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Prevalence of high-risk human papillomavirus infection and cervical cytology abnormalities among women up to age 40 in the Tuzla Canton, Bosnia and Herzegovina

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Abstract

Introduction: Cervical cancer is the second leading cause of female cancer in Bosnia and Herzegovina, and it is the most common female cancer in women 15 to 44 years old. Cervical cancer is etiologically associated with high-risk human papillomaviruses (HRHPV). Data on the prevalence of HRHPV in Bosnia and Herzegovina are scant. This study investigates the prevalence of HRHPV infection among women of reproductive age compared with cervical cytology in the Tuzla Canton.
Methods: We analyzed the results of HRHPV testing and Papanicolaou (Pap) test results in women up to 40 years old diagnosed at the Tuzla University Clinical Center (UCC) from January 2019 to March 2020.
Results: Among 880 women tested for HRHPV, 27.2% (n = 239) were ≤ 40 years. In this age group HRHPV was detected in 33.5% (n = 80) of women, and 23.8% (n = 19) were women < 30 years. Out of 239 women tested for HRHPV, 60.2% had an abnormal Pap smear result. Therefore, 40.7% (n = 59) of HRHPV-positive women had an abnormal Pap test result. Women with a normal Pap test result had an HRHPV-positive test in 22.3% (n = 21) of cases.
Conclusions: The results obtained contribute to the knowledge about HPV prevalence and the incidence of squamous cell abnormalities in the most populous canton in Bosnia and Herzegovina, possibly reflecting the situation nationally. The high prevalence of HRHPV in women of reproductive age calls for urgent implementation of an organized cervical cancer screening program and HPV vaccination.

Keywords: Papanicolaou test, *Papillomaviridae*, HPV, cervical cancer

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Introduction

Invasive cervical cancer is one of the most important cancers in women worldwide. It is a major public health problem in many developing countries and the major cause of death in women in low-income countries (1). According to the Globocan survey, invasive cervical cancer was responsible for 569,847 new cases and 311,365 related deaths in 2018 (2). Several viruses play an important role in the development of human cancer generally, and various stages of carcinogenesis can be facilitated by oncogenic viruses (3). Human papillomaviruses (HPV) cause the most common viral sexually transmitted infections, and high-risk HPV (HRHPV) genotypes are present in virtually all cervical cancers (4). In addition to cervical cancer, persistent HPV infection is also associated with other anogenital cancers as well as some head and neck cancers (5). In the majority of cases, HPV infection clears spontaneously. Patients with persistent infections with oncogenic HPV genotypes have an increased risk of acquiring squamous cell abnormalities, which can progress to cancer (6). Recognizing and treating precancerous cervical lesions at an early stage is highly effective and makes cervical cancer preventable.

The main role in cervical cancer prevention was played by the introduction of cytological screening in the late 1940s (7). Since the introduction of the conventional cytology smear, or Papanicolaou (Pap) smear, the incidence and mortality of cervical cancer has dramatically decreased in many developed countries (8). Developing countries such as Bosnia and Herzegovina bear some of the highest cervical cancer burden due to the lack of effective population-based cervical cancer screening. In Bosnia and Herzegovina, the age-standardized cervical cancer incidence and mortality rates were estimated at 13.7 new cases and 2.7 deaths per 100,000 women in 2012 (9), and in 2018 the age-standardized incidence rate was estimated at 23.9, with an age-standardized mortality rate of 7.9 (10).

Bosnia and Herzegovina consists of two autonomous entities: the Federation of Bosnia and Herzegovina, and Republika Srpska. A third unit, the Brčko District, is locally governed. The Federation consists of 10 territorial and economic units called cantons. Each canton has its own cantonal government, which covers all aspects of economics, politics, health, education, and so on.

Most national screening guidelines recommend annual screening starting at age 21, with three consecutive negative results, before lengthening the screening interval depending on women's risk group. In Bosnia and Herzegovina, implementing an effective cervical cancer screening program has not been a priority. Some progress was made in 2011, when the Federal Ministry of Health issued and published its Strategy for Prevention, Treatment, and Control of Malignant Neoplasms in the Federation of Bosnia and Herzegovina with various working groups, including a group for preparing a plan for malignant neoplasm prevention and early detection (screening).

