly functional system. Thus, our strategy is based on a simple tool that alerts the physician every



Figure 4. MRI aspect of the cervix uteri, with endocervical discontinuation in a 26-year-old patient with the cytology diagnosis of uterine cervix carcinoma



Figure 5. Macroscopic aspect of the cervix uteri, post-excision, in a 26-year-old patient with the cytology diagnosis of uterine cervix carcinoma

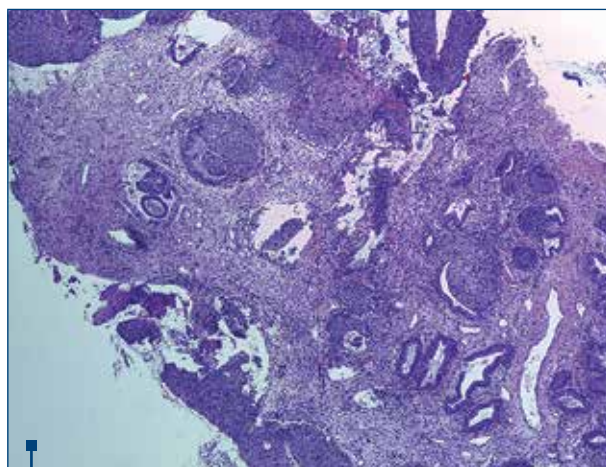


Figure 6. G2 microinvasive keratinized squamous cell carcinoma with intraglandular extension – overview. HE 4X in a 26-year-old patient



Figure 7. Colposcopy image of a newly diagnosed cervix uteri adenocarcinoma, in a 63-year-old patient

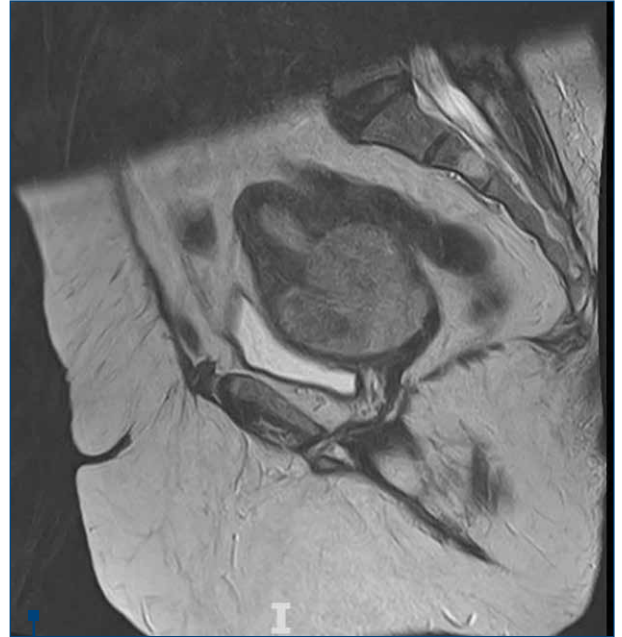


Figure 8. MRI aspect of the cervix at the moment of presentation. Cervix uteri adenocarcinoma in a 63-year-old patient

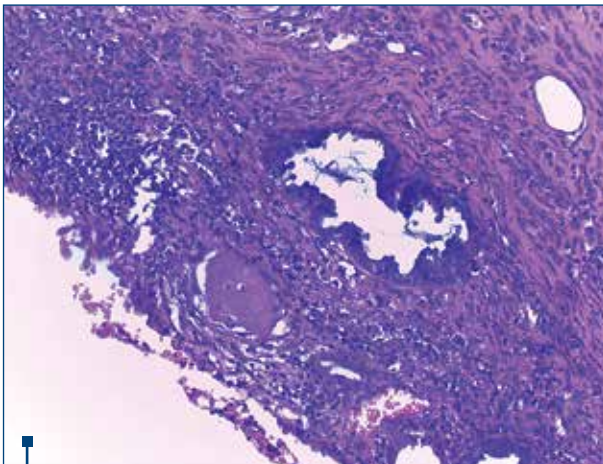


Figure 9. Microscopic aspect after appropriate oncological treatment, post-surgery. Reactive endocervical glands, pseudostratified nuclei. HE 40X

time he must access the patients he takes care of. The message is simple: “The following patients must be contacted and informed”, and the software cell corresponding to the investigation recommended is highlighted in a specific color. In order for the program to be functional, it is mandatory to register the personal identification number, based on which the sex of the patient is automatically noted and the age of the patient is calculated. Also, having the contact telephone number of each patient is a must (Figure 2).

