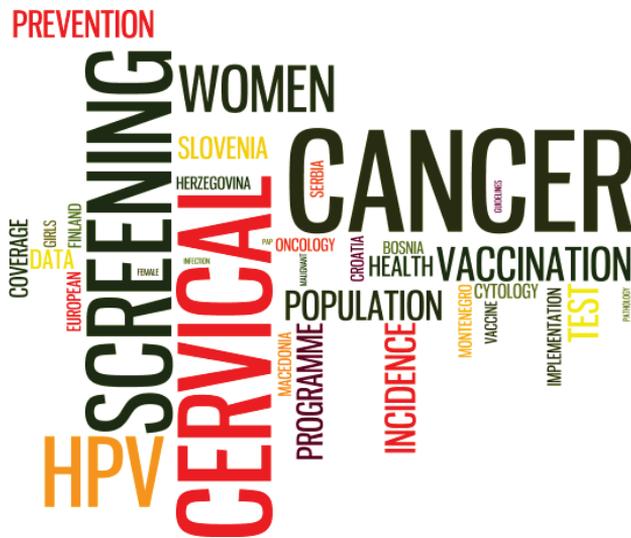


Slovenian Society for Gynaecological Oncology, Colposcopy and Cervical Pathology,

National Programme and Registration ZORA - Institute of Oncology Ljubljana,

Association of Slovenian Gynaecologists and Obstetricians



Prevention of cervical cancer in Balkan region and in Finland in the HPV era

Brdo Congress Centre, Slovenia

13. november 2019

Book of proceedings of the 4th Regional symposium on prevention of
cervical cancer

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in the HPV era

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Prevention of cervical cancer in Balkan region and in Finland in the HPV era: An introduction to brief reports from representatives of different countries

Špela Smrkolj, Urška Ivanuš

Dear participants of the 4th Regional Symposium on Prevention of Cervical Cancer,

We are glad that the tradition of regional meetings of experts working hard for cervical cancer prevention in our region continues and that the 4th meeting will take place in the beautiful Brdo Estate in Slovenia. Slovenian Society for Gynaecologic Oncology, Colposcopy and Cervical Pathology and National Cervical Cancer Screening Programme ZORA work hand in hand to fight this deadly yet almost completely preventable disease in Slovenia. We believe that working together is the key to success and the only way to reach the World Health Organisation's 2030 goals toward elimination of cervical cancer as the public health problem which are that 90% of girls fully are vaccinated against HPV by 15 years of age, 70% of women screened for cancer screening in a high quality programme at least at 35 and 45 years of age and that 90% of women with identified cervical disease receive treatment.

In the mid November days in 2019 we will exchange knowledge and experience in the field of cervical cancer prevention in the region and we will learn from each other. Successful cervical cancer prevention needs a good organisation and management, but also enthusiastic professionals with the good insight in the current evidence that are willing to push things forward in the evidence based way and adapted to local context, even when it seems that nothing can be done.

Dear colleagues gynaecologists, pathologists and epidemiologists from Croatia, Bosnia and Herzegovina, Serbia, Monte Negro, North Macedonia and Slovenia we come from different countries and different specialisations. But we do share a common history and common goal of the elimination of cer-

vical cancer in our region. And we all believe it can be done easier, if we will continue to work together!

We wish that the symposium will meet you expectations and that we will all go home with new ideas and boosted motivation how to approach the situation in this field in our own countries.



Associate Prof. Špela Smrkolj, MD, PhD
President of the Slovenian Society for
Gynecologic Oncology, Colposcopy and
Cervical Pathology



Urška Ivanuš, MD, PhD,
Head of Cervical Cancer Screening Pro-
gramme and Registry ZORA

Prevention of cervical cancer in Croatia

Dražan Butorac

What is the incidence of cervical cancer in the country?

Crude incidence rate 2018. 12,3; 2018. 266 new cervical cancer cases

How is cervical cancer screening program organized? Does it fulfil criteria for the organised population-based programme?

An opportunistic screening program based on the Pap test has been used in Croatia since 1953.

In this moment we are preparing a new organized screening program based on the combination of pap smear and hpv tests depending on age groups.

What are the age range of the target population and the frequency of screening?

There are three groups: 20-29 years, 30-34 years, and 35-64 years

- First - group Pap test,
- second co test Pap HPV,
- and third group HPV test

What test is used in the primary screening? Do they use liquid-based technology?

Pap test, HPV test, and co test.

We will not use liquid-based technology in program

How is the invitation system organised? What is the coverage of the target population with invitations? What is the coverage of the target population with screening tests?

We will see

HPV test used in the country and how is it used?

HPV for women in third age group 35-64 years , and cotest with Pap in second groups

How is vaccination against HPV organised? What is vaccination coverage? Do you vaccinate girls and boys

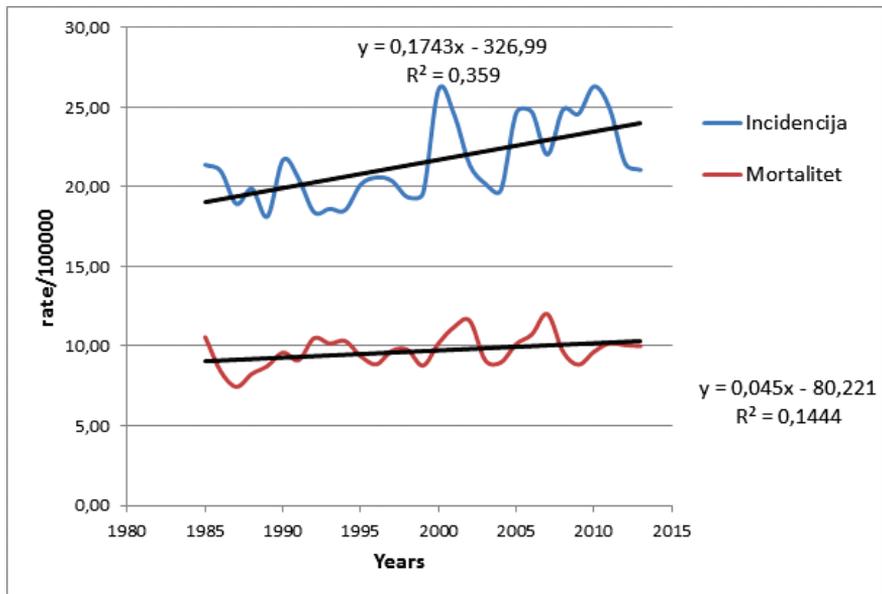
In 2019, the target group for vaccinations are girls and boys, eighth grade students. Due to more vaccines are recommended for high school girls and boys. Depending on the county, the response to the vaccination is 2-80%. On average 15%

