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ORIGINAL PAPER

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Epidemiological Aspects of Age and Genotypical Occurrence of HPV Infection Among Females of Canton Sarajevo Over a 10-year Period

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ABSTRACT

Background: Human papillomaviruses (HPV) are one of the most prevalent causes of cervical, anal, and oral cancer, and it is believed that nearly all sexually active males and females have been infected with HPV at some point in their lives.

Objective: The purpose of this study is to highlight epidemiological characteristics of the age and genotypical incidence of HPV infection among females in Canton Sarajevo during a 10-year period. **Methods:** This cross-sectional study was conducted in the period between January 2012 and December 2021 at the medical institutions "Zavod za Ginekologiju, Perinatologiju i Neplodnost "Mehmedbašić" among females who were admitted for a routine gynaecological exam in Canton Sarajevo in Bosnia and Herzegovina. **Results:** In total, 1517 patients who reported typical sexarche at 18.35±1.92, having one 721 (47.5%) sexual partner, regular use of contraceptive methods 820 (54.5%) with male condom 513 (62.6%) being the dominant choice of contraception and having gynecological hereditary oncological positive history 141 (9.3%), were included in the study from which 653 (43.05%) patients had positive HPV test and 864 (56.95%) had negative HPV results. HPV positive patients, 386 (59.1%) were infected either with one type of virus only, while 267 (40.9%) patients were infected with multiple virus strains where we have identified 166 virus strain combinations. Analysis showed that the patients infected by only one virus strain were one of next specific HPV viruses: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. HPV-16 was the predominately strain 16 (22.5%) identified among all the patients. Mean age of HPV positive patients was 33.38±7.85,

ranging from 18 to 61 years. **Conclusion:** This study highlights the significance of the most frequent HPV high-risk strains (HPV-16, -18, -31-33, -45, -52, and -58) among the Bosnia and Herzegovina population as one of the most common cancer-causing strains worldwide.

Keywords: HPV, Bosnia and Herzegovina, cervical cancer, screening

1. BACKGROUND

Human papillomaviruses (HPV), a family of Papillomaviridae that can infect the squamous epithel, are divided into two subgroups based on their carcinogenic abilities: low-risk or nononcogenic – 6, 11, 40, 42, 43, and 44 that cause condilomas in the anogenital region; and high-risk or oncogenic – 16, 18, 31, 33, 35, 39. (1) According to CDC studies, it is estimated that almost all sexually active males and females have been infected with HPV at some point in their life, (2) while a US study shows that approximately 14 million people get infected with HPV every year, and 79 million people have a persistent infection (1).

Infection with one of the high-risk strains is the most important risk factor in the development of cancer, and HPV infection is considered to be the cause of 99% of all cervical cancers, 90% of anal cancers, 65% of vulvar cancers, and may also cause penile and oropharyngeal cancer (2). The estimated global prevalence of cervical HPV in 2016, was 11.7% in females, with the most frequent types being HPV-16 (3.2%), HPV-18 (1.4%), and HPV-31 (0.8%). HPV-16 was responsible for 50% of all cervical malignancies,

while HPV-18 was responsible for 70% of the same (3) In the US (4), the prevalence of HPV was 24.5% in women aged 14-19, 44.8% in women aged 20-24, 27.4% in women aged 25-29, 27.5% in women aged 30-39, 25.2% in women aged 10-49, and 19.6% in women aged 50-59. (4)

The prevalence and distribution of HPV strains differs around the world, where HPV-16 (found in 50% of cervical cancer cases), HPV-18, HPV-31 and HPV-45 are the most common in Europe and the USA, whilst in China, the most commonly found type was HPV-52, followed by HPV-16, HPV-58, HPV-68, and HPV-33 (5, 6). Secondary prevention, in forms of screening for cervical cancer via PAPA tests has drastically lowered the incidence of cancer in recent years, especially as PAPA test has become a standard screening method. Also, HPV typisation must not be forgotten, as it is able to detect high grade dysplasia earlier than PAPA testing, with a high level of specificity, in women over 30 (7).

The purpose of this study is to highlight epidemiological characteristics of the age and genotypical incidence of HPV infection among females in Canton Sarajevo during a 10-year period, since the country presently lacks this critical data for the creation of adequate screening and secondary preventative programs. The results of this study, should appeal on governmental agencies to accelerate the development of HPV prevention programs which limit and reduce the morbidity and mortality from cervical cancer and HPV associated cancer in Bosnia and Herzegovina.

2. OBJECTIVE

The purpose of this study is to highlight epidemiological characteristics of the age and genotypical incidence of HPV infection among females in Canton Sarajevo during a 10-year period.

3. PATIENTS AND METHODS

This cross-sectional study was conducted in the period between January 2012 and December 2021 at the medical institutions "Zavod za Ginekologiju, Perinatologiju i Neplodnost "Mehmedbašić" among females who were admitted for a routine gynaecological exam in Canton Sarajevo in Bosnia and Herzegovina. All Helsinki declaration amendments were followed in the study settings.

