Medicinski podmladak

Medical Youth

Mini review article

THE IMPORTANCE OF THE CERVICAL CANCER ORGANISED SCREENING PROGRAMS

ZNAČAJ ORGANIZOVANIH PROGRAMA SKRININGA RAKA GRLIĆA MATERICE

Ivana Nikčević Kovačević[1,2], Tatjana Pekmezović[3], Nataša Milić[4]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Institut za javno zdravlje Crne Gore, Podgorica, Crna Gora
[3] Univerzitet u Beogradu, Medicinski fakultet, Institut za epidemiologiju, Beograd, Srbija
[4] Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku statistiku i informatiku, Beograd, Srbija

Correspondence: ivana.kovacevic@ijzcg.me

Abstract

According to the most recent published data from 2020, cervical cancer is among the first five most frequently diagnosed cancers in the female population. It is the second leading cause of cancer mortality in young, working women during their reproductive period. Prevention of cervical cancer through screening programs has been applied since the 1960s, and the scientific community agrees that it is a highly preventable disease with a strong possibility for cure if detected in a premalignant and early malignant phase and effective treatment administrated without delay.

Countries that effectively implement organized screening programs record a significant decrease in the incidence and mortality rates of cervical cancer. Their experience can be useful as a model for countries that still do not have established organized programs or have an unsatisfactory level of implementation or quality. These are mainly underdeveloped and developing countries, where exposure to risk factors is still very high, preventive activities are limited and consequently, the burden of cervical cancer is still at a very high level.

The challenge remains how to adapt screening program strategies to the conditions of those countries, to achieve high coverage of the target population with a test of appropriate performance, to establish control over the increasing trend and in the coming decades, to reach the targeted decline in incidence and mortality rates.

So far, it is the only malignant disease for which there is scientific evidence that it can be eliminated to a frequency that will no longer represent a public health problem. Reducing the incidence rates should be an effect that would be seen at the global level and to achieve it, it is necessary to strongly support countries in establishing adequate programs of prevention and early detection of cancer supported by effective treatment and care.

Keywords:
cervical cancer, organized screening programs, prevention, elimination

©
The authors declare no conflicts of interest.
doi:10.5937/mp74-45333
Editorial board: podmladak.med.bg@gmail.com

Sažetak

Rak grlića materice se, prema poslednjim publikovanim podacima iz 2020. godine, nalazi u prvih pet najčešće dijagnostikovanih formi raka u ženskoj populaciji. Kod mladih, radno aktivnih žena u reproduktivnom periodu predstavlja drugi najčešći razlog umiranja od raka. Prevencija raka grlića materice kroz skrining programe postoji i primjenjuje se od šezdesetih godina prošlog vijeka, a naučna zajednica je saglasna da se radi o visokopreventabilnoj bolesti sa dobrim izgledima za izlječenje ukoliko se bolest otkrije u premalignoj i ranoj malignoj fazi i bez odlaganja pristupi efektivnom liječenju.

Države koje efektivno sprovode organizovane programe skrininga bilježe značajan pad incidencije i mortaliteta od raka grlića materice. Njihovo iskustvo se može koristiti kao model zemljama koje još uvijek nemaju uspostavljene organizovane programe ili ih imaju, ali sa nezadovoljavajućim stepenom implementacije ili kvaliteta. To su uglavnom nerazvijene zemlje i zemlje u razvoju, gdje je izloženost faktorima rizika i dalje veoma visoka, preventivne aktivnosti ograničene i, posledično, opterećenje rakom grlića materice i dalje na veoma visokom nivou.

Ostaje izazov kako strategije programa skrininga prilagoditi uslovima tih država na način da se postigne visoki obuhvat ciljne populacije testom odgovarajućih performansi, da bi se uspostavila kontrola nad rastućim trendom oboljevanja i u narednim decenijama, kako bi se postigao pad stopa incidencije i mortaliteta.

Za sada je to jedini rak za koji postoje naučni dokazi da može biti eliminisan do učestalosti koja više neće predstavljati javnozdravstveni problem. Smanjenje incidencije bi trebalo da bude efekat koji bi se vidio na globalnom nivou, a da bi se on postigao potrebno je snažno podržati države u uspostavljanju adekvatnih programa prevencije i ranog otkrivanja raka podržanog efektivnim liječenjem i njegom oboljelih.