Prevention of cervical cancer in Serbia

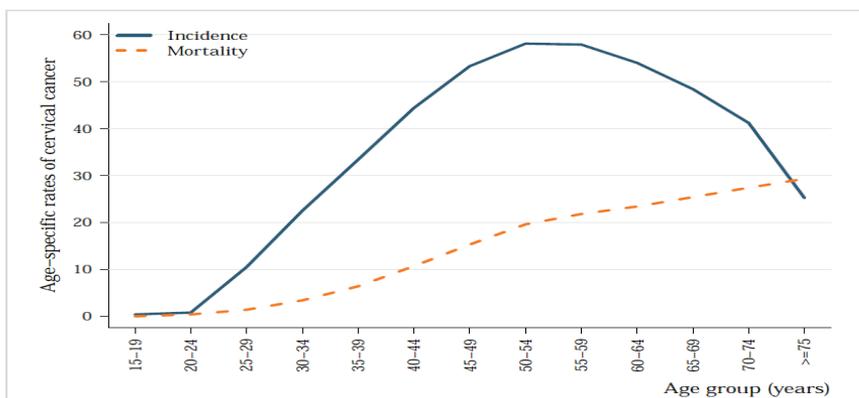
Aljoša Mandić

Oncology Institute of Vojvodina, Serbia

Cervical cancer is still one of the main problems in female population in Serbia. The incidence of cervical cancer in Serbia is among the highest one in the Europe. According to our National Register, cervical cancer is on fourth places among female cancers in Central Serbia but also in Vojvodina, North part of Serbia, with incidence rate 20-23/100.000. Graph 1. and 2



Graph 1: Linear-trend of incidence and mortality rate in Vojvodina



Graph 2. Comparison of age-specific cervical cancer incidence and mortality rates in Serbia (estimates for 2018)- ref.4

About 1,327 new cervical cancer cases are diagnosed annually in Serbia and the 2nd most common female cancer in women aged 15 to 44 years in Serbia.

About 551 cervical cancer deaths occur annually in Serbia. Cervical cancer ranks as the 6th leading cause of female cancer deaths in Serbia and the 2nd leading cause of cancer deaths in women aged 15 to 44 years in Serbia.

Despite the promotion of the cervical screening program, still we have opportunistic one, and small number of community-health center is covered with full capacities to organized such a program in their communities. The cervical cancer screening program is based on conventional PAP smear and the cornerstone for implementation of the program are the communities-health centers with their gynecologists and cytoscreeners.

According to our national screening program the target population that have to be screened are about 2.100.000 women, age 25 to 64, every three years. Co-testing with HPV test is not calculated but, HPV testing can be performed in triage in ASCUS, PAP smears. So, HPV testing is recommended in our National guidelines for prevention, detection and treatment of cervical cancer, mostly as triage test.

The coverage of the target population is about 35-40%,. According to screening program, target population will be called by post with brochure about importance of screening, schedule time for visiting the gynecologist with telephon number of community health center. Plan is to cover 700.000 in one year with our goal to cover about 75% of the target population

(550.000). In Serbia 15 Central laboratory are organized for screening program and according to standards we need 4-5 cytoscreeners with full time job and one supervisor in each center.

The primary prevention program for eradication of cervical cancer by implementation of HPV vaccination is still at the beginning and still we do not have plan for implementation. The HPV vaccination is in National vaccination calendar as recommended one, but we still do not have plan how to implement organizing vaccination program. The Quadrivalent and Bivalent HPV vaccines are registred in Serbia but the Health Insurance Fund does not cover them; they are quite expensive for ordinary citizens, and not easily obtained in clinics and pharmacies. In study Mitrovic J et al. quantitative research was conducted through the internet in December of 2016, using the survey method. Participants in the study were parents whose children were candidates for the vaccination. The research has shown that nearly one third of respondents do not know what HPV is, and about the same number of respondents know that HPV causes cancer. With adequate awareness of safety, 97% of respondents would decide to vaccinate their children but the main problem according to results was cost of vaccinae and only 39% of parents could afford the vaccination. Consequently, 97.5% of the respondents would option for vaccination in the case that it is free. Authors concluded that the social networks is the main stone in the campaign focuses on the raising awareness of the need for HPV vaccination and cancer prevention, including disseminating information to the target population. According to this and similar studies here in Serbia target population is still need more informations about HPV vaccination and the role of parents and health workers is crucial, as the vaccine is not mandatory, and parents' approval is required but also the government of Serbia, have to make a great steps for health promotion and disease prevention. The governments of the European Union countries, as well as the government of Serbia, currently only spend a small part of the health budget for health promotion and disease prevention – around 3%. Will it be enough for all these very important pre-steps to spread an information before decision to implement HPV vaccination to buy it and to cover as much as it is possible of target population. We can not separate information and promotion programs and our wish to get coverage that will justify the cost-effectiveness of the vaccination program.