The idea of this program can be adapted and used for any existing database and for other screening programs.

Discussion

The European recommendations for cervical cancer screening are represented by Pap smear performed at 21 years old or after the beginning of sexual activity, adapting the period of retesting according to the medical history and previous results. It is considered that a successful cervical cancer screening program can reduce the incidence, the morbidity and the mortality of this pathology with approximately 90%. Precancerous lesions (Table 1, Bethesda system) that precede the progression to cervical cancer are found in approximately 3.5% of cases. These lesions are treatable with minimally invasive surgical procedures and the regular specialized follow-up of these cases is essential.

According to the Romanian Society of Obstetrics and Gynecology, the latest recommendations regarding the screening for precancerous cervical lesions include, as the first step, the cytology, as it reduces significantly the incidence of cervical cancer and the mortality related to it, and it implies much lower costs compared to HPV cotesting⁽¹⁰⁾.

Furthermore, in order to increase the attention on this topic, we present the summary of three referential cases from our clinical experience.

Case 1. A 26-year-old female diagnosed with stage IA2 nonkeratinized microinvasive squamous cell carcinoma of the uterine cervix (Figures 3, 4, 5 and 6).

Case 2. A 63-year-old patient diagnosed with stage IIB cervix uteri adenocarcinoma managed through oncological treatment and surgically, with favorable outcome (Figures 7, 8 and 9).

Case 3. A 63-year-old woman with HPV 18 infection, diagnosed with poorly differentiated squamous cell carcinoma of the cervix (Figures 10, 11 and 12).



Figure 10. Colposcopy image of a 63-year-old woman with abnormal Pap smear result (H-SIL). Extensive aceto-white epithelium with mosaic areas



Figure 11. MRI aspect of the cervix of a 63-year-old woman with abnormal Pap smear result (H-SIL), with an endocervical restrictive, diffuse mass

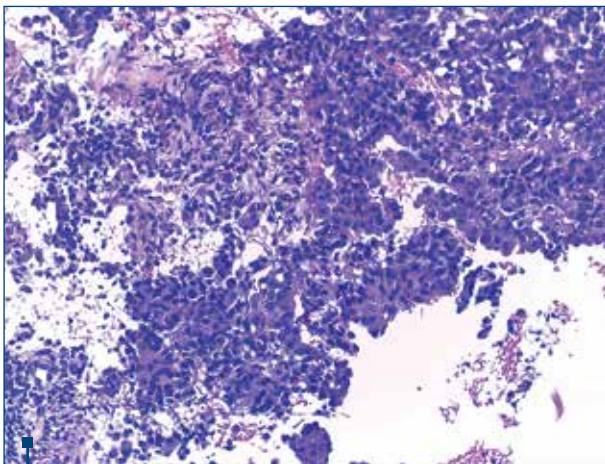


Figure 12. Microscopic aspect after surgical excision. Large cell squamous cell carcinoma, G3, undifferentiated - detail. HE 40X

Conclusions

Only 33% of the targeted population knew about the existence of the Romanian national screening program for the early detection of cervical cancer. Even though the testing was offered for free, only 6.3% of these women had benefited from it.

We consider this, along with Romania's leading position among European countries in terms of incidence and mortality of cervical cancer, an alarm signal.

Our hope is that the proposed strategy will be a first step in selecting and informing patients regarding the possibility of HPV vaccination and screening for precancerous cervical lesions. ■

Conflict of interests: The authors declare no conflict of interests.

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