Ključne reči:
rak grlića materice,
organizovani programi skrininga,
prevencija,
eliminacija

Introduction to the epidemiology of cervical cancer

Scientific discoveries in the last seventy years have led to a good knowledge of the etiology and characteristics of the disease. From an epidemiological point of view, cervical cancer is a challenge despite there being no significant doubts. There are evidence-based preventive measures that can effectively prevent this disease. If the disease does occur, by detecting it at an early stage, it can be cured without significantly impairing the quality of life. Despite these facts, cervical cancer continues to be a global public health issue.

Incidence and mortality

According to the most recent published data from 2020, cervical cancer is among the first five most frequently diagnosed cancers in the female population with an average global age-standardised (ASR) incidence rate of 13.3 per 100 000 (1). The overall number of newly diagnosed cases was estimated at 604 121 (1) and was the most present malignancy in 23 countries worldwide. Cervical cancer represented 6.5% of the overall cancer incidence in the female population in the same year; after breast cancer which accounts for nearly a quarter of the malignancy burden (24.2%), colorectal cancer which accounts for 9.4%, and lung cancer which accounts for 8.4% of all malignancies, corresponding to 3.1% of newly detected malignancies in both sexes. Regarding the burden of cervical cancer per continent, Europe ranked fourth with 9.6% cases per year (ASR 10.7 per 100 000). Africa had the highest incidence rate (ASR 25.6 per 100 000), the highest new cervical cancer cases percentage (58.2%) recorded in Asia, while Oceania and and Northern America (ASR 6.1 per 100 000) had the lowest load (2).

Cervical cancer was estimated to rank as the fourth leading cause of death worldwide for women in 2020 and was the ninth most frequent cause of death for both sexes, with a global ASR 7.2 per 100 000 and a total estimated death of 341 831, representing a cancer burden of 3.3% in both sexes (1). The most frequent cancer-related mortality was breast cancer, accounting for 16% (or 6.7% in both sexes). Lung cancer and colorectal cancer ranked second and third, respectively. Among cancers related to the reproductive period, it is the second most frequent cause of cancer mortality (3). The highest mortality rates were recorded in Africa (ASR 17.7 per 100 000) where incidence rates were also the highest, the largest percentage of mortality (58.5%) was observed in Asia, while Oceania, Western Europe, and Nothern America (ASR 2.1 per 100 000) had the lowest load. (2, 4).

Variations in age-standardized incidence and mortality rates are manifold globally. Incidence rates vary from 84.5 per 100 000 in Eswatini (Southern Africa) to the lowest recorded in Iraq (West Asia) 2.16 per 100 000 **(figure 1)** (2). Global mortality rates also vary significantly, from the highest recorded 55.7 per 100 000 in Estwani to 1.01 per 100 000 in Switzerland (Europe) **(figure 2)** (2).

Cervical cancer as a public health problem

The cervical cancer burden correlates strongly with the Human Development Index (HDI) countries worldwide and is an indicator of global social inequality. The world's least developed regions have the highest incidence

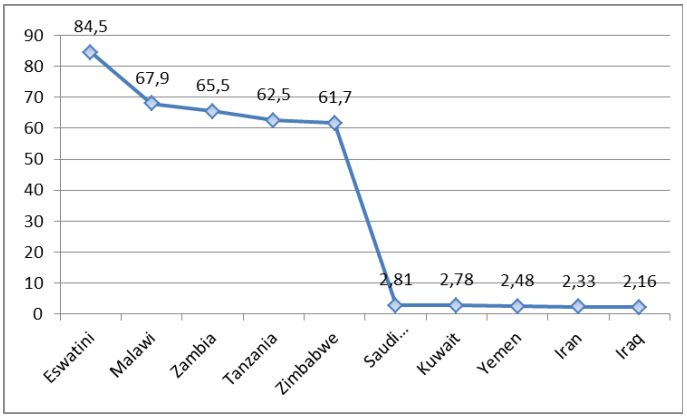

Figure 1. Differences between the five highest and lowest estimated incidence rates of cervical cancer (ASR/100000) by country globally in 2020.