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Prevention of cervical cancer in Republic of N. Macedonia

Goran Dimitrov

Crude incidence rate of cervical cancer in the Republic of North Macedonia was 14.5. About 151 new cervical cancer cases are diagnosed annually in Macedonia (2018). Cervical cancer ranks as the 6th leading cause of female cancer in Macedonia. Cervical cancer is the 3rd most common female cancer in women aged 15 to 44 years in Macedonia.

About 59 cervical cancer deaths occur annually in Macedonia (2018). Cervical cancer ranks as the 11th leading cause of female cancer deaths in Macedonia. Cervical cancer is the 5th leading cause of cancer deaths in women aged 15 to 44 years in Macedonia. [1]

Based on the specified screening age range (24-60 years), the population estimates for Macedonia in 2013 indicate the total eligible cervical screening population is $\approx 516,000$ women. Therefore, using a 3-year screening interval, the total annual target population would be $\approx 172,000$ women. [2]

Cervical screening has also been funded by the government since 2006 when a program was established giving every women the right to voluntarily access free of charge screening through public hospitals. However, the initial cervical screening participation rates were low so this service was transferred to PHC (Primary Health Care) gynecologists in 2010, who were also given responsibility for sending letters of invitation to eligible women registered with the HIF (Health Insurance Fund) and assigned to their practices. Approximately 90% of Macedonian population is registered with the HIF so this system would ensure the majority of women aged 24-60 (the cervical screening age range) receive an invitation. However, no other elements of an organized cervical screening program have yet been implemented. [2]

The type of screening test used in the Republic of N. Macedonia is not uniform: 80% of the testing is done with a conventional Pap smear, and 20% with liquid-based cytology. Cytotechnologists and cytopathologists at 12 government based or private cytology laboratories use modified Bethesda

classification to evaluate cervical smears; however, there is no quality control monitoring program for cytology laboratories in the country. [3] The coverage of the target population of women has been relatively low (estimated on 15–25%), since the beginning of the opportunistic screening in 1967 till nowadays (2018). The initial try for organized screening in 2012 was characterized with a very low response rate to invitation letters (10–15%) and this correlates well with estimates that only 20,000 women were screened, compared to the “projected” total annual target of 172,000 women. [2]

Although new updated screening Guidelines have been produced at the end of July, 2018 by an expert group formed by the Macedonian Society for Cervical Pathology and Colposcopy, Ministry of Health, Health Insurance Fund, UNFPA-Macedonia and other stakeholders there has not been any signs for its implementation. The emphasis was on HPV testing as primary screening tool.

The use of HPV testing is still for triage of women with borderline or abnormal cytology results. Recommended and reimbursed indication for HPV testing in addition to borderline and low-grade cytology is also prediction of the outcome after treatment of CIN2+ (test of cure). HPV testing is performed in government-based or private microbiology/virology laboratories, mostly by in-house PCR tests.

Both the quadrivalent and bivalent vaccine have been registered in Republic of North Macedonia: the quadrivalent one since 2007, and the bivalent one since 2008. The official recommendations for the use of HPV vaccines were issued in 2007 by the Commission for Contagious Diseases within the Ministry of Health, the Macedonian Association of Gynecologists and Obstetricians, the HPV Society of Macedonia, and the Macedonian Society for Cervical Pathology and Colposcopy. Vaccination was recommended for females between 9 and 26 years old. By a decision of the Ministry of Health from 2008, HPV vaccination was introduced into the national immunization program in October 2009 as obligatory for 12-year-old girls. The quadrivalent vaccine has been used in the national immunization program and is delivered through a school-based program. The catch-up vaccination (2009–2011) was provided for 13 to 26-year old girls and women, and was free of charge and delivered through healthcare facilities. HPV vaccine coverage is monitored at the national level. Coverage for three doses increased from 37% for the 2009/2010 school year to 67% for the 2010/2011 school year, and then declined to 65% for the 2011/2012 school year. [4] In the school

year 2014/2015, with the decision of the Ministry of Health according to a procurement act, a revert to the bivalent vaccine has been done. From that time till now the vaccination is with the bivalent HPV vaccine. In the school year 2015/2016 the coverage even for 2 doses (of the bivalent vaccine) dropped to less than 50%. From June 2018 there is a National recommendation for gender neutral vaccination but still only girls are vaccinated within the school Program.

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Prevention of cervical cancer in Bosnia and Herzegovina

Ermina Iljazović

Abstract: : Bosnia and Herzegovina do not have a population-based registry of malignant disease. Crude incidence rate in B&H was from 23.07 in 2011 to 29.14 in 2015 (per 100.000 women aged 15 and older). B&H has an opportunistic instead of organized screening, based on cytology (mostly conventional Pap test). According to the Strategy of the control, prevention and monitoring of malignant disease in FB&H for 2012-2020, a target population are woman aged 21 to 60 ys. The main aim is to reach women ages from 21 to 60 with recommended guidelines to reach 70% of recommended screening. According to the data from the Retrospective International Survey and HPV Time Trends Study Group (UCC Tuzla lab was participated in the project) the incidence of HPV infection in the cervical cancer tissue was 55.17%, mostly present as single infection. All types of HPV vaccine are registered in B&H, but without any recommendation who should be vaccinated.

Introduction: Bosnia and Herzegovina do not have a population-based registry of malignant disease and the number of new cases, of cervical cancer per year, varies depending on the size of the city or region. According to the recent study in East Europe, based mostly on the estimation from neighbouring countries, crude incidence rate for Bosnia and Herzegovina is 26.6.