However, to date a proper cervical cancer prevention program has not been established in Bosnia and Herzegovina (11). The country has an opportunistic screening program and a high cancer incidence rate in all age categories, corresponding to HRHPV prevalence.

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It has been proven that HPV testing is an effective tool for cervical cancer screening (12). This study assesses the prevalence of HRHPV infection among women up to 30 and 40 years of age compared with cervical cytology in the Tuzla Canton. In order to obtain the most relevant picture of the actual state of the frequency of abnormal Pap smear findings in the Tuzla Canton associated with HPV infection in women ≤ 40, we analyzed all Pap smears performed at the Tuzla University Clinical Center (UCC), as well all women tested for HRHPV with various cytology results.

Material and methods

Study population

All women up to age 40 that attended any gynecology polyclinic for HRHPV testing and with a documented Pap smear result from January 2019 to March 2020 were included in the study. All of them had abnormal Pap smear results or were advised to undergo HR-HPV testing by a gynecologist due to an abnormal or suspicious colposcopy. Because of the way the health system is organized in the Tuzla Canton as well as in the Federation, all women that had a routine Pap test in the same period at the gynecological clinic at the Tuzla UCC were also included in this study. Some of them also underwent HRHPV testing. Cervical cytology evaluations were performed for all the women, as well as histology for those with a suspicion of high-grade squamous intraepithelial lesions (HSIL).

The study was approved by the ethics committee of the Tuzla UCC (consent no. 04-09/2-34/20).

Methods

Cervical smears were stained with Pap stain following the standardized procedure. The Pap tests were interpreted by an experienced pathologist and reported according to the Bethesda System classification of 2014 in the following categories: negative for intraepithelial lesion or malignancy (NILM); atypical squamous cells of undetermined significance (ASCUS); atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H); low-grade squamous intraepithelial lesion (LSIL), encompassing HPV / mild dysplasia / CIN I; high-grade squamous intraepithelial lesion (HSIL), encompassing moderate and severe dysplasia, CIS, CIN 2, and CIN 3; squamous cell carcinoma (SCC); atypical glandular cell of undetermined significance (AGUS); and adenocarcinoma (ADC). Every cytological finding except NILM was considered abnormal. Cytology results suspicious for HSIL were referred to colposcopy followed by histology.

Samples of the cervical smear for HRHPV testing were taken during routine gynecological examinations using medical cotton swabs taken from the Qiagen Specimen Collection Kit on the entire surface portion using mild rotating motions from the outer cervical entrance. Detection of the presence of HRHPV in cervical smears was made using the Hybrid Capture II HPV Test (Qiagen, Germantown, MD, USA). The samples were tested for the presence of HRHPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Statistical analysis

The statistical analysis was performed using the software IBM Statistics V21. From the descriptive statistical parameters, the absolute and percentage frequencies were calculated, and from the non-parametric statistical method Pearson's chi-squared test was applied. Statistical significance was tested at an alpha level of 95%; that is, 5% risk (0.05).

Results

From January 2019 to March 2020, a total of 880 women were tested for HRHPV. Out of these, 28% (n = 246) were HRHPV-positive and 72% (n = 634) were HRHPV-negative; 27.2% (n = 239) were ≤ 40 years, and 17.2% (n = 41) were < 30 years. Out of the 239 women ≤ 40 years old, 33.5% (n = 80) were HRHPV-positive. In the group of women ≤ 40 years tested for HRHPV, 46.3% (n = 19) of those HRHPV-positive were up to 30 years, and 30.8% (n = 61) of those HRHPV-positive were between 30 and 40 years old. Most of the HRHPV-positive women up to age 40 were between 30 and 40 years old, 76.2% (n = 61).

In the group of women tested for HRHPV (n = 239, Group 1), 60.7% (n = 145) had abnormal Pap test results, with 13.9% (n = 20) younger than 30. The most significant number of patients with an abnormal Pap test result belong to the 30 to 40 age group (p < 0.130, Table 1). As expected, most of the HRHPV-positive women had an abnormal Pap test result, 40.7% (n = 59, p < 0.006), compared with 22.3% (n = 21) of women with a normal Pap test result. Pearson's chi-squared test proved a statistically significant (p < 0.003, x^2 = 8.62) connection between Pap test results and positive HRHPV status in patients (Table 2). The most common Pap test result among the women tested for HRHPV was ASCUS (42.3%, Table 3).