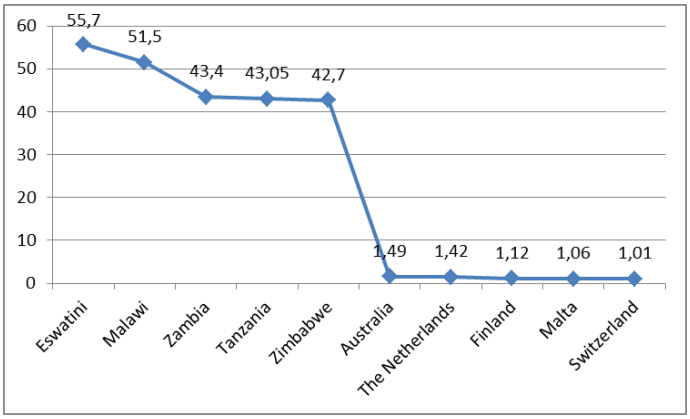

Figure 2. Differences between the five highest and lowest estimated mortality rates of cervical cancer (ASR/100000) by country globally in 2020.

and mortality rates (5).

In countries with medium or lower HDI, incidence and mortality rates are more diversified, suggesting that factors other than HDI may be responsible for the differences, but also indirectly related to HDI such factors as the prevalence of human papillomavirus (HPV) infection, differences in co-factors exposure, and the type and implementation of screening programs (opportunistic vs organized). In countries with high HDI there is much less variation (5). This could be attributed to a more consistent prevalence of HPV infection, but also by well-organized screening programs, and in the coming period the effect of vaccination will be more evident.

Cervical cancer incidence and mortality trends

The growth curve of incident cases of cervical cancer starts to rise from the age of 25 and in highly developed parts of the world reaches the maximum around the age of 40 and then decreases dramatically. In medium-developed and underdeveloped parts of the world, that curve is less steep and the high incidence rates extend to the age of 69 (2).

In some countries, cervical cancer incidence rates have declined, although not to the same extent. Two prevention strategies may explain the decline in incidence rates. In the Scandinavian countries, organized screening programs have been introduced since the 1960s and 1970s, and a decrease of almost 50% in cervical cancer incidence rates has been recorded (6). In India incidence rates are declining, despite the lack of organized screening programs. Lower incidence rates are mostly attributable to female population receiving greater education about cervical cancer and prevention possibilities (6).

The Baltic countries and Belarus continuously register an increase in incidence rates despite the existence of screening programs. This increase can be explained by the low coverage of opportunistic screening and the lack of quality control. An increase in incidence rates was registered in the analysis of 10 African registries, where, in addition to the lack of well-organized screening programs, a high prevalence of HPV infection is observed (9).

The cervical cancer incidence curve in China shows very high incidence rates up to the age of 40, although the overall incidence trend is decreasing. Greater exposure to HPV infection among young women is considered a possibility (10).

Inequalities in diagnosis and treatment worldwide are also reflected in the five-year survival rate from 2000 - 2014 and vary between 50 and 70% (11).

The role of HPV infection in the occurrence of cervical cancer

More than 90% of cervical malignancies are correlated with persistent oncogenic HPV genotype infection. Of the 12 most commonly diagnosed human papillomaviruses associated with cervical cancer, HPV16 (in the alpha-9 species) is responsible for two-thirds of all squamous cell carcinomas - about 60% and about 50% of adenocarcinomas. Another one, HPV18 (in the alpha-7 species) is associated with about 15% of squamous cell carcinomas and together with HPV45, with about 50% of adenocarcinomas. The prevalence of other genotypes is much lower (HPV31, HPV33, HPV35, HPV 39, HPV 51, HPV 52, HPV 56, HPV 58, and HPV 59) (5).

The first research records on the topic of human papilloma virus date back to 1896 by McFadyean and Hobday. They demonstrated the cell-free spreading of canine warts in England and Cuifo demonstrated the transmission of human warts in 1907 in Italy (12).