According to the report of Public Health Institute in FB&H, incidence of cervical cancer is on the second place, just after breast cancer. In this study we presented preliminary data of approximate cervical cancer incidence in Bosnia and Herzegovina, collected during the period of 2011 till 2015. Crude incidence rate in B&H was from 23.07 in 2011 to 29.14 in 2015 (per 100.000 women aged 15 and older). B&H has an opportunistic instead of organized screening, based on cytology (mostly conventional Pap test). According to the Strategy of the control, prevention and monitoring of malignant disease in FB&H for 2012-2020, a target population are woman

aged 21 to 60 ys. The main aim is to reach women ages from 21 to 60 with recommended guidelines to reach 70% of recommended screening.

Infection with one of the few oncogenic human papillomavirus (HPV) types is a necessary cause of invasive cervical cancer. HPV testing in Bosnia and Herzegovina started at 2000. in Tuzla University Clinical Center, and today is the most experience laboratory in this field and the greatest number of the performed tests (Qiagen HRHPV DNA II). There is not unique data incidence for whole country yet, but most complete and most reliable data (12 years data base) exist for the Tuzla region. According to the data from the Retrospective International Survey and HPV Time Trends Study Group (UCC Tuzla lab was participated in the project) the incidence of HPV infection in the cervical cancer tissue was 55.17%, mostly present as single infection. The frequency of HPV infection among female in the same region is between 31.37% (2001.) and 59.25% (2003.) with more stable rate over the past 6 years (app 45%). The HPV incidence at Sarajevo region is also app 45%, with 47.7% in 2005. and 45.9% in 2011.

All types of HPV vaccine are registered in B&H, but without any recommendation who should be vaccinated.

Conclusion: Presented data are of limited value due to lack of official last census data (2013) as well as lack of data base registry. Although of limited value, these data represent the more relevant results than the available data in the literature.

All those facts underline the importance of the adoption of organized screening programme. One of the first steps of Bosnia and Herzegovina in the near future should be establishing of the registry of malignant disease, Pap test database and setting up well-organized **cervical cancer** prevention programmes as proposed **by** the European Council Recommendation.

Key words: cervical cancer, HPV status, incidence, Bosnia and Herzegovina

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National Cervical Cancer Screening Programme in Montenegro

Đurđica Ostojić

1 What is the incidence of cervical cancer in Montenegro?

The first annual report of the Registry of Malignant Neoplasms of Montenegro presents the basic data on the morbidity and mortality from malignant neoplasms in Montenegro for 2013. The most frequent malignant neoplasms sites in females were:

- breast,
- non-melanoma malignant skin neoplasms,
- colon, rectum and anus,
- trachea, lung and bronchus,
- cervix uteri, and corpus uteri.

Among young adults (20-34 years), the leading malignant neoplasms site in males was testicular neoplasm (42.4%), and neoplasms of breast and cervix uteri were the most frequent sites in females (25.8% each). In the age group 35-49 years, most frequently reported sites in males were lung neoplasms (23.3%), and breast (36.6%) and cervix uteri (20.6%) neoplasms in females.

According the first annual report of the Registry of Malignant Neoplasms of Montenegro, 106 women are diagnosed cervical cancer in 2013. With an age-standardized incidence rate (world standard WHO 2001) of 27,6/100.000 Montenegro has one of the highest cervical cancer incidence rates in Europe.

2 How is cervical cancer screening program organized? Does it fulfil criteria for the organised population-based programme?

National cervical cancer screening program in Montenegro is being conducted in accordance with the recommendations of the European Guidelines for Quality Assurance in Cervical Cancer Screening Second Edition

Supplements, EU 2015 and the Comprehensive Cervical Cancer Control: A guide to essential practice - 2nd edition, 2014.

Legal framework for this programme and data management is in place.

The target group for the National Cervical Cancer Screening Programme are women registered to chosen doctors for women- gynecologists in Primary Health Care Centres. The organized screening programme which includes screening test, additional diagnostics and treatment is free of charge for all participants.

3 What are the age range of the target population and the frequency of screening?

According to the National Programme for early detection of cervical cancer in Montenegro, target population age range is 30-64. The screening pilot project began on July 18, 2016 in municipality Podgorica. Target population were women aged 30-34 years. Organised, population-based, nationwide screening programme was implemented on February 1, 2018. Target population were women aged 30-34 years, in Podgorica women aged 30-36 and from February 1, 2019. target population are women aged 30-42 years. Programme is managed by Ministry of Health and Institute for Public Health of Montenegro, which collect data, monitor and evaluate each step of the programme.

4 What test is used in the primary screening? Do we use liquid-based technology?

Screening is performed with HPV DNA test as a primary screening test within 18 Primary Health Care Centers in Montenegro. The screening cycle is five years. The accredited HPV testing laboratory is located at the Institute for Public Health of Montenegro.

The Abbott RealTime hrHPV test detects the following genotypes: HPV16, HPV18 and hrHPV (31,33,35,39,45,51,52,56,58,59,66,68). The result of the test can be: positive (with some of the genotypes individually identified or combinations), negative, inadequate and negative that should be repeated after 12 months.

HPV positive women are called for colposcopy and after three months liquid-based cytology (LBC) testing. The period between HPV DNA testing and LBC sampling is three months because tests that are used for these tests

are from different manufacturers. Premature sampling of the PAPA test by the LBC method in less than three months period from the HPV testing might induce false negative results.

The PAPA LBC method is examined by pathologists at the Pathology Clinic of Clinical Center of Montenegro.

5 How is the invitation system organized? What is the coverage of the target population with invitations? What is the coverage of the target population with screening tests?

Screening programme is conducted in Public health care system in Montenegro, organized in three levels:

1. Primary health care level (18 Primary Health Care Centers in all municipalities)
2. Secondary health care level (General Hospitals in the seven largest cities)
3. Tertiary health care level (Institute for Public Health and Clinical Centre of Montenegro in Podgorica).

Screening programme is supported by electronic health information system (e-HIS) at all health care levels and for every step of the process.