From January 2019 to March 2020, 4,691 Pap tests were analyzed at the Tuzla UCC. Out of 4,691 tests, 23.8% (n = 1,116, Group 2) were women under age 40, with 5.4% (n = 255) under age 30. About 9.6% (n = 107) of women were also tested for HRHPV, and 32.7% (n = 35) of these were positive. As in the previous group, most of the women that were HRHPV-positive were between 30 and 40

Table 1 | Papanicolaou (PAP) test results in women tested for high-risk human papillomaviruses (HRHPV) with respect to age (Group 1).

Age group	Pap test, *n* (%)		
	Normal	Abnormal	Total
< 30 years	21 (22.3)	20 (13.9)	41 (17.2)
30–40 years	73 (77.7)	125 (86.2)	198 (82.8)
Total	94 (100.0)	145 (100.0)	239 (100.0)

Pearson's chi-squared test = 2.93, df = 1, p < 0.087, Pap = Papanicolaou.

Table 2 | Relationship between Papanicolaou (PAP) test results and high-risk human papillomavirus (HRHPV) status (Group 1).

HRHPV	Pap test, *n* (%)		
	Normal	Abnormal	Total
Negative	73 (77.1)	86 (59.3)	159 (66.5)
Positive	21 (22.3)	59 (40.7)	80 (33.5)
Total	94 (100.0)	145 (100.0)	239 (100.0)

Pearson's chi-squared test = 8.62, df = 1, p < 0.003, HRHPV = high-risk human papillomaviruses, Pap = Papanicolaou.

Table 3 | Papanicolaou (PAP) smear findings in women under 40 years tested for high-risk human papillomaviruses (HRHPV) (Group 1).

PAP test	HRHPV testing, *n* (%)		
	UCC	Out of UCC	Total
NILM	40 (38.1)	54 (40.3)	94 (39.3)
ASCUS	47 (44.8)	54 (40.3)	101 (42.3)
AGUS	0 (0.0)	1 (0.7)	1 (0.4)
LSIL / CIN I	16 (15.2)	20 (14.9)	36 (15.1)
HSIL / CIN II	2 (1.9)	2 (1.5)	4 (1.7)
HSIL / CIN III	0 (0.0)	3 (2.3)	3 (1.3)
Total	105 (100.0)	134 (100.0)	239 (100.0)

UCC = University Clinical Center, NILM = negative for intraepithelial lesion, ASCUS = atypical squamous cells of undetermined significance, AGUS = atypical glandular cell of undetermined significance, LSIL / CIN I = low-grade squamous intraepithelial lesion, HSIL / CIN II = high-grade squamous intraepithelial lesion / moderate dysplasia, HSIL / CIN III = high-grade intraepithelial lesion / severe dysplasia, HRHPV = high-risk human papillomaviruses, Pap = Papanicolaou.

years old. There is a weak correlation between these groups, but it is not statistically significant ($p < 0.113$, $x^2 = 2.51$).

Out of 1,116 women under age 40, 15.6% ($n = 174$) had an abnormal Pap test result. Approximately 20% were under 30, and the rest were between 30 and 40 years old (Table 4). There is no statistically significant correlation ($p < 0.350$, $x^2 = 0.874$) between the incidence of normal and abnormal cytology results and the patients' age (Table 4). A statistically significant ($p < 0.022$, $x^2 = 5.26$) proportion of cases with an abnormal Pap test were among HRHPV patients (40.9%) compared with patients with benign cervical cytology (NILM, Table 5). HSIL was diagnosed in 18.0% of women between 30 and 40 years old, with no cases of HSIL in younger age groups.

In the group of women tested for HRHPV ($n = 107$), more than 60% had an abnormal Pap test ($n = 66$), with ASCUS as the most common cytology result (71.2%), followed by LSIL / CIN I at 25.8%. Most of the women with SIL were HRHPV-positive (33.3% LSIL, 7.4% HSIL). In 1,116 patients that had a Pap test at the Tuzla UCC, most of the cases, 84.6% ($n = 944$), had a normal cytology / NILM, followed by 12.5% ($n = 132$) of women with ASCUS. LSIL / CIN I was recorded in 2.8% ($n = 31$) of cases, HSIL / CIN II in 0.5% ($n = 6$) of cases, and HSIL/CIS in 0.1% ($n = 1$) of cases.