Papillomaviruses are a heterogeneous group of viruses associated with various types of tumors in humans and animals. The genome consists of double-stranded DNA with a size of about 8 000 base pairs, composed of early (E), late (L), second control regions (LCR) encoding characters (E1, 2, 4, 5, 6, 7, and L1, 2) and non-coding DNA (LCR) (12). Human papillomavirus contains more than 200 genotypes, which are categorized into genera: Alpha, Beta, Gamma, Mu and Nu (13).

Alpha genotypes, the most important HPV 16 and HPV 18, are closely correlated with squamous cell carcinomas: cervix (≥ 99%), rectum and vagina (70% - 90%), vulva (40%), penis (47%) and pharynx (25 - 30%). Low-risk genotypes of the alpha genus are correlated with condylomas

(HPV 6, HPV 11) and pharyngeal papillomas. Beta HPV viruses cause benign skin lesions, but also malignant neoplasms, as well as wart epidermodysplasias. Other genera are associated with skin warts in immunocompromised hosts (13).

The prevalence of HPV infection is 15.3% of females with normal cytological findings. Of all HPV genotypes, genotypes with oncogenic potential were present in 70% of the results. Among the oncogenic genotypes, HPV 16 (standardized prevalence, 3.5%) is the most prevalent, followed by HPV 18 and HPV 52 (1.3%), HPV 58 and HPV 31 no more than 1% (14).

A common feature of all HPV viruses is a pronounced tropism for the squamous epithelium. Although most women become infected with HPV during the reproductive period, the majority of these infections are spontaneously eliminated, and the cervix that is not infected with oncogenic genotypes is considered healthy, with no potential or with minimal potential for developing cancer.

HPV vaccination

Since the licensing of the 4-valent Gardasil and 2-valent Cervarix in 2006, followed by the 9-valent Gardasil vaccine in 2015, primary cervical cancer prevention has been made possible.

An increasing number of countries are recommending the vaccination of boys and girls (Austria, Australia, Canada, Denmark, Italy, Germany, Finland, Norway, the Netherlands, New Zealand, Slovakia, Switzerland, the United Kingdom, the United States, etc.). Vaccination from the age of 9 ensures an optimal immune response and includes cohorts who did not have the opportunity to become infected with HPV before vaccination (15). Vaccination effectively protects against new infections and diseases for up to 45 years (4, 16), ensuring a good immune response even if a single dose is administered. Despite the recommendations, most countries still do not have an organized vaccination program aimed at both sexes.

The importance of vaccination is highlighted as a priority for immunocompromised people or those living with HIV. Immunocompromised people should receive at least two doses and if possible, three doses. Vaccination of boys and older women is recommended if feasible and available (17).

Cervical cancer screening

The concept of cervical cancer prevention dates back to 1928 when pathologist Jorgos Papanikolaou visualized cervical cancer cells under a microscope from vaginal secretions in laboratory conditions and validated officially in 1941 and 1943.

The etiology of cervical cancer was unknown until the 1980s, but as early as the 1960s, the first screening programs based on conventional cytology and a five-stage classification system were implemented in Western Europe and British Columbia in Canada (6).

By the mid-1990s, persistent infections with certain HPV subtypes were identified as an essential factor of nearly all cervical cancer occurrences (6) and changed approaches to screening programs. The PAP tests which were previously widely used are slowly being replaced by HPV tests, and the number of colposcopies is decreasing. At the same time as HPV testing is being introduced into screening programs either as a primary test or as an adjunct after a positive PAP, the efficiency of reading PAP tests with cytology on a liquid medium, based on thin-layer plates is greatly improved, allowing for larger number of adequate samples. Higher compliance was achieved when the process was automated allowing simultaneous HPV testing and cytology on liquid medium cytology from the same specimen (6).

Molecular HPV testing has the appropriate sensitivity and specificity required for organized population-based screening programs, and studies conducted in Europe and North America have shown it to be an appropriate primary screening test for screening women in multiple cycles of screening programs (6).