Teams of chosen gynecologists call women (from the group of target population) by phone or SMS and schedule an appointment. If the woman does not respond, she is called two more times: after 3 and after 6 months. Screening participants fulfill two questionnaires. The first questionnaire aims to identify possible risk factors for cervical cancer, and the second questionnaire is eliminatory - with questions from personal and family history.

In 2018, 10,677 women or 52.23% of the planned cohort were invited to participate in the program. A total of 7,038 (65.92%) women responded to the invitation to participate in the cervical cancer screening program, and 6,634 (94.26%) were sampled for HPV testing (cervical swabs).

6 How is HPV vaccination organised? What is vaccination coverage? Do we vaccinate girls and boys?

Montenegro is in the process of implementation of HPV vaccination for girls. Start of the programme is planned for the end of the current year.

Cervical cancer prevention In Finland

Pekka Nieminen

Incidence in year 2017: 4,8 and mortality 1,0 (world standard) (www.cancer.fi)

Organized nationwide screening from year 1963

Also a lot of opportunistic screening

Invitations are drawn from the population registry. Call-recall system.

All 30-60 year old women are invited with 5 year interval, some municipalities invite also 25 and 65 year old women.

Target population: 1,3 million women

Coverage of invitations is 98 %, attendance rate to organized screening is 72 %

Referral to colposcopy 1,1%, follow-up cytology recommended in 5,4%

CIN 2+ cases 0,4% of screened women (in programme)

Over 90% of 20-65 year-old women have had at least one Pap-smear during the last 5 years (organized, opportunistic or both)

A shift from the conventional Pap-smear to HrHPV-test in primary screening is going on in Finland. Year 2019 the Southern Finland implemented HPV-screening with cytology triage. No co-testing.

Very little LBC is used in the screening.

National HPV vaccination started in year 2013. Target group is 10-11 year-old girls. School based vaccination. Coverage is 70%. The programme will be gender-neutral in year 2020, when boys will be included. Bi-valent vaccine presently.

Prevention of cervical cancer in Slovenia

Urška Ivanuš

What is the incidence of cervical cancer in Slovenia?

The population-level effects of organised population-based screening in Slovenia can already be observed with cervical cancer incidence reducing by half since the implementation of organised population-based cervical cancer screening programme ZORA in 2003 (Table 1). In the recent years, approximately 120 women are diagnosed and 40–50 women die in Slovenia every year because of cervical cancer. With an age-standardized incidence rate (world standard) of about 7/100.000 and mortality rate of about 2/100.000 women, Slovenia is one of the European countries with the lowest cervical cancer burden. This is an outstanding achievement, since Slovenia used to have one of the highest cervical cancer incidence rates in Europe.

In 2017, Slovenia observed a record low cervical cancer incidence with only 85 new cases of cervical cancer (Table 1). This is undoubtedly a good news, but it should be interpreted with caution and re-evaluated in a year or two because of the small number of patients. Nevertheless, the decreasing trend in cervical cancer incidence in the recent years indicates Slovenia is, similarly to other countries with well-organised screening and vaccination programmes, following a path outlined in the spring of 2018 by the World Health Organization – the path to cervical cancer elimination.

Table 1. The incidence of cervical cancer since the implementation of programme ZORA. Cervical cancer incidence data source is Cancer Registry of Slovenia, which is a dynamic database with possible changes in the number of new cases. Number of new cases is regularly updated in case of major changes via the website ZORA (<https://zora.onko-i.si/>). More information on cervical cancer and CIN3 up to 2016 can be found on the website SLOA (www.sloa.si).

YEAR	Number of new cervical cancer cases (incidence)	Number of new cervical cancer cases/100.000 women (crude incidence rate)	Age-standardized incidence rate of cervical cancer/100.000 women (world standard)
2017	85	8,2	4,9
2016	123	11,8	7,8
2015	119	11,4	7,4
2014	114	11,0	6,8
2013	124	11,9	8,0
2012	118	11,4	7,7
2011	142	13,7	9,0
2010	141	13,6	9,3
2009	131	12,7	8,8
2008	130	12,7	8,8
2007	154	15,0	10,5
2006	162	15,8	11,3
2005	182	17,8	12,7
2004	198	19,4	13,7
2003	211	20,7	15,3

How is cervical cancer screening program organized? Does it fulfil criteria for the organised population-based programme?

Organised, population-based, nationwide screening programme ZORA was implemented in 2003. The organised screening process includes screening, diagnostics, treatment and follow-up after treatment (Figure 1). Programme is managed by the coordination office at the Institute of Oncology Ljubljana, which (in collaboration with the experts) provide guidelines, collect data, monitor and evaluate each step of the process. Target population are women aged 20–64 years. Screening is performed with conventional cytology within primary health care network of gynaecologists every 3 years. National evi-

dence-based national guidelines are aligned with the European guidelines for women's management and laboratory procedures. Legal regulations exist for programme and data management (2 new regulations in 2018, aligned with GDPR). Centralised and personalised screening registry registers personalised data on women and is nightly synchronised with Central Population Registry, it is also linked to Cancer registry of Republic of Slovenia. Copies of all cervical cytology results, HPV test results and all cervical histopathology results including information about the hysterectomy from all women are sent to the central screening registry, regardless the reason for the test or procedure. Cytology and HPV data are standardised and received in electronic format, histopathology reports are not yet standardised and are received as a paper copy of the original report. Programme has public funding.

What are the age range of the target population and the frequency of screening?

Screening is performed with conventional cytology within primary health care network of gynaecologists every 3 years.

What test is used in the primary screening? Do we use liquid-based technology?