Table 4 | Prevalence of normal and abnormal cytology in different age groups (Group 2).

Age group	Pap test, *n* (%)		
	Normal	Abnormal	Total
< 30 years	220 (23.4)	35 (20.1)	255 (22.8)
30–40 years	722 (76.6)	139 (79.9)	861 (77.2)
Total	942 (100.0)	174 (100.0)	1,116 (100.0)

Pearson's chi-squared test = 0.874, $df = 1$, $p < 0.350$, Pap = Papanicolaou.

Table 5 | Correlation between Papanicolaou (PAP) test results and high-risk human papillomavirus (HRHPV) status.

HRHPV	Pap test, *n* (%)		
	Normal	Abnormal	Total
Negative	33 (80.5)	39 (59.1)	72 (67.3)
Positive	8 (19.5)	27 (40.9)	35 (32.7)
Total	41 (100.0)	66 (100.0)	107 (100.0)

Pearson's chi-squared test = 5.26, $df = 1$, $p < 0.022$, HRHPV = high-risk human papillomaviruses, Pap = Papanicolaou.

Discussion

In 2018, approximately 570,000 women developed cervical cancer and 311,000 women died from it. Most cervical cancers cases (84%) and 88% of all deaths caused by cervical cancer occurred in lower-income countries; in the highest-income countries, the cumulative rates of cervical cancer incidence and mortality were two to four times lower (13). Cervical cancer ranks as the second leading cause of female cancer in Bosnia and Herzegovina, and it is the most common female cancer in women 15 to 44 years old, with an age-standardized incidence rate estimated at 23.9 per 100,000 women per year in contrast to 7.8 in southern Europe and 13.1 globally (14). The annual number of cervical cancer cases in Bosnia and Herzegovina is 556, and annual cervical cancer deaths number 141 (14). A similar situation is recorded in neighboring Serbia, where the annual number of cervical cancer cases is 1,327, whereas in Croatia it is 266 and in Slovenia 110. The annual number of cervical cancer deaths in Serbia, Croatia, and Slovenia is 551, 175, and 65, respectively (15–17). Crude incidence rates per 100,000 women per year in Bosnia and Herzegovina are 31.2, in contrast to 29.6 in Serbia, 12.3 in Croatia, and 10.5 in Slovenia (14–17). These results reflect the absence of an organized screening program in Bosnia and Herzegovina in contrast to Slovenia, which has a national cervical cancer screening program. HPV vaccination is not mandatory, and there is no organized national vaccination program in Bosnia and Herzegovina, nor in Serbia, whereas in Croatia the national vaccination program began in 2016, and in Slovenia in 2009 (14–17).

The slow evolution from persistent infection to LSIL, and to HSIL and invasive cervical cancer provides an important opportunity for screening and early detection of precancerous cervical lesions. In Bosnia and Herzegovina opportunistic screening is in place, which depends on the individual woman's decision.

The Tuzla Canton is the most populous canton in Bosnia and Herzegovina, and it was the first to introduce HPV testing in January 2000 as an additional screening tool. Currently, the Tuzla Canton leads in HPV testing in Bosnia and Herzegovina. The Tuzla UCC is the largest medical institution, where most of the Pap smears for the Tuzla Canton are analyzed. However, a significant number of Pap smears are analyzed at private gynecology clinics. Due to the lack of an organized screening program, there is an unpredictable distribution of patients between private and public gynecology clinics, as well as a lack of a unique database, and we therefore have two separate datasets. One represents all woman tested for HRHPV at the Tuzla UCC (880 patients) from January 2019 to March 2020, with known Pap test results analyzed by an experienced pathologist at the Pathology Department of the Tuzla UCC, a primary healthcare clinic, or a private clinic. The second dataset is all woman under age 40 that had a Pap test at the Tuzla UCC during the same period, and some of them also had an HPV test, depending on the Pap test results. This study approach may be a limiting factor in the overall analysis and representation, and in fact it may not be a complete representative study of the entire female population; however, given the situation, it provides the best estimate of the real situation in the canton.