Patients

Patients which were sampled were females of Canton Sarajevo in Bosnia and Herzegovina which were admitted for a routine gynecological exam. Exclusion criteria were (i) being younger than 18 years and (ii) not being a Canton Sarajevo resident. All patients who were included in the study were informed about the study objectives, all information that its gathered, its purpose, potential outcomes, anonymity of the study data and a detailed informed consent that every patient had to fill out.

Study instruments and data collection

Each patient included in the study had a detailed anamnesis taken before the gynecological physical exam where data regarding the family history of oncological issues, beginning of the sexual activity, number of sexual partners, contraception methods that were used and any gynecological symptoms that were present, were taken.

After the initial interview, patients underwent a routine

gynecological physical exam, where bimanual and speculum examination was conducted and after a swab was taken for the HPV genotyping. The samples were analysed using the real time PCR kits for high-risk, potentially high-risk and low-risk HPV in genital swabs. The kit contains a specific ready to use system for detection of HPV.

Statistical analysis

All data that were collected, were properly organized and statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0. Normally distributed data were presented as frequencies, percentage and by mean \pm standard deviation, while not normally distributed by median (25th, 75th percentile). Descriptive statistics were conducted and data were presented during the 10-year timeline.

4. RESULTS

In total, 1517 patients who reported typical sexarche at 18.35 ± 1.92 , having one 721 (47.5%) sexual partner, regular use of contraceptive methods 820 (54.5%) with male condom 513 (62.6%) being the dominant choice of contraception and having gynecological hereditary oncological positive history 141 (9.3%), were included in the study. Out of all

Year	Total tested	HPV positive	HPV negative	HPV positive %	HPV negative %
2012	38	12	26	31.58%	68.42%
2013	158	64	94	40.51%	59.49%
2014	148	47	101	31.76%	68.24%
2015	170	39	131	22.94%	77.06%
2016	184	100	84	54.35%	45.65%
2017	240	126	114	52.50%	47.50%
2018	148	63	85	42.57%	57.43%
2019	160	68	92	42.50%	57.50%
2020	126	63	63	50.00%	50.00%
2021	145	72	73	49.66%	50.34%

Table 1. Numbers of patients with HPV positive and negative test results including corresponding percentages per each year

Type of HPV virus	Number of patients	% of patients
16	87	22.5
31	39	10.1
56	35	9.1
51	33	8.5
68	31	8.0
52	28	7.2
39	26	6.7
18	20	5.1
35	18	4.6
45	15	4.0
33	14	3.6
58	14	3.6
59	13	3.5
66	13	3.5

Table 2. Specific HPV strains which were identified among patients infected with only one virus strain

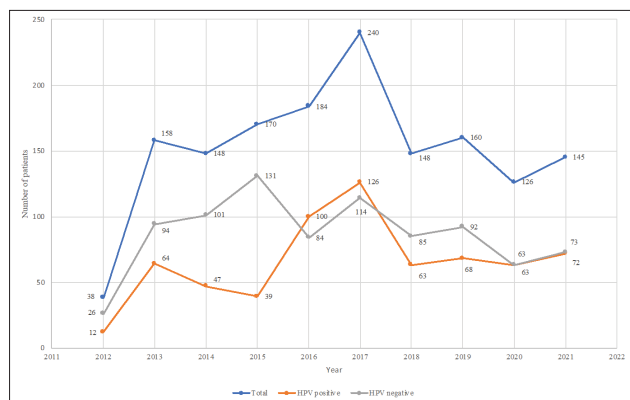


Figure 1. HPV positive and negative cases and total number of tested patients throughout the 10 year period

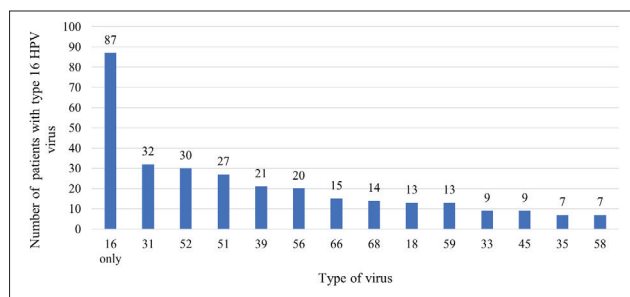


Figure 2. Patients infected with HPV strain 16 virus and in combination with other HPV viruses

patients, 653 (43.05%) had positive HPV test findings and 864 (56.95%) had negative HPV test results. Number of patients with HPV positive and negative test results including corresponding percentages per each year are displayed in Table 1., while the timeline of HPV positive/negative cases throughout the 10 year old period could be seen on Figure 1. Only in 2016 and 2017 number of HPV positive patients were higher than HPV negative patients. Mean age of all patients were 34.58 ± 8.3 (HPV negative 35.48 ± 8.52 ; HPV positive 33.38 ± 7.85), ranging from 18 to 72 years. (HPV negative 18-72; HPV positive 18-61)

Human Papillomavirus analysis

Out of all 653 (43.05%) HPV positive patients, 386 (59.1%) were infected with one type of virus only, while the other 267 (40.9%) patients were infected with multiple virus strains where we have identified 166 virus strain combinations. Analysis showed that the patients infected by only one virus strain were one of next specific HPV viruses: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. HPV-16 was the predominately strain 16 (22.5%) identified among all the patients. Specific HPVs which were identified among patients infected with only one virus strain are presented in Table 2. Mean age of HPV positive patients was 33.38 ± 7.85 , ranging from 18 to 61 years.