The influence of the organized cervical cancer screening program

The organized screening program is defined as "an explicit policy with defined age categories, methods, and intervals for screening; a defined target population; a management team responsible for implementation; a health care team for decision-making and care; a quality-assurance structure; and a method for identifying the occurrence of in the target population" (18). The strategy implies periodically organized invitation of participants to the primary testing, and in the shortest possible time triage test, further diagnostics, treatment, and follow-up, aimed at all women who are at average risk of cervical cancer and belong to the age groups previously defined (19). The process of an organized screening program is complex and requires multisectoral collaboration between decision-makers, screening program providers, and the target population, and requires monitoring, evaluation, and quality assurance (20).

Organized screening programs are a significantly more complex intervention compared to opportunistic programs, but their impact on incidence and mortality is also significantly greater (21), which is the aim of organized screening programs and an indicator of effectiveness.

Existing screening programs worldwide are currently based on cytology, HPV, or visual inspection primary tests. The sensitivity of detection of CIN2+ lesions is significantly lower than HPV testing despite the typically high specificity of cytology, ranging from 18.6% to 76.7% depending on the research (22). Primary HPV testing-based screening should not be recommended under the age of 30 because of the lower specificity. In Europe, the minimum screening interval for HPV testing at ages 30 - 65 is five years, while the maximum interval is ten years - depending on age, vaccination status, and the organization of the screening programs (23-25). To increase coverage and reach individuals who do not attend the screening the scree-

ning test could be administered at home (self-sampling).

Extending the interval leads to a reduction of the harm of the screening programs. A study conducted in Serbia showed that knowledge of a positive test result was associated with increased anxiety, greater concern about the result of further diagnostics, and fear of cancer, which leads to lower quality of life. The same study showed that women who were better educated about cervical cancer showed lower levels of anxiety, suggesting that there is a need for more detailed information about HPV infection. The clinical importance of this education is reflected in better acceptance of preventive measures (26).

Cervical cancer elimination strategy

In August 2020, the Seventy-third World Health Assembly supported the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem 2020 - 2030 (WHO, 2018, 2020) (1).

Achieving the strategy goals by 2030 could reduce incidence rates from the current average of 13.3 to less than 4 new cases per 100 000 women to ensure that cervical cancer is no longer a worldwide public health issue.

Interventions need to be strategically designed on three main pillars with a comprehensive approach: immunization, screening, and disease treatment. The recommended strategy (90-70-90) is to vaccinate 90% of girls under the age of fifteen with the HPV vaccine, and screen 70% of women at least twice, once before the age of 35 and again before the age of 45 with an appropriate test, and lastly, treat 90% of premalignant and invasive malignant lesions, which will lead to a decrease in incidence rates of cervical cancer about 42% by 2045 and 97% by 2120, saving about 62 million human lives cumulatively (1).

Conclusion

To overcome the growing incidence rate trends of cervical cancer in the coming years, especially in medium-developed and underdeveloped regions of the world, it is necessary to use strategies that integrate different levels of prevention, treatment and care. The model and experience of countries that have registered a decline in incidence and mortality trends could be used for those parts of the world where the disease burden is the highest. The challenge remains how to adapt these strategies to the conditions of individual countries level. Achieving the specific global strategy goals by 2030 could lead to a reduction of incidence rates from the current average of 13.3 to less than 4 new cases per 100 000 women to ensure that cervical cancer is no longer a worldwide public health issue. Organized screening programs are the most important secondary prevention strategy, however, impacts are not immediately evident, and it takes time to validate effectiveness using quantitative indications. That is a specific challenge to sensitizing decision-makers to consider well-coordinated screening programs as a priority public health activity that is conducted at the national level.

To be optimally effective, organized screening programs have high standards for quality assurance, which leads to the minimization of harm as a consequence of the intervention on a population that perceives itself as healthy due to the absence of disease symptoms. It is necessary to work on educating and raising awareness about the importance of the screening program, explaining the benefits but also the harm, through well-planned, organized campaigns targeting decision-makers and providers of the screening program - especially the general population. It must stay in focus on women - their needs, cultural, social, educational, religious, and economic barriers, respecting and upholding women's rights, privacy, and dignity.