There is no unique prevention system in Bosnia and Herzegovina at the state, entity, or canton level, and therefore there is no common database of Pap test results or HPV testing results, which is one reason why the prevalence of HPV in the country is still not clearly defined. In this study, 28% ($n = 246$) out of 880 patients were HRHPV-positive. According to the data, HPV infections are most common in young women, and its incidence tends to be much lower after age 45 (18). This is the main reason why we decided to analyze HRHPV status and Pap test results in women under 40. Women in these age groups are of reproductive age and sexually active, with a high probability of abnormal Pap smear results. Out of 239 women under age 40, 33.5% ($n = 80$) were HRHPV-positive. Similar results were recorded in a study by Maslić et al. conducted in Serbia (19), with a high HPV prevalence of 41.3%, whereby 31.6% of HPV-positive women had HPV 16/18 types. In a study by Sousa et al., HRHPV infection prevalence varied by age, ranging from a maximum of 17.1% at age 25 to a minimum of 6.2% at age 64, as expected (20). Similar results were recorded in Slovenian women during the pre-vaccination period, with HRHPV prevalence ranging from 21.7% in the 20-to-29 age group and 10.9% in the 30-to-39 age group to 4.0% for the 50-to-64 age group (21). Interesting data from our study show that the proportion of HRHPV-positive women was higher in women over 30, at 76.2% ($n = 61$), in contrast to the women under 30, at 23.8% ($n = 19$). Our data are consistent with results of Maslić et al. in Serbia as well as with some studies from low-resource settings of Africa and Asia, which reported high prevalence in all age groups, as well as in the age group older than 35 (22).

Among the women tested for HRHPV, 60.2% ($n = 145$) had an

abnormal Pap test result. We considered the high incidence of Pap smear abnormalities among this group of women to be the consequence of a recommendation for HRHPV testing among women with abnormal cytology results. Therefore, in the group of women that had a Pap smear during their routine gynecological exam during the same period, the incidence of an abnormal Pap smear in women ≤ 40 years was much lower, about 15.6%, but still higher compared with data in the Serbian study (10.3%) (19), or in Bangladesh (8.2%) (23). The higher prevalence found in our study—approximately 22% of squamous cell abnormalities, excluding inflammatory smear results—was also similar to that recorded in southwestern Nigeria (24).

To date, the rate of cervical smear abnormalities is higher in high-risk areas and in areas with a higher prevalence of HPV infection, including Russia (9.8% Pap smear abnormalities), India (10.8%), and South Africa (17.3%) (25–27). In our study, there was an abnormal Pap smear result in 40.3% (n = 58) of HRHPV-positive women.

The most common Pap smear result in our study was ASCUS, at 42.3% in Group 1 and 12.5% in Group 2. The explanation might be the same as mentioned above; that is, due to repeated abnormal findings in cytology. ASCUS remained the most common category among squamous cell abnormalities, as in Romania (28), or in Jordan at 2% of cases (29). A similar percentage of ASCUS was recorded in low-risk regions such as Kuwait (2.2%) and Saudi Arabia, compared to a higher rate in Russia and South Africa, with rates of 7.5% and 4.7%, respectively (27, 28, 30, 31). These disparities could be the result of differences in lifestyle, country resources, and the number and age of women included in the studies; in addition, male circumcision, a common practice among some religions, has a protective effect on the risk of HPV transmission to female partners (32). Although circumcision is very common in Bosnia and Herzegovina, mostly due to cultural and religious habits, HRHPV prevalence is still high. One explanation may be that circumcision has a limited protective role in individuals with risky sexual behavior.

As expected, the prevalence of HSIL was higher among HRHPV-positive women and in women over 30.

In this study, the samples were tested for the presence of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Previous results from Iljazović et al.'s study confirmed the overall contribution of HPV 16/18 in most cases of invasive cervical cancer in Bosnia and Herzegovina, and showed that licensed HPV vaccines could potentially prevent up to 78% of cervical cancer cases (11).

In conclusion, this study contributes to knowledge about the prevalence of HPV infection and squamous cell abnormalities in the most populous canton in Bosnia and Herzegovina and probably largely reflects the situation at the country level. Information on the population prevalence of HPV is crucial for informed implementation of organized screening in Bosnia and Herzegovina and monitoring HPV vaccination. The relatively high prevalence of HRHPV in younger women in the region requires tailored screening solutions.

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