When virus strain combinations were examined the majority of patients were infected with HPV-16 or HPV-18 in a combination with other HPVs. Figure 2. shows number of patients infected with HPV-16 only as well as combination of infections with HPV-16 and other types of viruses 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, not excluding other types of viruses in particular combination, while Figure 3. shows number of patients infected with HPV-18 only as well as combination of infections with HPV-18 and

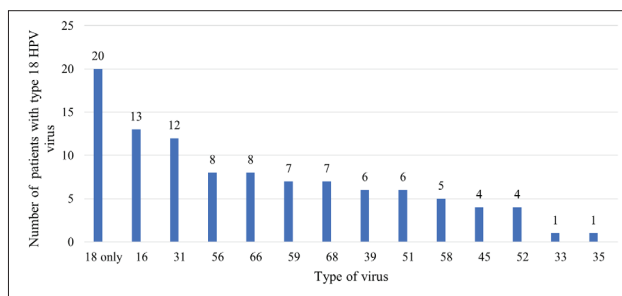


Figure 3. Patients infected with HPV strain 18 virus and in combination with other HPV viruses

other types of viruses 16, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, not excluding other types of viruses in particular combination.

5. DISCUSSION

Bosnia and Herzegovina has just recently started introducing HPV vaccination programs among its population (8) to reduce the overall HPV-related cancer morbidity and mortality. Our study sample with predominantly young females, older age of sexarche, typically one sexual partner, regular use of contraceptive methshowed a relatively prevalent HPV infection with HPV-16, HPV-31, HPV-56, HPV-51 being the most dominant when analyzed among patients who were infected only with one HPV strain. HPV was common more among younger females. Patients had also a trend of being infected with multiple strains and with two and more onco-potent strains thus increasing the likelihood of developing cancer. An increase in HPV infection among patients was reported throughout a 10-year study period in Bosnia and Herzegovina females.

When compared to a similar study (9) conducted in Bosnia and Herzegovina, our study showed a different distribution of the most prevalent strains among the patients. In our study HPV-16 was similarly the most prevalent, followed by HPV-31, HPV-56 and HPV-51 which differ to the previous study (9) and could be explained by different sampling techniques as the previous study (9) only included patients with abnormal cytology limiting the inclusion of other females, larger sample size in our study and different sample collection timeline. The results of our study show a similar distribution of HPVs as observed in the region, Croatia (10) and Serbia (11), and other European (12) countries.

When age distribution of the patients was analyzed, HPV infected patients were younger than patients who were not infected with HPV viruses. Many studies confirm a similar finding (13, 15) which could be attributed to poverty, number of sexual partners, age at sexual debut and marital status. Younger individuals are also more prone to go and visit gynecologist for a routine examination and do a HPV test as part of the screening programs compared to the elderly. This difference could be attributed to cultural and educational differences between younger and elderly females. Modern lifestyle, as well as the introduction of HPV vaccine contributes to the changes in HPV prevalence and its fluidity through the population. Furthermore, improved HPV tests today detect HPV at lower quantities which could be one of the technological reasons for such findings.

Our study has several limitations. Firstly, the study set-

ting as cross-sectional makes very difficult to infer causality. Patients were sampled only in the Canton Sarajevo, so different regions of the country were not included in the study sample. Future studies should, also include these regions. Furthermore, our study setting mostly included patients from urban environments, while remote and rural environments weren't included in the study. Future studies should include the most vulnerable groups and from regions which are remote.

6. CONCLUSION

This study highlights the significance of the most frequent HPV high-risk strains (HPV-16,-18,-31.-33,-45,-52, and -58) among the Bosnia and Herzegovina population as one of the most common cancer-causing strains worldwide. (12). The study provides detailed and comprehensive data on the distribution of certain HPV-strains among Bosnia and Herzegovina women throughout a ten-year period, with HPV-16 being the most widespread genotype. The results of this study should appeal on governmental and health agencies for the extensive implementation for HPV vaccination programs among the population thus decreasing morbidity and mortality from HPV associated cancers.

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- **Author's contribution:** All authors were involved in all steps of the preparation this article. Final proofreading was made by the first author.
- **Conflicts of interest:** There are no conflicts of interest.
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