Literature

1. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Pineros M, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2020. Available from: https://gco.iarc.fr/today
3. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020; 8(2):e191–203.
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71(3):209–49.
5. IARC. Cervical cancer screening. IARC Handb Cancer Prev. 2020; 18:1–456. Available from: https://publications.iarc.fr/604.
6. Dhillon PK, Yeole BB, Dikshit R, Kurkure AP, Bray F. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976–2005: an age-period-cohort analysis. Br J Cancer. 2011; 105(5):723–30.
7. Vaccarella S, Franceschi S, Zaridze D, Poljak M, Veerus P, Plummer M, et al. Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study. Lancet Oncol. 2016; 17(10):1445–52.
8. Ojamaa K, Innos K, Baburin A, Everaus H, Veerus P. Trends in cervical cancer incidence and survival in Estonia from 1995 to 2014. BMC Cancer. 2018; 18(1):1075.
9. Jedy-Agba E, Joko WY, Liu B, Buziba NG, Borok M, Korir A, et al. Trends in cervical cancer incidence in sub-Saharan Africa. Br J Cancer. 2020; 123(1):148–54.
10. Li X, Zheng R, Li X, Shan H, Wu Q, Wang Y, et al. Trends of incidence rate and age at diagnosis for cervical cancer in China, from 2000 to 2014. Chin J Cancer Res. 2017; 29(6):477–86.
11. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018; 391(10125):1023–75.
12. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human Papillomaviruses. Lyon (FR): International Agency for Research on Cancer; 2007; 90: 1-689.
13. Poljak M, Kocjan B, Oštrbenk A, Hošnjak L. Značilnost okužbe sa HPV. Zbornik predavanj, 5. izobraževalni dan programa ZORA 2014; 24-33.
14. Bruni L, Serrano B, Diaz Sanchis M, Bosch José FX, de Sanjosé Llongueras S. Update of global estimates of HPV prevalence: meta-analysis of 2.4 million women with normal cytology. Presented at International Papillomavirus Conference, Sydney, Australia. 2016.

15. Joura EA, Kyrgiou M, Bosch F, Kesic V, Niemenen P, Redman C et al. Human papillomavirus vaccination: The ESGOeEFC position paper of the European society of Gynaecologic Oncology and the European Federation for colposcopy. Eur J Cancer. 2019; 116:21-6.
16. Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Canc. 2011; 105(1):28-37.
17. World Health Organization. Human papillomavirus vaccines (HPV). Available from: https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/human-papillomavirus-vaccines-(HPV). [Accessed 19th March 2023].
18. IARC Working Group on the Evaluation of Cancer Preventive Strategies. Cervical cancer screening. IARC Handb Cancer Prev. 2005; 10:1–302.
19. Basu P, Lucas E, Carvalho AL, Sauvaget C, Muwonge R, Herrero R, et al. Cancer screening in five conti¬nents. Available from: https://canscreen5.iarc.fr. [Accessed 19th March 2023]
20. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European guidelines for Quality Assurance in Cervical Cancer screening. Second edition – summary document. Ann Oncol. 2010; 21(3):448–58.
21. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer. 2004; 101(S5):1201–13.
22. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer. 2006; 119(5):1095–101.
23. Ronco G, Arbyn M, Meijer CJLM, Snijders PFJ, Cuzick J. Screening for cervical cancer with primary testing for human papillomavirus, S1. In: Anttila A, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S et al, Editors. European guidelines for quality assurance in cervical cancer screening. 2nd ed, Suppl. Luxembourg: Office for Official Publications of the European Union; 2015.
24. Von Karsa L, Arbyn M, DeVuyst H, Dillner J, Dillner L, Franceschi S, et al. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus Res. 2015; 1:22–31.
25. Federation of European Academies of Medicine. Statement on the Council cancer screening recommendations. Available from: https://www.feam.eu/statement-on-the-european-council-cancer-screening-recommendations/. [Accessed 19th March 2023].
26. Marić G, Birčanin Đ, Kisić V, Dotlić J, Zarić M, Kisić-Tepavčević D, et al. Parental perspective on human papillomavirus (HPV) vaccination in Serbia: Knowledge, attitudes and practice. Sex Reprod Healthc. 2018; 16:192–8.