Conventional cytology is used for screening since the introduction of the programme in 2003. Due to the good quality of smears (inadequacy rates are lower than 1%) there was no need to introduce liquid-based cytology in the past. However, according to new HPV-related knowledge and new technologies available, Slovenia is considering the introduction of HPV screening in women aged 35(30) years and more and in girls who were vaccinated against HPV within the national vaccination programme. The two of the first steps in the project of the renewal of the Slovenian cervical cancer screening policy are: (1) the introduction of liquid-based technology, that enables reflex testing with different tests (project started in 2019); (2) the renewal of the cervical cancer screening information system, that enables the real-time exchange of data between clinicians, laboratories and different national databases (including HPV vaccination registry) which will in the future enable risk-stratified screening, according to women's age, HPV-vaccination status and some other risk-factors (project started in 2017).

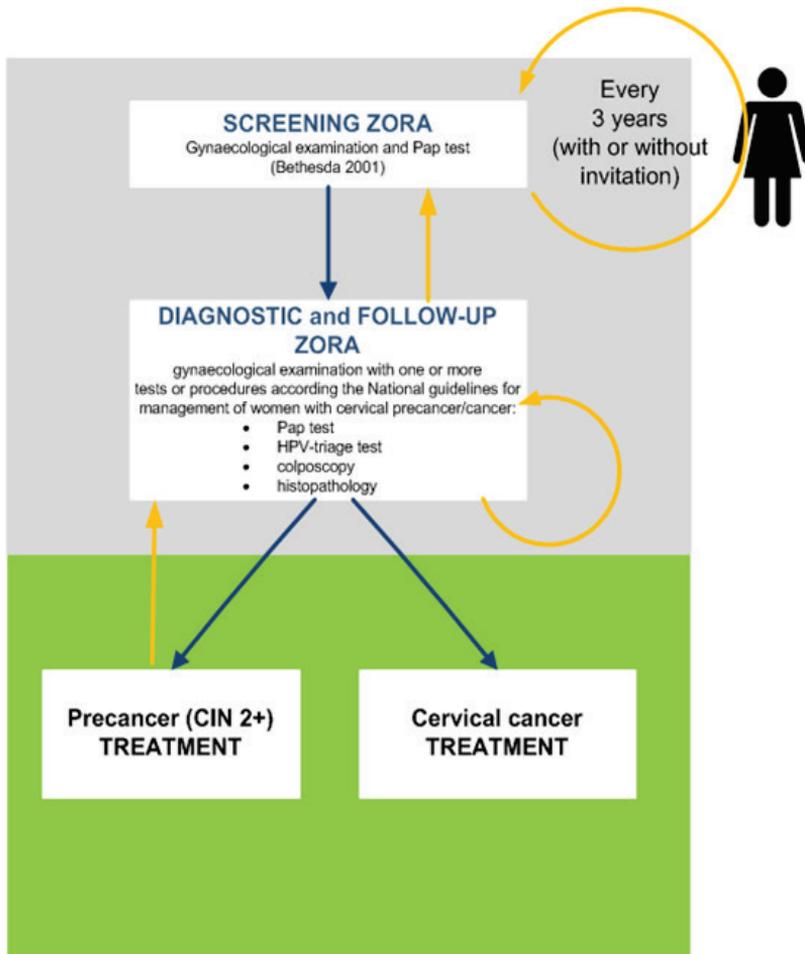


Figure 1. Clinical path of women in Slovenian cervical cancer screening programme ZORA

How is the invitation system organised? What is the coverage of the target population with invitations? What is the coverage of the target population with screening tests?

Women have free access to their personal gynaecologists and do not need a special invitation to schedule a screening appointment. If a woman fails to make an appointment on time, her personal gynaecologist should invite her to make one (with a reminder if needed). The central cervical screening registry serves as a final supervisor of screening attendance. Women who not

had cytology result registered for four years, receive a central invitation, which is sent to her in the fifth year by the central coordination office at the Institute of Oncology Ljubljana. With the new information system that is under development, gynaecologists will have an option to choose to continue to use the current invitation protocol, or all the protocol where all the invitations will be sent from the central coordination office.

Regular screening attendance is key for diagnosing precancerous and early cancerous lesions of the cervix. In the past five years, a little over 80% of women in the target population were screened in Slovenia, which places us amongst the most successful European countries. The recent three-year screening test coverage rate in Slovenia is over 70%, which is in line with our goals (Figure 2). The coverage rate in women aged 50 to 64 years has not reached our target values; however, in this age group coverage is slowly increasing (Figure 1). There are also differences in the coverage between the administrative units, three out of nine regions did not reach targeted 70% coverage in the last 3-year period (Figure 3).

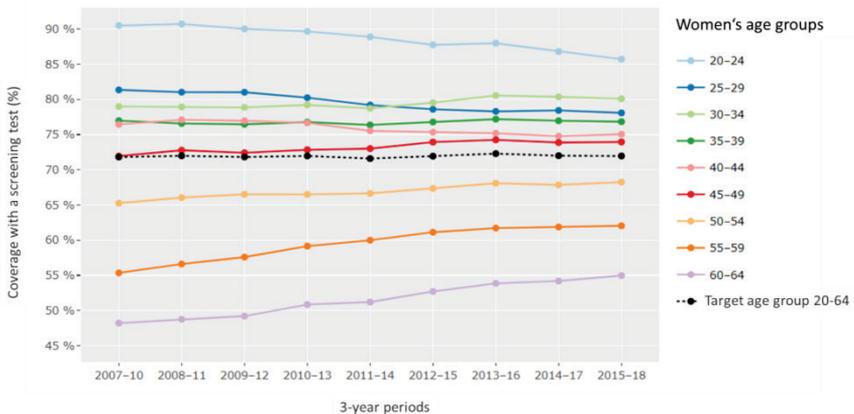


Figure 2. The three year coverage of the target population (%) by age in three three-year intervals (1 July 2009–30 June 2012, 1 July 2012–30 June 2015, 1 July 2015–30 June 2018). (Reference: Zora Registry, Institute of Oncology Ljubljana, January 2019, available at <https://zora.onko-i.si/publikacije/kazalniki>).

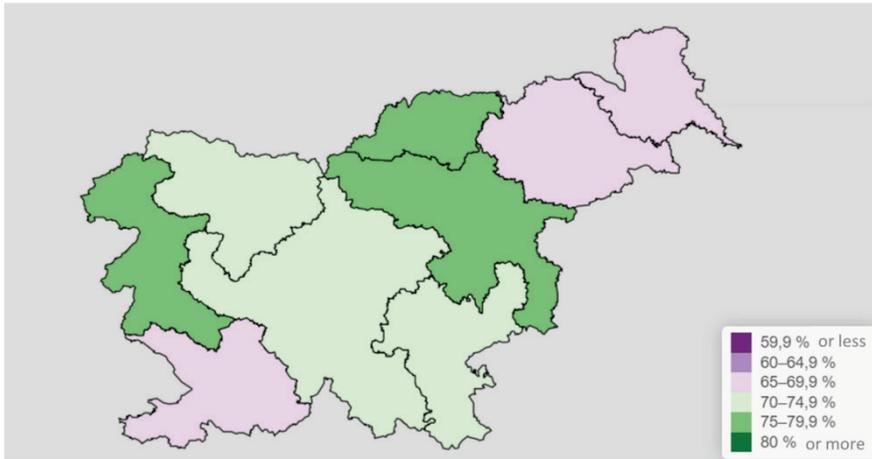


Figure 3. The three year coverage of the target population in Slovenian regions in last three three-year interval (1 July 2015–30 June 2018). (Reference: Zora Registry, Institute of Oncology Ljubljana, January 2019, available at <https://zora.onko-i.si/publikacije/kazalniki>).

HPV test used in Slovenia and how is it used.

HPV test was introduced in Slovenian cervical cancer screening programme ZORA in 2011 as a triage test and as test of cure after HSIL treatment. Indications for HPV triage are low grade cervical pathology (cytological confirmed ASC-US, cytological confirmed LISL \geq 35 years old or histologically confirmed LSIL) or histologically negative AGC-NOS. Hybrid Capture 2 test (Qiagen, Germany) is used since the introduction of HPV test in 2011. According to the Regulation on cancer screening two laboratories in the country, can perform HPV testing. If HPV test will become a screening test in the future, we will strongly consider to select only one, clinically validated HPV test for all indications where HPV test will be used: screening of older women and HPV vaccinated, triage of younger women still screened with cytology and possibly also for HPV-self sampling of non-responders to regular screening. We are and we will strongly recommend against opportunistic use of HPV test outside the organised screening, especially in young women.

How is HPV vaccination organised? What is vaccination coverage? Do we vaccinate girls and boys?

Slovenia has been vaccinating girls in the 6th grade of primary school against HPV free of charge since 2009, with the possibility of free vaccinations for order girls who missed their scheduled vaccination (catch-up vaccination). In last years, a 9-valent vaccine is used. According to the National Institute of Public Health (NIPH), the routine HPV vaccination coverage is around 50%, which is too low. In 2019 NIPH proposed to include also boys at 6th grade in the national vaccination schedule, however this is not yet implemented.

Main messages on cervical cancer screening

Cervical cancer is an exception amongst cancers, since we now have sufficient knowledge and technology available to be able to prevent almost every new case. This is why in 2018, the World Health Organization issued a global call for action towards the elimination of cervical cancer as a public health problem with HPV vaccination, organised cervical cancer screening and treatment of cervical lesions with the cut-off level for elimination set at cervical cancer incidence rate (world standard) 4/100.000 women.

The slow and gradual development of cervical cancer allows us to use different ways of preventing cervical cancer with primary prevention measures (healthy lifestyle, HPV vaccination) as well as with secondary (early detection and treatment of precancerous and early cancerous cervical lesions in organised population-based screening programmes (Figure 4). Vaccination is very effective and safe and it is able to prevent 70-90% of all cervical cancers and high-grade precancerous lesions. Because vaccinated women can still develop disease from a HPV genotype not covered by the vaccine, vaccinated women should also attend screening.

In order to achieve the optimal balance between harms and benefits of screening, only organised, population-based screening should be considered and implemented. Screening programmes should be organised according to Council recommendation on cancer screening (2003) and European guidelines for quality assurance in cervical cancer screening (2008 with extension about HPV testing and vaccination in 2015).

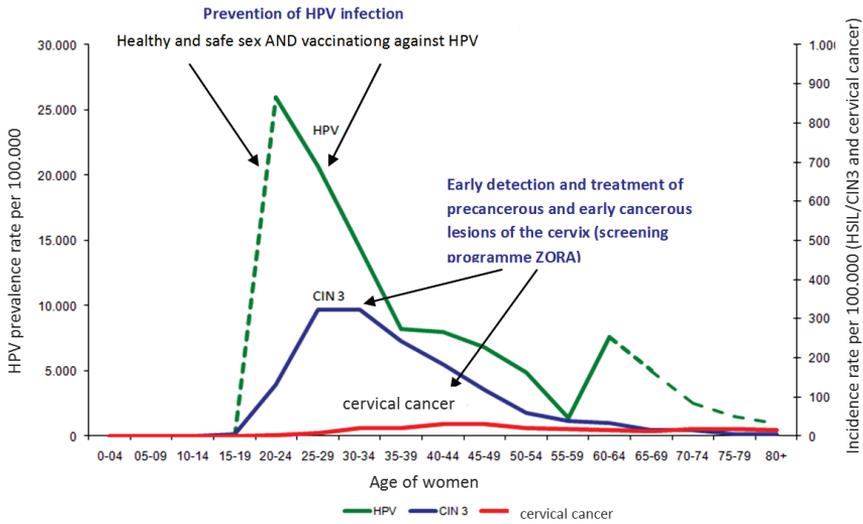


Figure 4. The prevalence of infection with at least one high risk HPV (green line, left axis) and the incidence of precancerous lesions HSIL/CIN3 and cervical cancer (blue and red line, right axis) in Slovenia, by age. The dashed line represents data extrapolated from foreign studies, since Slovenian data for these age groups do not exist. Reference: prevalence study of HPV infections in Slovenia (Učakar et al, Vaccine 2012) and website of Cancer registry of Slovenia – SLORA, for years 2005–2009 (Institute of Oncology Ljubljana).

What can we learn from each other in our region? Suggestions for future activities

Joško Zekan, Southeast European HPV Forum

Abstract: During the transition period, most of the Southeast European countries experienced significant changes in the healthcare system, especially in the area of medical general practice. Privatization waves have significantly influenced health standards and the availability of health care. Part of the health care has been significantly improved. However, one part of health care has maintained the previous standards or there has been a weakening, especially in the case of diseases and conditions that have a public health significance. Among the world's leading causes of morbidity and mortality, cervical cancer have understandably been the primary focus of research and development and the dominant motivation for international cooperative efforts at prevention and control.

Objectives: Successfully organized, population-based cervical cancer screening programs have not yet been implemented in most southeast European countries, despite the greatest burden of cervical cancer. Effective performance of the national program of organized screening in Slovenia started in 2003. Incidence of cervical cancer decreased since then by 44%. However, from 2012 to 2016 the incidence of cervical cancer recorded the plateau. HPV vaccine coverage is about 50%. In Croatia, the organized cervical cancer screening started in 2012. Through 3 years of program, the incidence of disease was reduced by 18%. Since 2015, gender-neutral vaccination has been integrated into national immunization schedule and currently provides routine vaccination free of charge to the primary target population.

Unfortunately, coverage by vaccination is less than 20% at the state level. In Bulgaria, Romania, Serbia, and Macedonia the implementation of organized cervical cancer prevention programs are in progress, current standard is opportunistic screening. Montenegro implemented organized HPV-based screening program In July 2016 (the only HPV-based program in the region). Also, there are no reliable data on HPV vaccination uptake. National-

based screening solutions need to be found, while being cognizant of the criteria that have enabled successful screening programs.

Conclusions: The reframed programs of cervical cancer prevention will include strategic combinations of at least two major components: extension and advancement of existing screening programs using HPV-based technology and routine introduction of HPV vaccines to both sex in all countries. Success in basic, clinical and epidemiological research has expanded the possibilities of cervical cancer prevention by introducing HPV-based cervical cancer screening and most importantly, by making available remarkably efficacious prophylactic HPV vaccines. Understanding the nature of these tools, how to use them and how to evaluate their impact is a pressing social demand for the scientific, medical and public health communities. HPV vaccine uptake is reported, and support for conceptual models that move beyond purely motivational accounts of HPV vaccine uptake is adduced. The Southeast European HPV Forum is a non-profit and non-governmental organization of southeast European countries with a goal to promote the research of all aspects of human papillomavirus (HPV) infection, to study diseases caused by HPV and help to implement and/or improve primary and secondary prevention programs of cervical cancer and other HPV-related tumors.

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Cervical cancer

Vitaly Smelov

WHO recommends a comprehensive approach for cervical cancer prevention and control that has 3 pillars:

- **Primary prevention**, which consists mainly in HPV vaccination of girls 9-13 years. HPV vaccination does not fully abolish the need for cervical cancer screening in vaccinated cohorts as it does not prevent 100% of cervical cancers.
- **Secondary prevention**, which consists in screening and for those found positive, follow-up and treatment. Cervical cancer screening should primarily be ensured for women aged 30-49.
- **Tertiary prevention**, which ensures that women with invasive cancer have rapid access to diagnosis and effective treatment, as well as palliative care if needed.

WHO guidelines on cervical cancer screening specify that:

- **HPV test, PAP smear** and visual inspection with acetic acid (VIA) are all recommended screening tests, with a preference for HPV test. Pap test is not recommended if it is not already existing and functioning in the country. HPV test can be used alone or be followed by a triage test
- **Cryotherapy**, loop electrosurgical excision procedure (e.g. **LLETZ** or **LEEP**) and thermal ablation can provide effective and appropriate treatment for the majority of women who screen positive for cervical pre-cancer;
- Screening needs to be performed at least **once in a lifetime** for every woman aged 30-49. If resources allows, frequency of screening should be intensified, up to every 5 years if using HPV test and every 3 years if using PAP smear. Shortening further screening intervals increase costs without bringing any substantial health benefit.
- Screening should primarily be proposed to **women aged 30-49**. If high coverage is obtained and resources are available then older co-

horts may be screened, up to 60 or 65 year of age. Screening with HPV test before age 30 is not recommended because of the high rate of false positives. Screening with cytology or VIA before 25 is not encouraged for the same reason.

Screening does not only carry potential for benefit but also for harms (e.g. false negative/positive tests, too aggressive/suboptimal treatments of pre-cancerous lesions, anxiety, (in)direct financial costs associated, etc).

To secure the benefits of screening and minimize the harms, quality is the key. Low quality screening results in no benefit while harms were observed, which is unethical and has to be avoided at all cost.

High quality screening requires:

- Minimizing false positives and false negatives: those depend highly on performance of professionals running the tests. Professionals must be informed about their performances in order to be able to improve, keeping in mind that false positives and false negatives can never be totally avoided.
- Rapid, efficient, safe and free-of-charge follow up for women screened positive: Follow-up is fully part of the screening program and has to be planned, given resources and implemented prior to launching the program. A referral system should also be implemented.
- High screening coverage of the target population: Population-based screening has to be preferred to opportunistic screening.
- Equity: special efforts need to be made to screen “hard to reach” women (e.g. poor/rural population).
- Information systems: monitoring of process and outcome are crucial for attaining and for maintaining quality, and for guiding further improvement.